

**USING QUALITY OF LIFE AND FRAILTY AS PREDICTORS OF RECOVERY IN
CARDIAC SURGERY PATIENTS.**

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Abstract

Background: Frailty is a state characterised by a subclinical decline across multiple organ systems. High frailty is an independent predictor of poor outcome post cardiac surgery. The relationship between patient reported health related quality of life (HRQOL), their frailty status and the impact of cardiac surgeries to their quality of life and functional status has never been investigated in pre and post cardiac surgery.

Objective. The objective of this study was to evaluate the relationship between frailty and QoL in pre-and post-cardiac surgery; the predictive value of frailty, pre-cardiac surgery symptoms, comorbidities, and their impact on QoL at four time points post-operatively.

Method: The Reported Edmonton Frail Scale (REFS) was applied to all patients to evaluate their frailty score pre-operatively. The influence of frailty to baseline characteristics and quality of life at four time points was calculated. The QoL was assessed in both pre- and post-operatively. Generalised estimation equation (GEE) was applied to measure the influencing factors of quality of life at the four different time points. A wrist worn accelerometer was also applied to patients in order to objectively measure their physical activity levels in both pre-and post-operatively.

Results: 105 patients (mean age of 77.22 ± 10.55 years) were successfully enrolled to the study of which 93 (88.57%) patients participated the follow-up period. High frail patients were twice more likely to have longer in-hospital stay than non-frail (Mean 21.2 vs. 9.6 days, $p=0.016$). The study proved baseline HRQOL has a direct relationship to post-operative HRQOL and survival. Frailty influenced in three out of the four activity levels. Postoperatively, high frail cohorts were more prone to higher complication rates compared to non-frail.

Conclusion: The quality of life (QoL) of the vast majority of frail patients improved post cardiac surgery, few may appear to experience poor projection in QoL. Hence, it is inevitable to develop prediction models for recovery and expected improvement in QoL

Dedication.

*I dedicate this thesis to my beloved father “**Sheikh Siyat**” who passed away during the first year of this milestone and my beloved mother “**Masar**” to whom I owe my life.*

*I would also give special thanks to my lovely wife “**Ikran**”; her care and love was the secret ingredient for the successful accomplishment of this great work. To my Son “**Abdulmalik**” and my daughter “**Maryam**”; the apples of my eyes and the joy of my life!*

*I also dedicate this work to my sisters; **Fatma, Mumina, Anisa and Maryam** and brothers **Ibrahim** and **Abdulrahman**; thank you for the consistent support and motivation, you mean to me the whole world!*

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Declaration of Originality

I declare that this is an original work and has not been submitted for the ward of any other degree or any scientific and financial project. All valuable contributors are acknowledged and relevant information is appropriately referenced.

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List of Abbreviations.

CABG Coronary Artery Bypass Graft

CAF Comprehensive Assessment of Frailty

CCG Clinical Commissioning Group

CCI Charlson Comorbidity Index

CFS Clinical Frailty Scale

CGA Comprehensive Geriatric Assessment

CHS Cardiovascular Health Study

CI Confidence Interval

CSHA Canadian Study of Health and Aging

EFS Edmonton Frail Scale

EQ-5D EuroQOL Quality of Life Score

HRQOL Health Related Quality of Life

GEE Generalised Estimation Equation

MAR Missing At Random

ADL Activities of Daily Living

ASA American Society of Anaesthesiology

AUC Area Under Curve

BMI Body Mass Index

ERAS Enhanced Recovery After Surgery

ERP Enhanced Recovery Protocol

EuroSCORE European System for Cardiac Operative Risk Evaluation Score

FI Frailty Index

FORECAST Frailty predicts death One year after CARDiac Surgery Test

HR Hazard Ratio

IADL Instrumental Activities of Daily Living

ITU Intensive Therapy Unit

LOS Length of Stay

MACCE Major adverse cardiovascular and cerebral events

MDT Multidisciplinary Team

QoL Quality of Life

QI Quality Index

RCT Randomised Controlled Trial

ROC Receiver Operating Characteristic

SMW Six Minute Walk

STS Society of Thoracic Surgeons

TAVI Transcatheter Aortic Valve Implantation

UK United Kingdom

USA United States of America

HADS Hospital Anxiety and Depression Scale

SIP Sickness Impact Profile

Publications and Presentation.

Published Papers.

1. **Yusuf S. Abdullahi**, Leonidas V. Athanasopoulos, Roberto P. Casula, Marco Moscarelli, Mark Bagnall, Hutan Ashrafian and Thanos Athanasiou. *Systematic review on the predictive ability of frailty assessment measures in cardiac surgery.* @ Interactive Cardiovascular and Thoracic Surgery 24 (2017) 619–624.
2. **Yusuf S Abdullahi**, Leonidas V Athanasopoulos, Marco Moscarelli, Roberto P Casula, Giuseppe Speziale, Khalil Fattouch, Sebastiano Castrovinci, Thanos Athanasiou. *What are the benefits of a minimally invasive approach in frail octogenarian Patients undergoing aortic valve replacement?* @ Journal of Geriatric Cardiology (2016) 13: 514-516.
3. Leonidas V. Athanasopoulos, Roberto P. Casula, P Punjabi, **Yusuf S. Abdullahi**, and Thanos Athanasiou. *A technical review of subvalvular techniques for repair of ischaemic mitral regurgitation and their associated echocardiographic and survival outcomes.* @ Interactive Cardiovascular and Thoracic Surgery 2017 Dec 1; 25(6):975-982.

Presentation.

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Publication arising from the study to be submitted soon.

- 1. Yusuf S Abdullahi, Leonidas V Athanasopoulos, Roberto P Casula and Thanos Athanasiou. *What is the clinical utility of accelerometry to predict early outcome in high risk frail patients undergoing cardiac surgery?***
- 2 Yusuf S Abdullahi, Leonidas V Athanasopoulos, Roberto P Casula and Thanos Athanasiou. *Frailty consideration in Cardiovascular team meeting and Measuring the quality of MDT Process. National Survey of Heart Team.***
- 3 Yusuf S Abdullahi, Nina Al-Saadi, Leonidas V Athanasopoulos, Roberto P Casula and Thanos Athanasiou. *Systematic Review: Accelerometer applications in adult patients with cardiovascular disease.***
- 4 Yusuf S Abdullahi, Roberto P Casula and Thanos Athanasiou. *The Impact of Valve Surgery on the Quality of Life of Elderly Patients: Systematic Review.***
- 5 Yusuf S Abdullahi, Roberto P Casula and Thanos Athanasiou. *Systematic Review on Quality of Life of Elderly Patients after isolated Coronary Artery Bypass Grafts (CABG).***
- 6 Yusuf S Abdullahi, Roberto P Casula and Thanos Athanasiou. *The relationship between Health Related Quality of Life (HRQOL), Frailty Scores and Post-operative Outcome in Cardiac Surgery.***

1.0 Chapter 1

Introduction and Background to Cardiac Surgery, Frailty, Quality Of Life and Accelerometer Measurement.

Cardiac procedures carry immediate, early and delayed risks of complications. Little objective data exists on how patients recover physically from surgery or the impact on their quality of life and this information can help to determine the surgical or medical course of treatment for patients. Objective mobility data can be used as a measure of health and to evaluate the relevance of certain medical treatments and to estimate the quality of life of an elderly patient.

It is over 50 years since the first coronary artery bypass graft (CABG), was performed in 1964 [1] Furthermore, in 1977 the initial percutaneous coronary intervention (PCI) was also performed [2]. Since the pioneering of both these revascularisation techniques, there have been on-going developments, particularly in the systematic use of arterial conduits in the instance of CABG and the initiation of stents.

Over the years the most commonly performed therapeutic intervention has become PCI [3]. Progress has resulted in an established decline of peri-procedural adverse events, resulting in favourable outcomes with both of the aforementioned revascularisation techniques. However, the differences between the two revascularisation strategies should be recognized: CABG involves the suturing of bypass grafts onto the native vessel beyond the offending lesion with the aim of restoring or improving blood flow to the myocardium and protecting it from the effects of further proximal obstructive disease, such as ischaemia; the focus of coronary artery stents on the other hand, is to restore normal blood flow of the intrinsic coronary vasculature by localised

management of the offending obstructive lesions but without offering the additional advantage of protecting against further disease to the stent.

1.1 Rationale for revascularisation.

Before patients undergo any revascularisation due to the presentation of coronary artery diseases, they must be managed medically in accordance with the accepted national guidelines. This has been shown to lead to more favourable outcomes in terms of both symptom relief as well as prognosis [4].

The symptoms for PCI or CABG include flow-limiting coronary stenosis with the aim to reduce the advent of myocardial ischaemia and its associated unfavourable clinical consequences [5] [6] However, patients with coronary artery diseases who have tenacity of symptoms following medical management as well as those who are considered to have a potential prognostic benefit should be considered for revascularisation [4]. Accordingly, revascularisation and medical therapy should be viewed in harmony to one another.

In addition, living with angina condition is linked with a plethora of difficulties from having a reduced quality of life and a compromised exercise capacity to suffering with mental depression and having recurrent bouts of hospitalization and outpatient visits [7]. Compared management by medical therapy alone, angina can be much more effectively relieved by revascularisation, using either PCI or CABG, which can also limit the use of anti-anginal drugs and vastly improve the exercise tolerance and quality of life of these patients [8, 9].

In patients with coronary artery diseases, ischaemia is of prognostic importance, especially when it occurs at workloads of a lower threshold [10, 11]. Medical treatment by itself is not as successful at alleviating myocardial ischaemia and there are a myriad

of studies that demonstrate that techniques utilising revascularisation have more favourable outcomes.

Coronary angiography or coronary computed tomography (CT) angiography are employed to assess the site, degree and severity of coronary artery obstruction (figure 1), all of which, in addition to ischaemia and left ventricular function, are vital factors in prognosis [12, 13]. The indication for revascularisation with PCI or CABG as opposed to medical treatment is reported in several randomised controlled trials (RCTs) [14] [15].

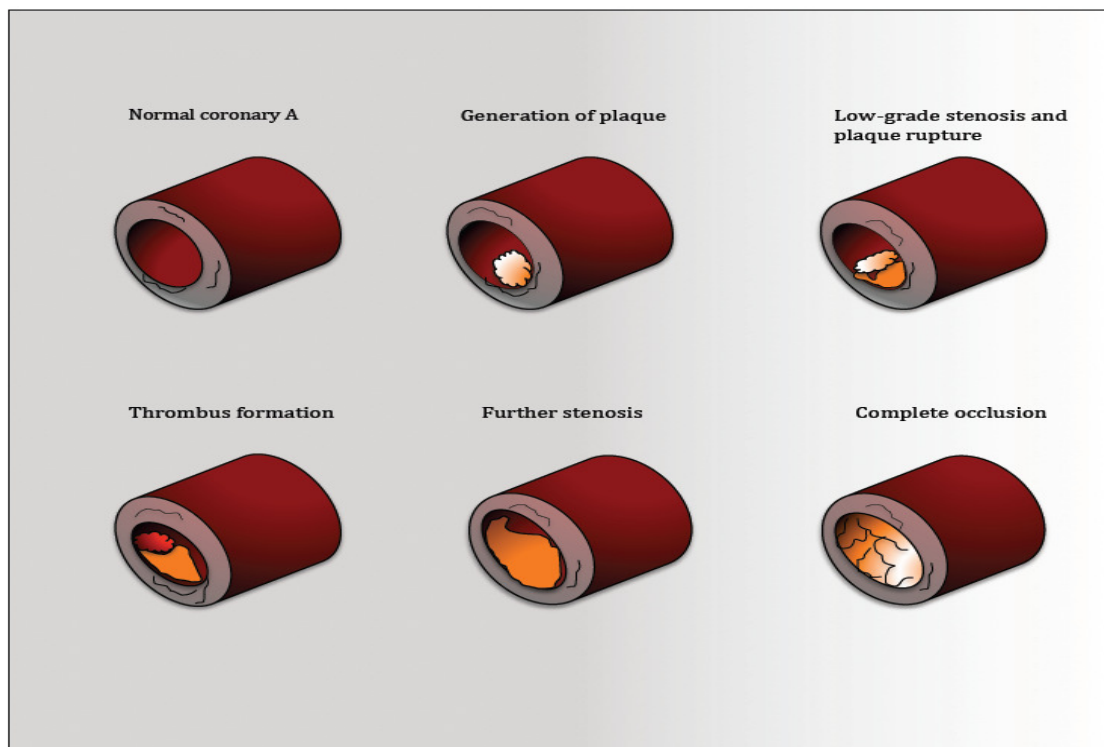


Figure 1 – Figure 1.1 Vascular ischaemia.

Demonstrates the effect of build-up of lipid and macrophage secretions causing thickening of the blood vessel wall that leads to narrowing of the arterial lumen and consequent ischemia. Ref.....

1.2 Revascularisations with the use of coronary artery bypass grafting.

The findings from a meta-analysis of seven RCTs highlighted the absolute merit of the CABG technique to an approach of initial medical therapy for comprehensive subgroups of SCAD [16]. It established that those patients with LM or three-vessel SCAD, there was a significant advantage in terms of survival, in particular when the proximal LAD coronary artery was complex.

Those who suffered from severe symptoms, had early positive exercise tests, and impaired LV function demonstrated experiencing a greater level of benefit. Remarkably, in these initial research findings, only 10% of CABG patients received an internal mammary artery (IMA) graft, which is a significant predictive element of CABG. Moreover, the follow-up revealed that there was an overlap of around 40% of patients in the medical and CABG groups. According to a more recent meta-analysis there is a reduction in mortality with CABG in comparison with medical therapy alone (HR 0.62; 95% CI 0.50–0.77) [17].

PCI and CABG were compared in a random MASS II medical therapy trial and at 10 years, CABG was associated with reduced amounts of myocardial infarction (MI), angina and cardiac mortality compared to medical therapy [15]; 1212 patients that had CAD and a left ventricular ejection fraction (LVEF) of $\leq 35\%$ were randomly allocated to either medical therapy or CABG in the Surgical Treatment Ischemic Heart failure (STICH) trial. All patients showing LM disease were excluded from the study, and by the conclusion of the follow-up period, 17% of patients on medical therapy underwent CABG and 6% of patients underwent PCI. Treatment analysis of the study showed no significant difference in mortality rate with CABG compared with medical therapy (36% vs. 41%; HR 0.86; 95% CI 0.72–1.04; $p = 0.12$); whereas patients with cardiovascular symptoms being treated with CABG showed significantly lower

mortality or hospitalisation (58% vs. 68%; HR 0.74; 95% CI 0.64–0.85; $p < 0.001$). The results indicate that CABG was associated with improvement in all secondary clinical outcomes as well as the ‘as treated’ analysis indicating the association of reduced risk for the primary outcome and death with CABG cohort (HR 0.70; 95% CI 0.58–0.84; $P < 0.001$) [18].

None the less, the more recent, 10 year follow up on STICHES trial evaluating the effects of CABG in patients with ischemic cardiomyopathy reported significant decrease in all-cause mortality or hospitalisation due to cardiovascular problems amongst patients who had undergone CABG and received medical therapy compared to those patients whom only received medical therapy [19].

1.2.1 Proximal left anterior descending coronary artery disease.

A meta-analysis including nine RCT’s studied 1210 patients with remote proximal LAD lesions for 5 years [20] and a second study including six RCTs analysed two non-random trials comprising 1952 patients with isolated proximal LAD lesions who were followed for up to 4 years [21]. These two meta-analyses studies showed no significant difference in MI, stroke or mortality but showed a three-fold increase in angina frequency and the need for repeat revascularisation was five times more likely with PCI compared to CABG. Furthermore, after a 10 year follow-up it was reported that a single IMA in patients with multi-vessel CAD had positive effects [22].

1.2.2 Left main coronary artery disease.

CABG has been considered the best care for patients with LM who were suitable for surgery, based upon the Coronary Artery Surgery Study (CASS) registry for the last few decades [16]. The success of PCI in LM lesions is dependent on two major

pathophysiological features: firstly, about 80% of LM disease involves the bifurcation and there is an increased risk of re-stenosis; secondly, at least 80% of LM patients have multi-vessel SCAD and CABG presents a survival benefit independent of LM disease [22, 23].

A leading randomised trial run comparison study recruiting 600 patients with known left main coronary artery disease and divided patients into PCI or CABG groups [24]. After one year follow-up, the composite rate of MI, mortality, stroke or repeat intervention was 6.7% in the CABG group and 8.7% in the PCI group ($P=0.37$). However they also reported that over a period of 2 years there were no significant differences between the two groups and this was also valid for mortality (3.4% in the CABG group and 2.4% in the PCI group; $p = 0.45$) and for the composite rate of death, myocardial infarction, or stroke (4.4% in the CABG group and 4.7% in the PCI group; $p = 0.83$). In contrast to the findings in SYNTAX, the incidence of stroke was similar for PCI (0.4%) and CABG (0.7%). More recent large RCTs (EXCEL and NOBLE) studies on LMCA reported conflicting results. EXCEL results indicate PCI is non-inferior to CABG whereas NOBLE study reports the superiority of CABG over PCI for LMCA [25]

A pooled result of three RCTs investigating PCI vs. CABG for LM disease with a study population of 1611 patients assessed one year outcome in a meta-analysis [24, 26, 27]. The reported findings of composite death, MI, stroke or TVR were observed in 11.8% CABG patients compared to 14.5% who underwent PCI ($P=0.11$).

Finally another meta-analysis involving six randomised trials with 6055 patients compared CABG with arterial grafts and PCI [28]. The meta-analysis noted superiority of CABG procedure over PCI with respect to mortality (RR 0.73; 95% CI 0.62-0.86), MI (RR 0.58; 95% CI 0.48-0.72) and repeat revascularisation (RR 0.29; 95% CI 0.21-

0.41). However there was a marked increase of stroke in the CABG group (RR 1.36; 95% CI 0.99-1.86; p=0.06)

1.3 Coronary Artery Bypass Graft (CABG).

Currently no randomised study has compared an early CABG strategy with a delayed strategy. The general opinion for patients that have had PCI to an offending lesion and exhibit lasting severe CAD is to wait 48-72 hours.

Analysis of cohort patients with ACS in a large database revealed that early CABG is associated with low in-hospital mortality even in high-risk patients [29]. Patients who underwent early (≤ 48 hours) or in-hospital late (>48 hours) surgery showed no differences in their unadjusted and adjusted analyses, even-though CABG was usually delayed in the high risk patients suggesting that timing could be determined by multidisciplinary team decisions [30].

The timing of the procedure for patients undergoing CABG surgery should be determined on the patient's precise symptoms, haemodynamic stability, coronary anatomy, and signs of ischaemia. Other studies recommended that patients in cardiogenic shock or STEMI with anatomy unsuitable for PCI should be considered to undergo CABG surgery [31, 32]. However another study challenged the perceived merit associated with CABG for STEMI patients with coronary occlusion to not adaptable to PCI highlighting the increased risk associated with the prolonged time to surgical reperfusion [33].

1.4 Practical Features of Coronary Artery Bypass Grafting

1.4.1 Pre-operative management

The majority of patients admitted to undergo CABG surgery are on medication that alleviates their pain. Even though their individual prescription varies, polypharmacy is common and their medication may include prescriptions of angiotensin-converting enzyme (ACE) inhibitors, antiplatelet drugs, beta-blockers, statins and drugs for angina relief. Patients continue taking statin as well as beta-blockers until surgery whilst ACE inhibitors and other drugs are normally discontinued 48 hours prior to surgery.

1.4.2 Blood management

1.4.2.1 Blood salvage interventions: The superiority of using cell-savers in order to reduce allogenic blood product exposure is widely documented. One study established (OR 0.63; 95% CI 0.43–0.94; $p < 0.02$), that cell salvage is associated with a reduction of red blood cell transfusion requirement with a mean volume of total allogenic blood products transfused per patient ($p < 0.002$) [34].

1.4.2.2 Pharmacological plans: Strategies are devised to counter blood loss post-operatively, in order to reduce allogenic blood cell transfusion and the potential of having to re-operate due to post-operative bleeding. The most commonly used drugs to effectively counter such complications are Antifibrinolytic drugs as well as lysine equivalents i.e tranexamic acid which have few adverse side effects [35].

1.4.2.3 Blood transfusions: There is strong evidence indicating that the amount of red blood cell units transfused is an independent risk factor that might predict adverse outcome following cardiac surgery [36, 37]. A study looking into the relationship between transfusion and 30-day mortality and composite complications reported haematocrit of 24% is as safe as more intensive transfusion strategy to achieve haematocrit of 30% [38]. In the event of poor haemostasis in patients exposed to P2Y12

inhibitors, platelet transfusion is administered. The multicentre TITRe2 trial investigated whether the restrictive blood transfusion is superior to a liberal threshold for adult cardiac surgery, reporting there was no difference between the two cohort in the primary composite outcome [39].

1.5 Surgical Procedures

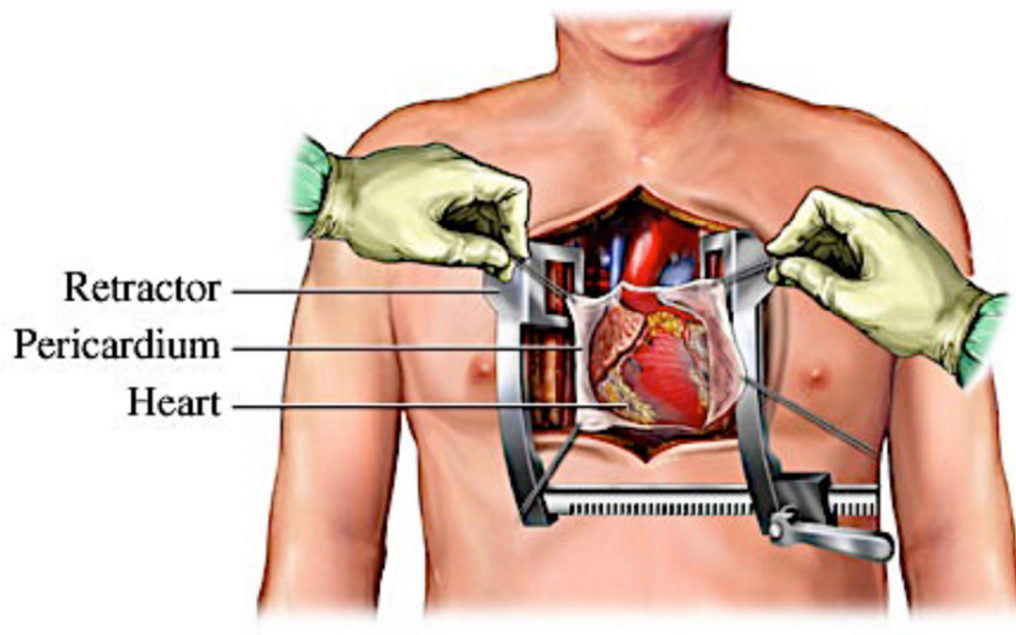


Figure 2 - 1.2 Open Heart Surgery

Median sternotomy is performed via midline skin incision to expose the chest while pericardium is excised to fully expose the heart. Figure adopted from (<http://www.heart-valve-surgery.com/surgeon-database/median-sternotomy.jpg>).

1.5.1 Conduit harvest saphenous vein harvest

Saphenous veins are harvested using either open or endoscopic methods. The latter presented into the clinical practice recently to harvest radial artery and vein grafts. In addition, some studies noted no difference in graft patency, either short or long term between the two techniques but again endoscopic vein harvest benefits from reduction

in risk of donor site infection [40-43]. Furthermore the endoscopic technique demands a highly skilled surgeon or experienced practitioner to access the site and retrieve the required vein or artery graft [44]. Other studies highlighted the “no touch” policy when executing open SVG harvest maintains vein integrity and reduces graft injury [45-47].

1.5.2 Mammary artery harvesting

The internal mammary artery is dissected from the chest wall, usually as a pedicled graft. In some cases the artery can be harvested in isolation without the internal mammary veins (skeletonised vessel). Whilst the skeletonised technique is technically more difficult and has a higher risk of vessel injury, there are potential advantages such as a longer conduit which allows grafting of distal targets and sequential anastomoses; preservation of chest wall blood supply reduces the risk of deep sternal wound infections [48-50].

1.5.3 Coronary vessel.

CABG aims to revascularise coronary arteries with a flow-reducing luminal stenosis, restoring blood supply to an area that is at risk. This increases coronary flow reserve and creates a more favourable myocardial supply-demand ratio.

The characteristics of the conduit and the native vessels influence the patency of a bypass graft. Important conduit characteristics include conduit choice, manipulation during harvesting and the size and quality of the conduit [1]. Crucial factors of the native vessel characteristics are the internal lumen size, the severity of proximal stenosis affecting the degree of competitive flow, the quality of the wall at the site of anastomosis and the distal vascular bed which affects the quality of the run-off.

1.5.4 Completeness of revascularisation.

The underlying principle of complete revascularisation is to supply sufficient coronary flow from the bypass grafts into all areas of the myocardium with ischaemic burden and that are supplied by coronary arteries with a flow-limiting stenosis. Factors which guide the strategy of surgical revascularisation include (i) the size of the vessel; (ii) the severity of the lesion; (iii) the ischaemic burden caused by the lesion and (iv) the sustainability of the depending myocardial area [51].

The anatomical definition of complete revascularisation, defined as bypass grafting to all epicardial vessels ≥ 1.5 mm with a diameter reduction $\geq 50\%$ in at least one angiographic view [52]. None the less, other clinical trials use different definitions of completeness of revascularisation e.g. Bypass graft in each major myocardial territory including the anterior wall, lateral wall and inferior wall. Studies have shown CABG patients with incomplete revascularisation have an outcome that was either comparable [53, 54] or sub-standard [55, 56] to that of patients with complete revascularisation.

1.5.5 Construction of central anastomosis.

The use of *in situ* grafts, but connected to their native proximal vessel (LIMA, right IMA, and right gastroepiploic artery) side-steps the need for a proximal anastomosis and maintains a living vessel with the potential benefit of superior native endothelial function. When free internal mammary graft, vein grafts or radial artery are utilised, the arterial inflow into the bypass vessels requires supplementary central anastomosis. The construction of central anastomosis to the ascending aorta is permitted by partial or total aortic cross-clamping [57]. To reduce aortic manipulation and the risk of embolic events, a single cross-clamp technique is favoured. It is reported a strict no-touch aorta technique is effective in minimising embolisation of atherosclerotic material [57]. In

such event, grafts are anastomosed end-to-side in a Y- or T-shaped formation to the IMAs, in order to enable smooth arterial inflow.

1.5.6 Bypass grafts. The use of arterial grafts such as the IMA warrants the long term benefit of CABG [58]. This grafts include the IMA, radial, and gastroepiploic arteries. Studies have shown that the LIMA to LAD arterial graft is constructed for almost all patients undergoing CABG surgery [58, 59].

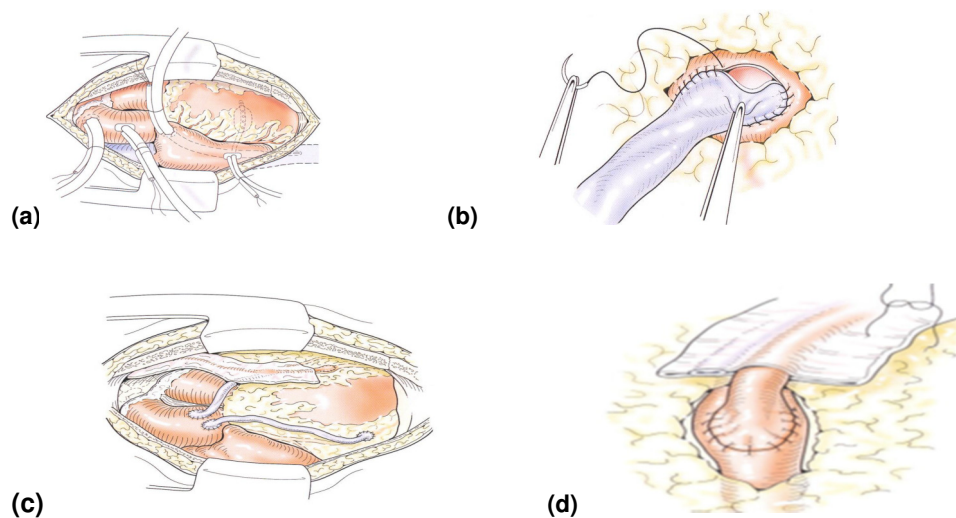


Figure 3 - 1.3 Practical CABG Surgery

Figure 1.3 Practical CABG Surgery : (a) cannulation of aorta (arterial) and atria (venous) during surgery, (b) distal venous and (c) arterial anastomosis to the coronary artery and finally (d) anastomosis of proximal ends to the aorta. Figure adopted from <http://www.wcccd.edu/dept/pdf/AF/LectureCABG.pdf>.

Studies from non-randomised trials have shown that bilateral IMA is linked with long-term survival, lower MI rate, angina frequency, and re-operation rate with diabetic patients benefiting most [22, 60, 61].

In contrast a recent randomised controlled trial looking at the use of bilateral IMA grafts has shown no significant survival benefit at five years, but a significant increase in deep sternal wound infections. However, given the historical data showing that the most

significant benefit of arterial grafts occurs after ten years, it will be necessary to reassess this study with the longer term results [62].

The radial artery is a useful option as a second arterial graft in patients in whom bilateral BIMA is at higher risk of deep sternal wound infection such as patients with obesity and diabetes: and in patients where the quality of the other conduit is sub-optimal. The current evidence indicates its advantage in terms of survival and non-adverse events over the saphenous vein [63], but its inferior to the IMA use [64]. Due to the radial artery being a free arterial graft, there is a risk of spasm so graft patency is strongly related to native vessel flow. This itself is influenced by the severity of the proximal stenosis which affects competitive flow, and the quality of the distal native vessel. Several studies reported significantly worse graft patency when the native coronary artery stenosis is $<70\%$ and optimal outcomes when the native coronary stenosis is $>90\%$ [65]. None the less, the number of arterial anastomosis is increased by the use of radial artery grafts compared to the use of both, although the prognostic benefit is currently debatable. Graft flow problems may be indicated by haemodynamic instability or inability to wean the patient from cardio-pulmonary bypass, new regional wall motion abnormalities on trans-oesophageal echocardiography, or ventricular arrhythmias [66].

1.6 Aortic Valve Surgery.

The heart is a muscular organ that pumps blood throughout the body and consists of four chambers categorised as upper chambers consisting of the right and left atria and lower chambers consisting of the right and left ventricles [67]. The right and left atria connect to their respective ventricles. The right ventricle connects to the pulmonary artery and the left ventricle connects to the aorta. Four valves are present at these

locations in order to maintain uni-directional blood flow through the heart [68]. The four valves in the heart are: aortic, mitral, tricuspid and pulmonic valves figure 1.4.

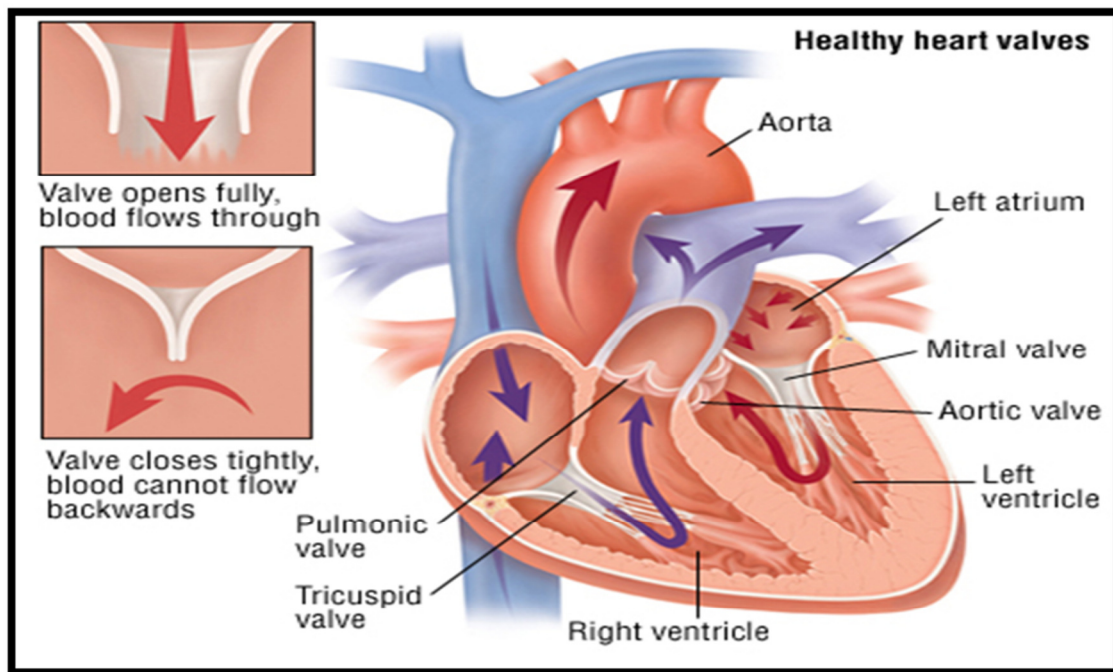


Figure 4 - Figure 1.4 present the four valves of the heart and the directions of blood flow.

Figure 1.4 present the four valves of the heart and the directions of blood flow. Figure adapted from www.google.co.uk/search?q=anatomy+of+the+heart+with+valves.

The aortic valve is positioned between the left ventricle and the aorta, which is the largest artery in the body. When the heart contracts the aortic valve opens and blood is pumped into the aorta and when the heart relaxes the aortic valve closes to prevent blood from leaking back into the left ventricle [69].

A normal aortic valve has three smooth cusps that open widely and close tightly. However when the aortic valve becomes diseased it does not work as efficiently and this increases the workload on the left ventricle. The two main causes of such conditions are:

- **Aortic stenosis:** this is a condition whereby a thickened, stiff or inflexible valve leaflet causes narrowing of the aortic valve thereby limiting the blood flow

figure 1.5. The aortic stenosis is further exacerbated by calcium deposits on the valve leaflets severely obstructing the blood flow during systole [70, 71].

- **Aortic regurgitation** (also known as valvular insufficiency or leaky valve): occurs when the valve leaflets do not close tightly which leads to blood ejected by the heart to immediately flow back into the left ventricle during diastole. The regurgitation can be caused by floppy leaflets (prolapse), a congenital deformed valve (bicuspid or unicuspid), endocarditis, dilation of aorta (aneurysm), holes in the leaflets or rheumatic valve disease [71].

1.6.1 Causes of aortic valve disease.

The main causes of aortic valve disease can be categorised into two:

1.6.1.1 Congenital aortic valve disease: is a condition that stems from birth defects, most commonly involving a bicuspid aortic valve. Instead of the normal three leaflets or cusps, the bicuspid aortic valve has only two and the absence of the third leaflet may lead to either the valve opening and not closing tightly (regurgitant) or not opening completely thereby causing narrowing (stenotic) as shown in the figure 1.6

1.6.1.2 Acquired aortic valve disease: occurs when the structural integrity of the aortic valve is compromised by either [71].

- Infective endocarditis – a bacterial infection of the inner lining of the endocardium that result the inner lining of the heart to be infected. This happens when bacteria enter the blood stream from another site of minor infection e.g. tooth abscess.
- Aortic valve degeneration – is the most common cause of aortic stenosis or regurgitation in people over the age of 65 due to biological wear and tear in the

leaflets of the aortic valve causing the valve to become heavily calcified over time.

- Rheumatic fever – this is caused by a bacterial infection of the throat i.e streptococcal. Even though the valve itself is not infected, the antibodies generated cross-react with the heart valves causing inflammation of the valve leaflets.
- Other causes may include cardiomyopathy, myocardial infarction, rheumatoid arthritis, chronic inflammatory disease and less commonly tumours and drugs or radiation given for lymphoma and other cancers.

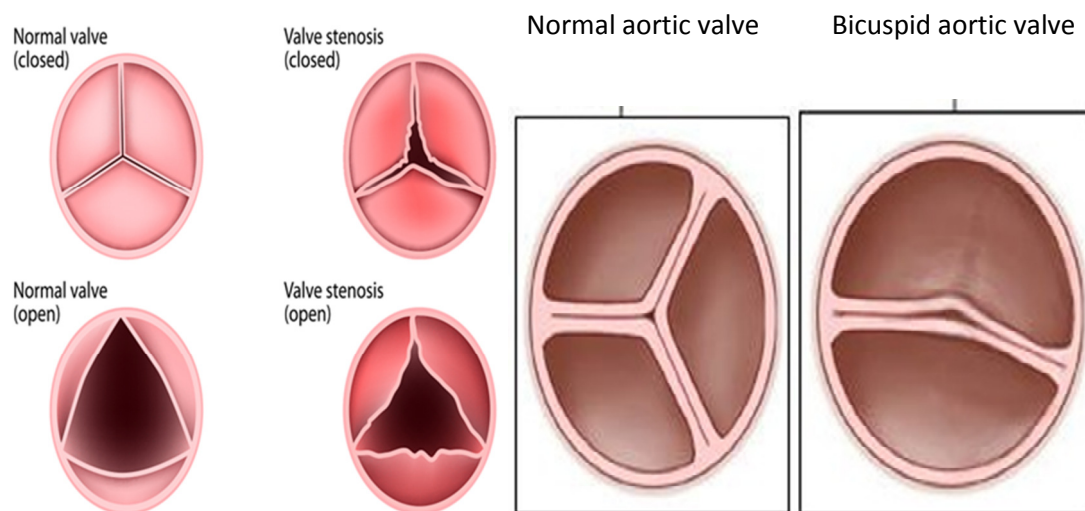


Figure 5 - Figure 1.5 shows healthy valve vs. stenotic one and compares bicuspid anatomy to normal tri-leaflet valve

Figure 1.5 shows healthy valve vs. stenotic one and compares bicuspid anatomy to normal tri-leaflet valve. Figure adapted from <https://www.pinterest.co.uk/pin/426364289706069169/>.

1.6.2 Surgical procedures

A severely diseased aortic valve should either be repaired or replaced. However the majority of the patients in this study had aortic valve replacement rather than repair. Just prior to surgery patients are cannulated in the arm; an IV line for fluid, pain management and sedation are administered. A urinary catheter is inserted and the patient is intubated via endotracheal tube for breathing purposes.

Under general anaesthesia a median sternotomy (6-8cm incision in the sternum) or right thoracotomy (2-4cm small incision through the ribs) is performed. Then the protective membrane protecting the heart (pericardium) is opened to expose the heart. Heparin is administered as anticoagulant in preparation for cardiopulmonary bypass (heart-lung machine). Cardiopulmonary bypass is used to circulate blood around the body during the operation and the body is also cooled.

The aorta is clamped and heart stopped with Cardioplegia which is a potassium-rich solution via an aortic root cannula. The surgeon will then open the aorta to expose the aortic valve and make an incision above the damaged valve and remove the native (original) valve. The aorta is sized using a valve sizer prior to implant in order to determine the correct valve size, and then a new valve is sewn to the annulus of the native valve figure 1.6. The aorta is then closed and the process of de-airing the heart begins by manipulating the left ventricle, inflating the lungs and sucking blood and air through the aortic root cannula. The clamped aorta is removed and the heart beats again; De-airing continues through the aortic root cannula.

If necessary external pacing is applied by placing temporary pace maker wires on the surface of the heart to re-start the heart or a shock is applied to terminate abnormal rhythms. At this point if the normal function of the heart is restored and the new valve is functioning well, cardiopulmonary bypass is weaned. The sternum is then closed and patient taken to the recovery unit where vital organ functions are monitored.

The choice of type of replacement valve may be influenced by the age and gender of the patient. Mechanical or Tissue (biological) valve is the available options. Although the majority of aortic valve replacement are performed with a tissue valve, patients are informed by their surgeon of the tissue valve options i.e biological (tissue) valves from either porcine or bovine sources or allografts/ homografts from humans (a donated

human heart) both cases of the tissue valves are treated with antibiotics and frozen under sterile conditions. The surgeon will then advise the patient of the most suitable option in their case and this discussion takes place during pre-operative assessment well before the operation date.

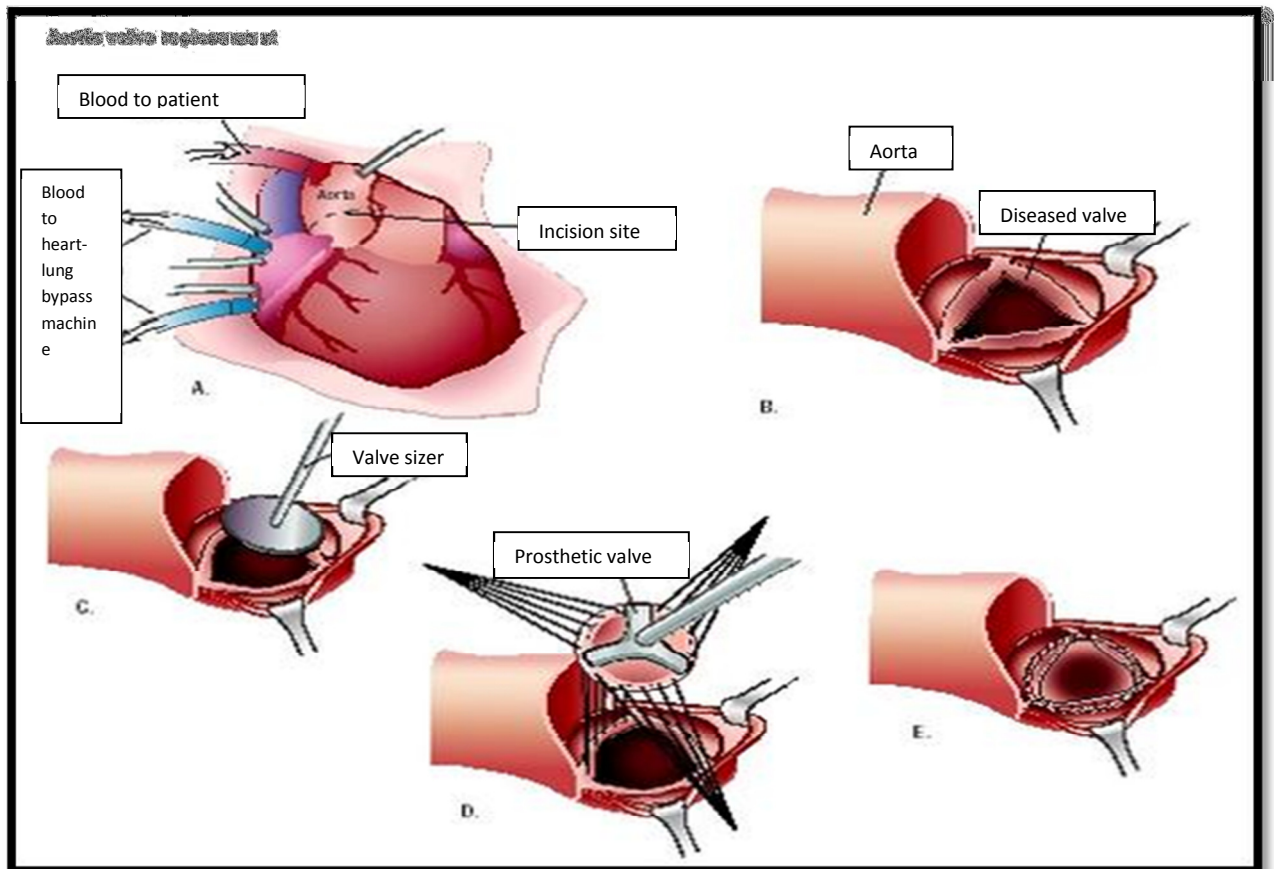


Figure 6 - Figure 1.6. Presents aortic valve being sized using a valve sizer prior to valve implantation in and the sewing of a new valve to the annulus of the native valve

Figure adapted from <http://www.surgeryencyclopedia.com/A-Ce/Aortic-Valve-Replacement.html>

1.7 Mitral Valve Surgery.

The mitral valve facilitates the movement of blood between the left atrium and left ventricle and is anatomically situated between the left atrium and left ventricle figure 1.4. During diastole, the mitral valve opens permitting blood to flow from the left atrium filling the left ventricle. This prepares for the next contraction (systole) whereby the mitral valve closes preventing blood flowing back into the atrium and allows the left ventricle to pump blood to the aorta and the systemic circulation [72].

The mitral valve is made up of two flaps (leaflets). These leaflets are composed of very fine and flexible material that are attached on one end to papillary muscle which helps to prevent prolapse during contraction. The mitral valve can become diseased just like the aortic valve described earlier and the two main types of mitral valve disease are [72, 73].

- mitral valve stenosis - a condition caused by the hardening of the leaflets due to calcification leading to the valve not opening widely enough to enable sufficient blood flow.
- Mitral valve regurgitation – a condition that allows blood to leak/flow backwards from the left ventricle into the left atrium either due to damage to the structure of the valve or because the leaflets are being pulled apart or not opposing tight.

A faulty mitral valve with severe stenosis or regurgitation requires surgery [74]. Depending on the severity of the disease, the patient will be advised prior to surgery of the most suitable intervention for his/her case i.e mitral valve repair or replacement. In both cases the procedure will be carried out under general anaesthesia. Anticoagulation (heparin) is administered via a central line and cardiopulmonary bypass is established.

The heart is slowly cooled and a clamp applied to the ascending aorta as the surgeon opens the heart to assess the mitral valve.

Mitral valve repair - involves a surgical procedure to remove tissue, holes and ruptures in the valve or reshaping collapsed flaps manually [75]. During assessment if the problem is with the posterior leaflet, this is corrected with a small resection of the abnormal or damaged part of the valve whilst anterior leaflet repair requires annuloplasty which involves a complete or partial ring placed around the annulus of the valve figure 1.7. The size of the ring is carefully matched with patient's own valve size. This repair enables the valve to function normally.

There are two types of surgical approach for mitral valve repair that can be effectively utilised: conventional median sternotomy or a minimally invasive right thoracotomy.

Mitral valve replacement - when the valve is too severely damaged it needs replacement via a surgical procedure that replaces the diseased native valve with either a mechanical or biological tissue valve [76]. This procedure is performed when valve repair surgery is ruled out as a treatment option. The mechanical valves are made of metal or carbon and function in a similar manner to the patient's native valve with a design merits that last for a lifetime. However this is not suitable for women who want to have children as the mechanical valve requires the patient to take blood-thinning medication (warfarin) for the rest of their life in order to reduce the risk of valve related thromboembolism and stroke [73]. In such circumstances patients are advised to have their replacement done with a biological tissue valve made from either a cow tissue (bovine), pig tissue (porcine) or human tissue (allografts or homografts) valves.

One of the advantages of biological valves is that the majority of patients do not require a lifelong blood thinning medication such as warfarin [77, 78] however for the younger patients they will need a re-replacement after a period of about 15-20 years as the

functional agility of the valve declines. The size of the replacement valve is matched with the patient's own native valve, sutured in place and fitted into position. The heart is then closed with sutures and the process of de-airing begins and continues whilst the cross clamp is removed. The continuation of the de-airing is a safeguard to ensure that no air is delivered into the systemic circulation.

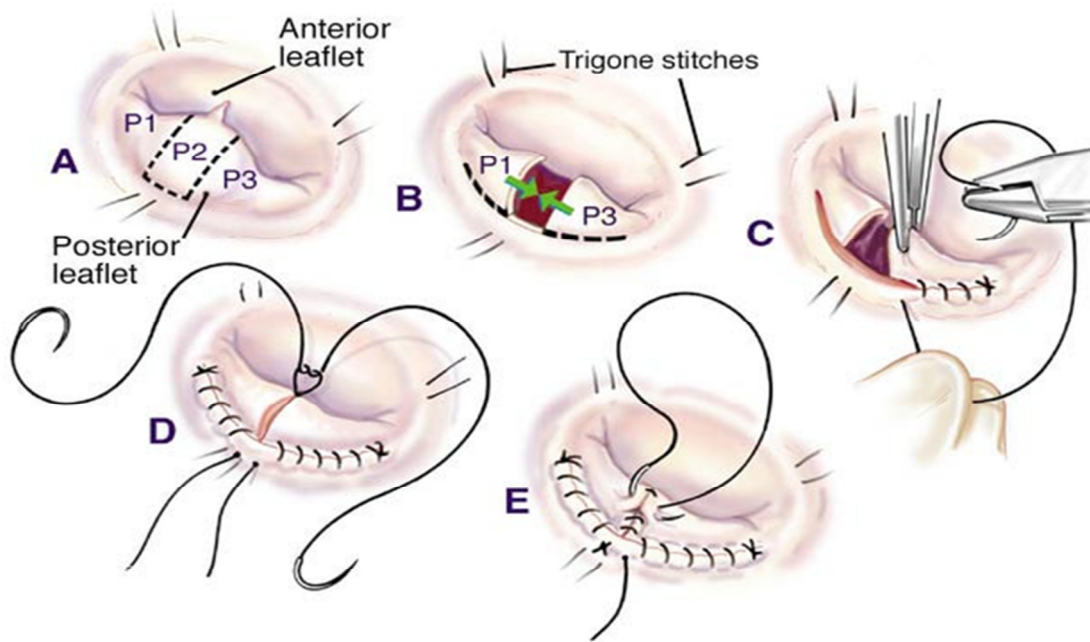


Figure 7 - Figure 1.7 Describes mitral valve annuloplasty which involves a complete or partial ring placed
https://www.google.co.uk/search?q=mitral+valve+repair+and+replacement+p1-p2-p3&dcr=0&source=lnms&tbm=isch&sa=x&ved=0ahukewiap4c5gylzahucfywkhskwacuq_aucigb&biw=1920&bih=937&surl=1

1.8 Frailty

Frail patients can be defined as those ≥ 75 years who are least adaptive to the process of ageing while frailty can be defined as a clinical condition of multi-system weakening that results in a decreased physiological reserve and diminished dexterity to stressors i.e. increased vulnerability [79]. Rockwood *et al* defines as “multidimensional loss of reserves (energy), physical ability, cognition and health” whilst Walston *et al* defines it as “a condition in which the individual is in a vulnerable state and at increased risk of adverse health outcomes and / or dying when exposed to a stressor” [80, 81].

The British Geriatric Society acknowledges frailty in its Consensus Best Practice Guideline, defining it as a health-related characteristic concomitant to the ageing process that compromises the integrity (reserves) of multiple body systems [82]. Frail patients are at risk of adverse outcomes such as sudden change in their physical or mental wellbeing due to their inherent vulnerability to challenges from the environment such as an infection or side-effect from a medication. However as there is no universally agreed definition of frailty it is important to differentiate the overlapping characteristics between frailty, multi-body conditions and disability [83]. There might be mild frailty in patients who are known to have long-term health conditions but the focus of the clinician may only be on treating the apparent illness rather than assessing the underlying frailty condition. Furthermore there is ostensible overlap between disability and frailty. A large number of patients diagnosed with frailty do have some form of disability but many patients with known physical disability are clinically not frail, hence the conditions are not identical and failure to diagnose frailty in its earlier stage may lead to patients becoming bed bound and immobile [83].

In addition functional status fluctuates substantially among elderly adults; some will remain independent with their daily activities, majority will loss the appetite of doing their usual activities and will need some form of help whilst those with frailty

conditions may be affected severely, potentially leading to disability or death. Nonetheless research has shown that many older adults living with frailty will cultivate ways of coping and make alternative choices [83]. It has been reported that in any community-dwelling elders, frailty is present 15% in over 75years old and this rate increases to 40% at 85 years, whereupon there is no further increase [84]. Furthermore a number of studies revealed a steep rise in the ageing population worldwide, from 461 million over the age of 65 years in 2004 to a projected 2 billion in the year 2050 [84, 85]. This rapid increase in elderly population, coupled with ever increasing large number of clinically frail patients amongst them might have its roots in lifestyle which can be modified. It is known there is a worldwide increase in obesity and other unhealthy behaviors such lack of routine exercise, malnutrition and rampant smoking. This will inevitably necessitate health and social care leaders to plan in advance and formulate working strategies that will accommodate the intense implications of delivering personalised care to a frail elderly population.

1.8.1 Potential features of frailty.

The common features of frailty can be categorized into two distinct models:

- **Phenotype Model:** describes the composite of the patient's observable characteristics or traits and includes: sarcopenia (decrease in muscle mass and strength), unintentional weight loss, compromised balance and impaired gait speed, severe deconditioning and low energy expenditure.

The presence of three or more of the above characteristics assumes the patients to be frail and that can predict poor outcome when they are subjected to a surgical insult. Seydall *et al* [86] cohort study looking into phenotype type to define frailty has shown that a prevalence of 8.5% in women compared to 4.1% in men for the age group 65-74 years. This highlights age as the single most risk

factor followed by sarcopenia as an essential feature of physical frailty. The effect of sarcopenia on muscle strength might be more crucial than changes in muscle mass. Muscle power agility is maintained by muscle homeostasis: muscle cell formation, hypertrophy and protein loss. Normal homeostasis balance is maintained by the brain, endocrine system and immune system which are all on the other hand affected by diet and physical activity [87].

- **Cumulative deficit Model:** mainly describes cumulative clinical cases ranging from anorexia, dementia, hearing loss, fatigue, malnutrition and tremor. These symptoms can occur with ageing and when combined increases the frailty index as described by Rockwood as part of CSHA study in Canada [81].

1.8.2 What may cause frailty?

The frailty syndrome affects overlapping and multiple organ systems due to ageing that initiate and enhance vulnerability to stressors figure 1.8. Hence the crucial question that needs studying is how frailty stimulates aggregate decline in multi organ systems, followed by the diminution of homeostatic reserve and susceptibility to environmental changes? These could be explained by the underlying genetic and environmental factors that regulate stem cell differentiation [88, 89].

In addition when an individual cellular and molecular complex accumulates lifelong damage at a rate that supersedes the repair and maintenance mechanism that afford physiological reserve and which recompense for age and disease-related changes then the onset of frailty syndrome can be predicted [90]. However the specific extent of cell damage that confers loss of function or abnormal in an organs function is yet to be explored in any study [91]. On a related note a number of studies have demonstrated the effect of frailty on the brain, immune system and growth hormones.

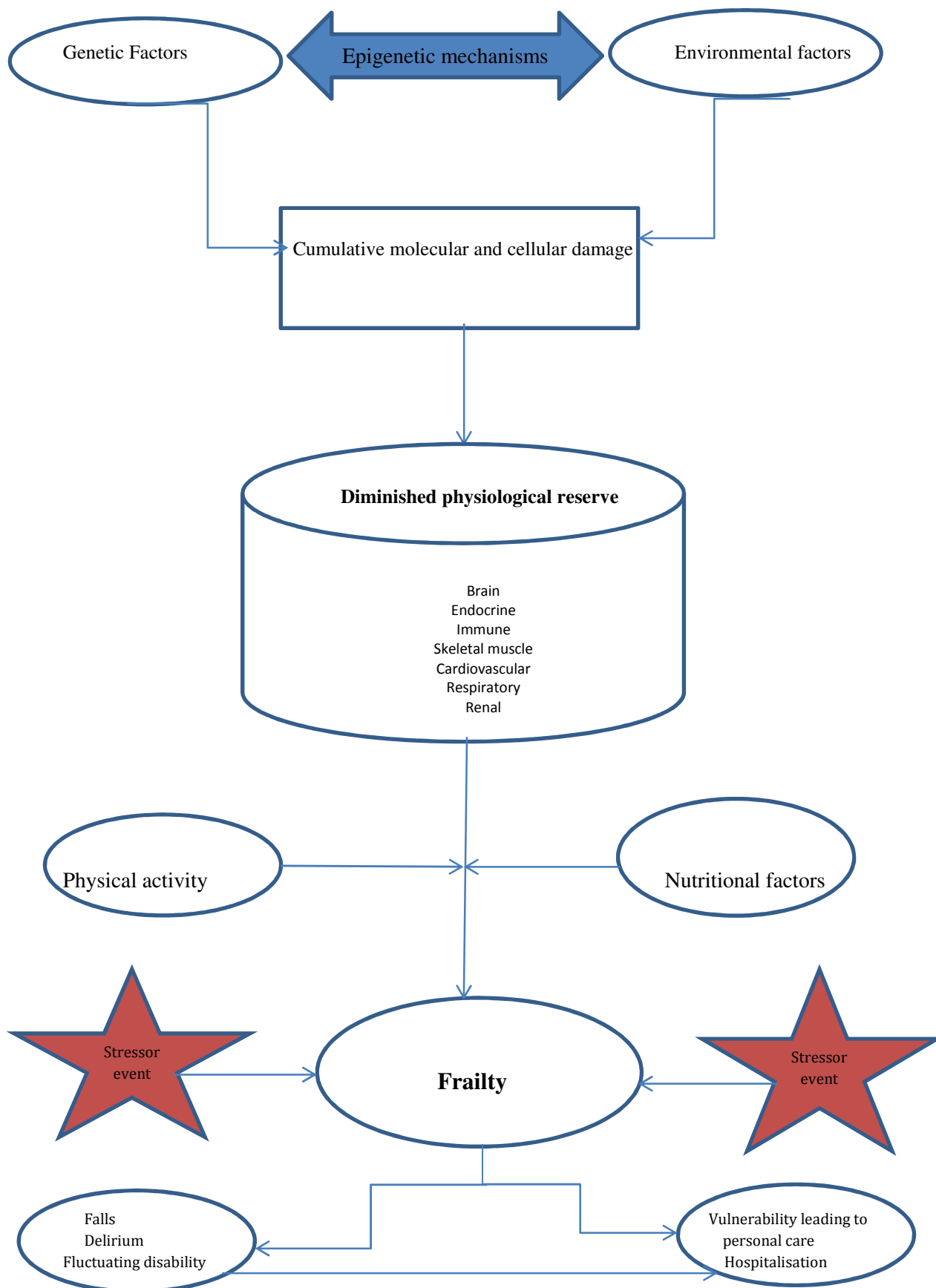


Figure 8 - Figure 1.8 describes pathophysiology of frailty syndrome. Figure modified from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4098658/>.

1.8.2.1 The impact of frailty on the endocrine system

Changes in the central regulators of homeostasis (hypothalamic-pituitary-adrenal axis) in studies of older animals highlighted a reduced capability to terminate the adrenocortical response to stress as well as a reduction in hippocampal glucocorticoid receptors. Furthermore it was found that the production of three major circulating hormones decreases due to ageing [92]. To begin with, the pituitary gland production/storage of growth hormone diminishes implicating the production of a group of peptides that enable anabolic activity in many cells known as insulin-like growth hormone factor 1(IGF-1) by the liver and other organs. A study has shown lower concentration of IGF-1 in frail patients when compared with age matched controls [92]. Ageing further implicates the plasticity of the neurons and skeletal muscle strength which are all crucial aspects that are deficient in frailty syndrome [93]. Secondly there is an increase in release of luteinizing hormone and follicle-stimulating hormone caused by a decrease in oestradiol and testosterone output (loss of negative feedback regulation). Another study demonstrated a relationship between testosterone concentration and frailty [94]. Thirdly a steady rise in cortisol release occurs alongside reduced activity of the adrenocortical cells that are responsible for the production of sex steroid precursors and sulphates as described in one cross-sectional study evaluating an independent link between persistently elevated diurnal cortisol concentration and frailty [95].

1.8.2.2 The impact of frailty on the brain

Frailty impacts on both the structural and physiological characteristics of normal brain function. The loss of distinct neurons mainly in cortical regions is low however the metabolic demand of the hippocampal pyramid neurons is insufficient due to changes in synaptic function, protein transport and mitochondrial function [96].

One study recognised that the hippocampus constitutes an important stress response and relays information via negative feedback to the hypothalamus as soon as it detects rise in glucocorticoids [97]. It also plays a crucial role in facilitating the pathophysiology of cognitive decline and Alzheimer's disease [96]. The microglial cells that are present in the CNS and act as immune cells become hyper-responsive to small stimuli that can potentially lead to damage [98] and neural death for frail brain population [99, 100].

On a related note a cohort study (n=750) of octogenarians revealed that after a period of follow-up for 12 years a distinct relationship between the rate of cognitive decline and frailty (HR 1.63, 95% CI 1.2 – 2.08) [101] as well as frailty being independently associated with dementia [102, 103].

1.8.2.3 The impacts of frailty on the immune system

Frailty is believed to weaken an individual's immune system. The frail immune system is associated with T cell dysfunction and weak phagocytic activity of neutrophils, macrophages and natural killer cells [104]. This further facilitates an increase susceptibility to lymphoproliferative conditions, vulnerability to infection and autoimmune syndromes. Studies have associated [105-107] several inflammatory cytokines including interleukin 6, C-reactive protein, tumour necrosis factor- α (TNF α) and others with frailty. In addition characteristics in the cumulative deficit model such as catabolism of skeletal muscle waste and adipose tissue as well as anorexia is directly linked to inflammation [108].

1.8.3 Why the need to recognise frailty.

Frail patients have reduced bodily reserves to tolerate the stresses of major surgery and the introduction of new analgesia can cause an unanticipated adverse outcome; hence for a particular individual, the knowledge that they are clinically frail will better inform clinicians and social care service delivery team members to pre-plan and take action to avert poor outcomes as the patient's frailty makes them more susceptible to post-operative complications and morbidity [109]. One study (n=754) of older persons with a 18 month follow-up period evaluated the trajectory of disability in final year of life [110] and revealed that frailty was the most common cause of disability figure 1.9.

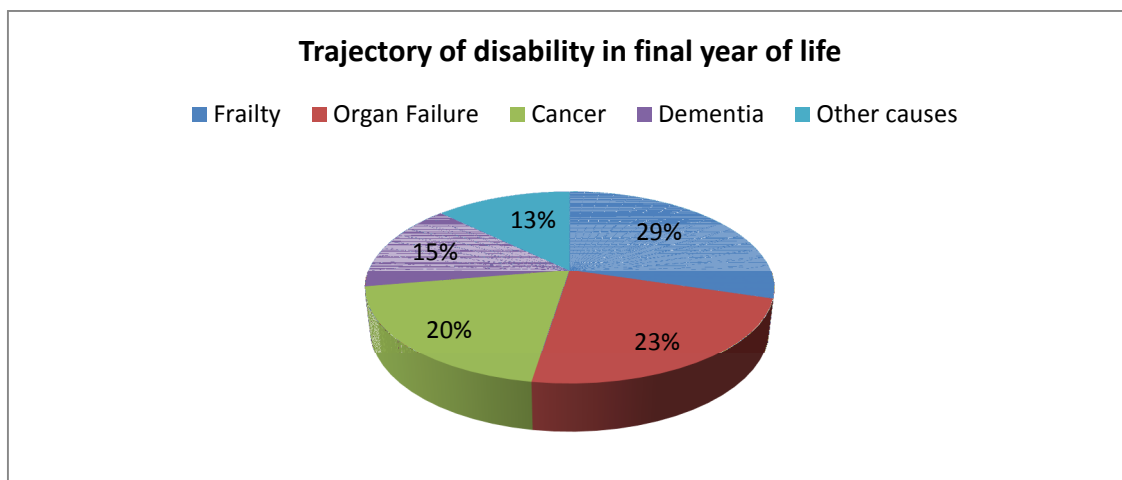


Figure 9 - Figure 1.9 illustrates the relationship between frailty and disability in final year of life.

Figure adopted from <http://www.nejm.org/doi/full/10.1056/NEJMoa0909087#t=article>.

From this it can be deduced that as frailty increases the potential for recovery decreases. On the other hand, frailty is not currently routinely measured in surgical patients in the pre-operative or post-operative settings. However, with accurate evaluation of frailty, clinicians may make better decisions regarding which treatment is optimal for the

patient, seeking additional support from the intensive care team when indicated, and even delaying an operation until the above aims are achieved or invasive treatment with surgery is not considered to be in the patient's best interest. In some special circumstances, greater life expectancy and quality of life can be achieved with conservative management [109, 111].

On a related note, the growing economic constraints on healthcare systems necessitate the refinement or accurate selection of frailty assessment tools in order to enable a sensible estimation of risk and to guide patients towards personalised treatment plans. This will help to optimise resource distribution and to avoid costly but ineffective interventions [112]. It is also important to ascertain whether in an individual, their frailty can be made better or worse. Early screening and frailty detection is likely to result in favourable outcomes. Where patient outcome post-surgery is poor, failure to thrive may lead to a non-reversible stage and death [113]. Frailty is a long-term condition just like diabetes mellitus or renal disease and it should not be viewed as an inevitable consequence of ageing.

In this study frailty screening was implemented in the pre-assessment clinic weeks before surgery using the Reported Edmonton Frail Scale. Furthermore tri-axial accelerometer (wrist band) was used to quantify the physical activity level of each patient two weeks before surgery and 1 month post-operatively. The findings from these two tools will be compared and discussed later in chapter 5 in order to highlight the implications of frailty in patients undergoing cardiac surgery.

1.9 Accelerometer

Measuring activity levels on older institutionalised people especially outside of a laboratory environment is an arduous task [114]. In hospitalised elderly patients monitoring the activity levels may result in implementation of changes towards improved mobility and functional independence. Different methods have been tried in the past for estimation of activity levels and these include: questionnaires, energy expenditure measurements and activity monitors (AM), the latter being amongst the oldest tools used [115]. AM have evolved over time from pedometers to uni-, bi- and tri-axial accelerometers [116]. It has been reported that pedometers were first invented by Leonardo da Vinci in the 1500s [114], but it was not until the 1980s that accelerometer, providing an integrated method of measuring physical activity (PA) were developed [117].

Accelerometers are electronic motion sensors which later evolved with the capacity to detect any mechanical force and thus any bodily acceleration. The acceleration measured is represented as a voltage which is then converted into counts; the greater the count, the greater the intensity of physical activity (PA) [118]. Accelerometers have been validated in labelled water techniques (indirect calorimetry) [119], and their measurements have been found to be directly proportional to energy expenditure [120].

Algorithms which are in-built into the devices are used to convert energy expenditure into the counts which can then be categorised into light, moderate, or vigorous intensity levels. The threshold for the intensity of exercise was described by Esliger et al [121]. Thus, accelerometers allow the determination of both the quantity and intensity of any activity and can be used to describe the sum and distribution of PA [117, 119]. In the past few decades' accelerometers have further evolved into small, lightweight

instruments, which can measure acceleration in one, two or even three axes and store data minute by minute [117].

Studies have revealed that the most popular accelerometers in PA research are the Actigraph Uniaxial GT1M Accelerometer and the Triaxial GT3X accelerometer which was developed and released much later [122]. Whilst the GT1M measures both static and dynamic accelerations, the GT3X measures accelerations in three planes of motion and provides an overall value of PA [123]. Apart from this a biaxial accelerometer also exists which measures PA in two axes [116].

As the GT3X measures PA in a greater number of axes it should in theory also provide a more reliable assessment of PA. Originally the Actigraph Uniaxial Accelerometer, worn on the hip, was the most used accelerometer. It was used in the 2003-2006 National Health and Nutrition Examination Survey (NHANES) to give the largest database of monitored PA [124]. However, the 2011-2014 NHANES used the Actigraph GT3X+ accelerometer which was worn on the wrists and reported that wearing an accelerometer on the wrist instead of the hip increased compliance and also allowed for the examination during sleep; with the triaxial accelerometer they were able to measure a wider range of movements. In terms of analysis, although linear regression models for the uniaxial accelerometers have been shown in studies to be effective in analysing the data, there is limited research validating the algorithms used for the analysis of data collected by triaxial accelerometers.

Accelerometers have many advantages when compared to alternative methods of PA measurement. These include being able to track intensity, duration and frequency of an activity [125]. Some accelerometers, such as GeneActive can detect different levels of

activity in many planes (triaxial) [121]. This characteristic makes them applicable for use in the measurement of PA in patients with cardiovascular disease, patients are increasingly inactive and their low intensity PA may be picked up by accelerometers and would not be otherwise accurately measured on other means such as patients self-reporting on perceived exercise capacity and tolerance.

1.9.1 The need to measure PA in patients with cardiovascular disease.

PA is described as any bodily movement, produced by skeletal muscles, which results in energy expenditure [126] and has been shown to be fundamental for optimal health and well-being [127]. It has also been shown to both improve the quality of life, and readiness for discharge from hospital, reducing the mortality of patients with cardiovascular disease [128-130]. However, it is no routine practice to quantify activity level in a clinical setting, showing a potential gap in the overall assessment of a patient before discharge.

Scientific evidence has repeatedly linked PA to cardiovascular health outcomes, with the overall view being that individuals who partake in PA regularly are less likely to develop coronary heart disease (CHD) and heart failure (HF) [131]. Lack of or reduced PA is not only one of the major risk factors for the development of cardiovascular disease, but PA also has a favourable effect on many of the other risk factors. Regular PA and exercise can help reduce blood pressure, LDL and total cholesterol levels and can improve glycaemic control in diabetics [132]. PA is therefore one of the core focuses for the prevention of cardiovascular illness via cardiac rehabilitation [133]. As lack of PA is a modifiable risk factor for cardiovascular disease [116], PA and its monitoring becomes crucial in the management of cardiac patients [134, 135]. Chapter

4 will discuss further this topic reviewing systematically previous studies on accelerometer use in cardiovascular.

1.10 Frailty influence consideration in heart team and the quality of MDT meeting.

The MDT (multidisciplinary team) usually comprises a surgeon, an interventional and non-interventional cardiologist, cardiac anaesthetist, geriatrician, nurse practitioners as well as other non-clinical staffs and allied health professionals i.e. cardiac physiologist.

It is normally chaired by an interventional cardiologist and the outcome and decision are populated into an MDT proforma by the MDT co-ordinator. It is worth noting not every patient undergoing cardiac surgery goes through the MDT route.

MDT meetings encourage better teamwork with the sole purpose to improve patients' safety and care; such prolific meetings also offer an environment for education and training. MDT meetings are characterised by an evidence based approach to decision-making. However shared decision-making for advanced heart failure has become both more challenging and more crucial as a result of longer life expectancy and disease duration and increasing treatment options [136]. It has been reported that heart failure affects 2.4% of the adult population and this number increases to 11% for adults over the age of 80 years [136].

A study by Hannan et al [137] and Lee et al [138] reported that in a study directed at both patients and cardiologists asking why CABG was carried out, that their respective responses showed lack of consistent targets and aims. Hence it is necessary to have reproducible transparency in MDT decision-making.

Risk stratification information that incorporates frailty factor must be presented to the MDT in a comprehensive manner to ensure an all-inclusive assessment of each patient.

Evidently cardiothoracic procedures carry immediate, early and delayed risks of complications. Little objective data exists on how patients recover physically from surgery or the impact surgery has on their quality of life. Such an important data, which helps patients and clinicians to determine which course of treatment suits best, is under researched.

To investigate further this important topic, a national survey was conducted and sent via the Society of Cardiothoracic Surgery (SCTS) to all cardiac MDT members in UK and N. Ireland. The detailed result will be discussed in chapter 6, strategies to improve and measure the quality of adult cardiac MDT will be explored as well as

1.11. Quality of Life.

The Quality of Life of an individual explains how the illness or the treatment impact on more than one key domain of life. The WHO defines Quality of Life as “individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”.

One of the measures of quality of life is the Health Related Quality of Life (HRQOL). Some fundamental evidence is accumulating to suggest the HRQOL [139] is a multi-dimensional construct that can include two or more domains of health. Within this context, health consists of social, physical and emotional components [139] including the patient’s own perception of their health [140].

The purpose of measuring HRQOL in this project is to accurately investigate the health-related effectiveness and cost-effectiveness of surgical interventions. Conventional cardiac surgery procedures are evaluated and compared with newer less invasive procedures such as mini sternotomy and minimal access cardiac surgery. Traditionally

outcome measures of these procedures have been described in terms of operative mortality, morbidity, survival and relief of symptoms. However, there is a recent trend towards assessing patient-reported outcomes measures (PROMs) which may be of value both for risk assessment and outcome measures [141]. Therefore, the health-related quality of life (HRQOL) assessment approach is used to reflect from a patient's perspective how a disease affects their overall health, both pre-and post-operatively. The following HRQOL instruments were used to measure QoL before and after surgery as discussed in detail in chapter 7.

Medical Rand positive item contains a checklist of 36 items integrating a large number of comorbid conditions, disabilities, cognitive impairment, mood disturbance and mobility limitations.

EQD5-3L provides a generic health measure on five dimensions that includes mobility, self-care, usual activity, pain or discomfort and Anxiety or depression whilst for frailty measurement the Reported Edmonton Frail scale item that classifies patients on a scale of 1-18 with one being very fit and 18 being severely frail was used.

2.0 Chapter 2

Systematic Review on the Predictive Performance of Frailty Assessment Measures in Cardiothoracic Surgery

`Direct extract from this chapter has been published with permission`.

2.1 Introduction

During the last decade the age of patients undergoing cardiac surgery has increased significantly, studies have delineated this increase to be more predominant in the advanced age category. This has largely been attributed to frailty, which is present in approximately 15% of people over 75 years old with this figure increasing to 40% by the age of 85 [142]. Frailty can be defined as a “biologic syndrome of reduced reserve and resistance to stressors, resulting from cumulative declines across several physiologic systems causing eventually increased potential for adverse outcomes” [80].

Advancing age is a key risk factor when it comes to mortality and major morbidity notably in cardiac surgery. Since age is non-modifiable risk factor, emphasis has therefore been primarily focused on developing and improving risk-scoring methods in an effort to better predict mortality and morbidity, which will then allow for early detection, intervention and prevention where possible. The most frequently used scoring systems at present include the logistic European risk evaluation (EuroSCORE I and EuroSCORE II) [143] and the Society of Thoracic Surgeons (STS) score where the former is prevalent in cardiac surgery and the latter is predominantly used in thoracic related procedures [144].

Present evidence appears to indicate that mortality can be predicted much more accurately using STS score than it can with the EuroSCORE system [144]. However, the EuroSCORE tool [145] has had amendments made to it, which have vastly improved their predictive power and as such are now referred to as EuroSCORE II. A major pitfall of these predictive models is that they fail to encompass the diminishing physiological reserve that accompanies advancing age, that is, frailty. As a result, EuroSCORE II is known to overrate preoperative risk in healthy elderly patients, whereas STS underrates the risk posed by surgery in higher risk frail patients with similar morbidities [109].

Evidently, frail patients have reduced physical reserves for tolerating a major operation; this could possibly increase the manifestation of postoperative complications. As a result, clinical researchers have developed and promoted the introduction of frailty measurement tools in trials. Advocating the addition of frailty scores into risk assessment preoperatively can lead to the prediction of higher mortality, morbidity or prolonged length of hospital stay which may warrant anticipation of post-operative rehabilitation or residential care plans.

There is currently no routine measurement of frailty in surgical patients, be that in the pre-operative or post-operative period. However, with accurate evaluation of frailty, clinicians would be better informed to make decisions on optimal treatment for the patient, thus seeking additional support from specialist medical and intensive care teams where indicated, delaying surgery if needed. With careful management in some special circumstances, greater life expectancy and quality of life can be better persevered [109, 111].

There is currently no consensus on which method should be utilised, this may be due to several factors; the lack of a clear comprehensively known definition of frailty hampers the clear-cut description and dimension of frailty; the measurement of frailty may be for different objectives which includes assessments, screening, case finding or predicting patient prognosis; the instruments used to measure frailty is also different depending upon objectives [146].

Our aim was to review (i) the strength of association between frailty tools and cardiothoracic outcomes; (ii) identify which measures of predictive accuracy are utilised to assess these outcomes; (iii) Assess how frailty scores compare to existing risk scoring tools such as EuroSCORE and STS score; and (iv) if there is variation between frailty and risk scoring tools, to identify which tool is most accurate in predicting post-operative outcomes.

2.2 METHODS

2.2.1 Literature Search Strategy

Data was sourced from EMBASE, CINAHL, MEDLINE, Cochrane, PubMed and other web based science electronic database for the period from 1980 to 2015. The following search terms were used to retrieve potential published articles for inclusion: ('Frailty', 'Frail', 'Elderly') AND ('Cardiac surgery', 'Thoracic surgery', 'Cardiothoracic surgery',) AND ('Risk', 'Risk score', 'Risk stratification', 'outcome',).

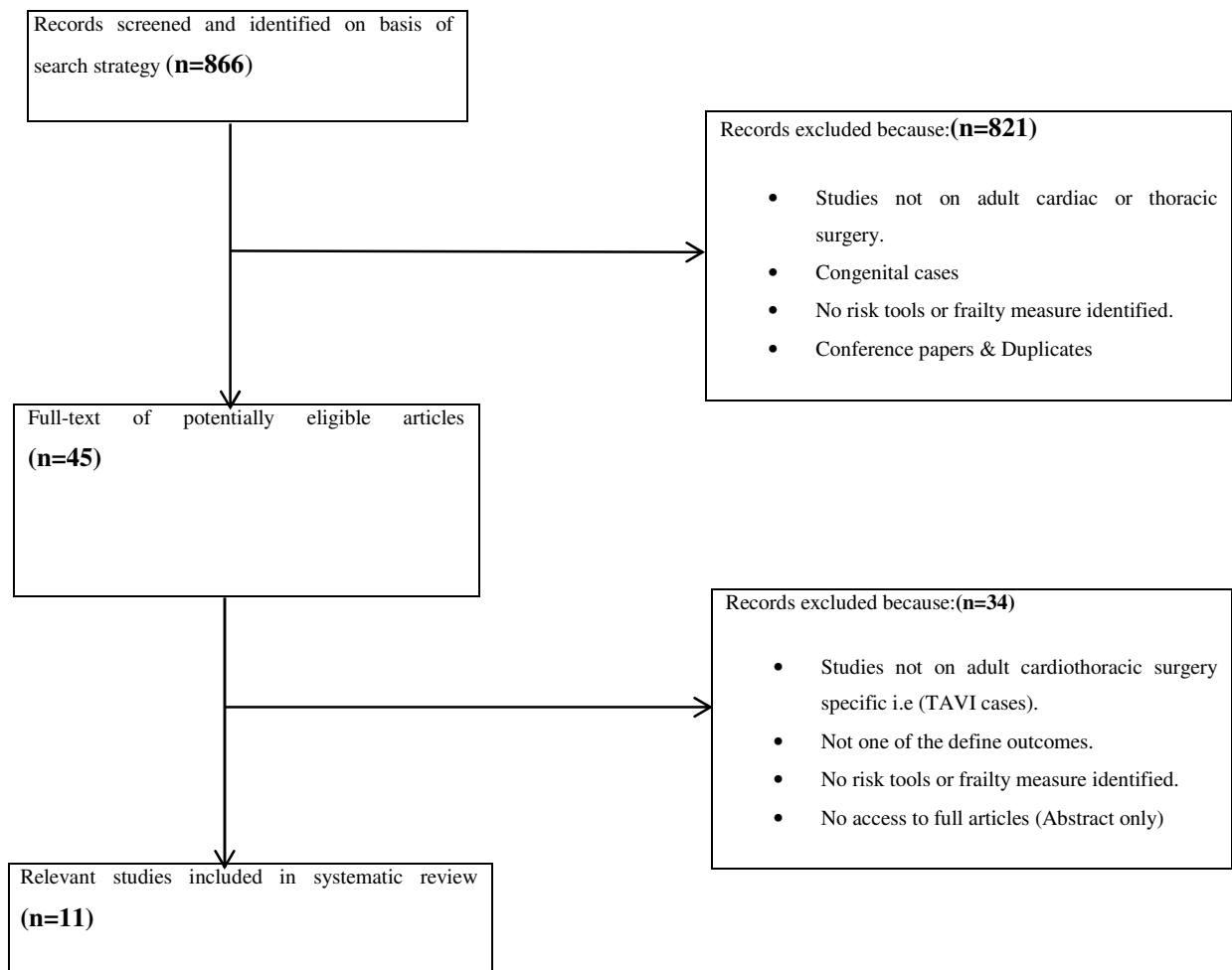
2.2.3 Study Inclusion Criteria

Selection criteria included (i) studies defining their measuring instrument, including frailty as a multidimensional tool and not only physical status deterioration such as hand grip or walking; (ii) studies based on a patient population undergoing either cardiac or thoracic surgery; (iii) studies offering predictive accuracy data of frailty tools on cardiothoracic outcomes (for example effect size of association, calibration and classification measures).

2.2.4 Evaluation of Quality and Risk of Bias

Each study was appraised for risk of bias using the TRIPOD (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) checklist to measure its quality. Tripod is a tool to assess the reporting of studies developing, validating, or updating a prediction model study. It consists of 37-elements from a 22-item checklist detailing the essential information that should be included in a report of a prediction model study. Each study is then rated with a number for each element in the checklist[147].

Figure 10 - 2.1: Flow diagram of study selection



Statistical Pooling of Outcomes

Differences in Odds Ratio (OR) were pooled through meta-analytical, inverse-variance, random-effects model methodology. This was performed using Stata 13 (StataCorp., College Station, Texas, US). The I^2 statistic was used to estimate the degree of heterogeneity between studies, where larger values indicate increasing heterogeneity.

2.3 RESULTS

Our literature search yielded 866 studies, of which 11 articles fulfilled our stringent inclusion criteria. Eight studies focused on cardiac population (10,226 patients) and three on thoracic ones (12,961 patients). From them, only one study presented calibration analysis data (Hosmer-Lemeshow test) for their predictive model [112] whilst four reported discriminative analysis data (Area under the Curve) [109, 148]. There were no studies mentioning c-index or brier score. A bootstrap procedure was performed on 200 subsamples, and 95% confidence interval (CI) of the ROC was reported depending on bootstrap distribution. Comparisons of frailty measures were made with established risk stratification scores (**Table 1**). The median study quality according to TRIPOD checklist was low-to-moderate at 23.5 (out of 37). A flow chart of our search results according to PRISMA guidelines is shown in **Figure 1**. Overall, 11 different frailty assessment tools were used in cardiac or thoracic surgery (**Table 1**). The predictive value of these tools as applied to morbidity and mortality outcomes was reported by odds ratios (OR) and 95% confidence intervals (CI) comparing frail vs. non-frail cohorts (**Table 2**). Outcome included 30-day, in-hospital and 1-year mortality, composite outcome (mortality, major morbidity and complications) and prolonged length of stay or time to institutional discharge.

Table 1 - 2.1: Frailty tools utilised in cardiothoracic surgery

test 1

Tools / Measure	Frailty Characteristics	Frail vs. Non-frail cut-off value
Gait Speed	Walking a distance of 5m at comfortable pace x3 and averaged.	Slow:>6s, Very slow:>7-8s, Extremely slow:>>10s
The Katz Score	Independence of activities of daily living (bathing, dressing, transferring, walking, toileting, and feeding)	An abnormal score was defined as dependence in one or more activity of daily living.
The Mini-Cog	Measures cognition using a paired three-item recall and clock draw task	An abnormal cognition was defined as a Mini-Cog score ≤ 3
The Charlson Index	Measures burden of disease by summing 19 categories of co-morbidities weighted on their risk of one-year mortality	An abnormal chronic disease burden was defined as a Charlson score ≤ 3
Anaemia	Anaemia of chronic disease also measured disease burden	Anaemia was defined as Haematocrit < 35%.
Nutrition	Poor nutrition was defined as serum albumin level	Level below 3.4 g/dL.
Geriatric syndrome of falls	Measured by asking the individual how many times they have fallen in the six-months prior to surgery	A positive score of falls was defined as ≥ 1 fall in the six-months prior to the operation
CHS scales	Gait speed, Handgrip, Inactivity, Exhaustion, Weight loss	Slowness, weakness, Questionnaire, Questionnaire, weight loss>10 lbs respectively
CAF	Fried + CFS + Disability + Balance + Blood	CAF score ≤ 11
FORECAST	chair rise x3, subjective reported weakness, stair climb, CFS, serum Creatinine	FORECAST score ≤ 5
7 Frailty	The Timed Up-and Go measures the time needed to stand up from a chair, walk 10 feet, return to the chair, and sit	An abnormal score was defined as ≥ 15 seconds

Table 2 - 2.2: Synopsis of included studies

Source	N	Gender M/F	Age mean (SD) years	Frailty Measure	Description	Primary Study outcomes	Main Outcome	TR* Score (Max=22)
							Odd ratio/ Confidence Interval	
Sundermann SH et al 2014 Interact CardioVasc Thorac Surg [149]	450	227/223	79 ± 4	CAF	6 domains questionnaire	30 day mortality, 1 year mortality	30 day mortality OR: 1.1 (95% CI: 1.06 - 1.2)	15.2
							1 year mortality OR: 1.1 (95% CI: 1.06 - 1.1)	
							1 year mortality independent of age OR: 1.091 (95% CI: 1.049 - 1.135)	
							When added to known EuroSCORE, 1 year Mortality OR: 1.089 (95% CI: 1.045 - 1.135)	
							When added to known STS score, 1 year Mortality OR: 1.087 (95% CI: 1.037 - 1.139)	
Sundermann SH et al 2014 Interact CardioVasc Thorac Surg [149]	450	227/223	79 ± 4	FORECAST	5 domains questionnaire	30 day mortality, 1 year mortality	30 day mortality OR: 1.3 (95% CI: 1.2 - 1.5)	15.2
							1 year mortality OR: 1.3 (95% CI: 1.2 - 1.4)	
							1 year mortality independent of age OR: 1.265 (95% CI: 1.143 - 1.401)	
							When added to known EuroSCORE, 1 year Mortality OR: 1.271 (95% CI: 1.141 - 1.415)	
							When added to known STS score, 1 year Mortality OR: 1.264 (95% CI: 1.116 - 1.431)	
Lee DH et al 2010 Circulation [111].	3826	2828/998	65 ± 10	Katz index of ADL/Ambulation independence / Dementia Diagnosis	5 domains questionnaire	In-hospital mortality and discharge to an institution.	Adjusted in hospital mortality OR: 1.8 (95% CI: 1.1 - 3.0)	16
							Adjusted reduced Mid-term survival HR 1.5 (95% CI: 1.1 - 2.2)	
							Adjusted prediction for institutional discharge OR: 6.3 (95% CI: 4.2 - 9.4)	

Williams J B et al 2013 Am J Cardiol [150]	148	98/50	75.8 ± 4.4	HADS	14 Items (7 for anxiety: HADS-A & 7 for depression: HADS-D)	All-cause mortality or major morbidity	Unadjusted HADS-A Mortality/Morbidity OR: 4.1 (95% CI: 1.2 - 14.4) Adjusted HADS-A Mortality/Morbidity OR: 5.1 (95% CI: 1.3 - 20.2)	13
Afilalo J et al 2012 Circ Cardiovasc Qual Outcomes [109]	152	100/52	75.9 ± 4.4	Gait speed	5-meter gait speed more than 6 Seconds	In hospital mortality or major morbidity	Mortality or major morbidity OR: 2.63 (95% CI: 1.17 - 5.90) When added to STS-PROMM, Mortality or major morbidity OR: 2.53 (95% CI: 1.15 - 5.52) When added to Parsonnet Mortality or major morbidity OR: 2.28 (95% CI: 1.02 - 5.21)	15.7
Afilalo J et al 2012 Circ Cardiovasc Qual Outcomes [109]	152	100/52	75.9 ± 4.4	Nagi scale	7 Items	In hospital mortality or major morbidity	Mortality or major morbidity OR: 1.28 (95% CI: 1.06 - 1.54) When added to STS-PROMM, Mortality or major morbidity OR: 2.66 (95% CI: 1.18 - 5.96) When added to Parsonnet Mortality or major morbidity OR: 2.17 (95% CI: 0.93 - 5.04)	15.7
Afilalo J et al 2010 J Am Coll Cardiol [112]	131	87/44	75.8 ± 4.4	Gait speed	5-meter gait speed more than 6 Seconds	In hospital mortality or major morbidity	Adjusted Mortality or Major Morbidity OR: 3.17 (95% CI: 1.7 - 2.59) Mortality or Major Morbidity after adjusting for STS risk score OR: 3.05 (95% CI: 1.23 - 7.54) Adjusted prolonged post-operative length of stay OR: 2.32 (95% CI: 0.95 - 5.67) Adjusted discharge to a healthcare facility OR: 3.19 (95% CI: 1.40 - 8.41)	16.3
Ekerstad N et al 2011 Circulation [151]	307	157/150		CSHA CFS	7 Points scale	30 day composite outcome of mortality and major morbidity	Adjusted composite outcome OR: 2.17 (95% CI: 1.28 - 3.67) Reduced 1 month survival after adjustment for CAD index + cardiovascular risk OR: 4.7 (95% CI: 1.7 - 1.3)	15.4
Robinson TN et al 2013 Am J Surg [148]	129		73 ± 6	Katz, Timed up and Go, Charlson index, Mini- Cog, Albumin, Anemia & Fall	7 different frailty tools	Complications	Increase in complications for every 1 year increase in age OR: 1.015 (95% CI: 0.943 - 1.092) Likelihood for frail people to have a complication OR: 6.697 (95% CI: 2.565 - 17.483).	15

Velanovich V et al 2013 J Surg Res [152]	5083 Card			MFI	11 Items	Mortality & Morbidity	RVU for cardiac operations < 25: Mortality for each unit increase in FI 2.04 (95% CI: 1.37 - 3.04)	12.4
							RVU for cardiac operations 25 - 75: Mortality for each unit increase in FI 1.24 (95% CI: 0.98 - 1.58)	
							RVU for cardiac operations >75: Mortality for each unit increase in FI 1.87 (95% CI: 1.63 - 2.14)	
							RVU for cardiac operations < 25: Morbidity for each unit increase in FI 1.42 (95% CI: 1.22 - 1.65)	
							RVU for cardiac operations 25 - 75: Morbidity for each unit increase in FI 1.40 (95% CI: 1.24 - 1.59)	
							RVU for cardiac operations >75: Morbidity for each unit increase in FI 1.37 (95% CI: 1.30 - 1.44)	
Velanovich V et al 2013 J Surg Res [152]	4648 Thor			MFI	11 Items	Mortality & Morbidity	RVU for Thoracic operations < 25: Mortality for each unit increase in FI 1.80 (95% CI: 1.18 - 2.73)	12.4
							RVU for Thoracic operations 25 - 75: Mortality for each unit increase in FI 1.84 (95% CI: 1.57 - 2.14)	
							RVU for Thoracic operations >75: Mortality for each unit increase in FI 1.57 (95% CI: 1.28 - 1.93)	
							RVU for Thoracic operations < 25: Morbidity for each unit increase in FI 1.24 (95% CI: 1.06 - 1.45)	
							RVU for Thoracic operations 25 - 75: Morbidity for each unit increase in FI 1.53 (95% CI: 1.38 - 1.69)	
							RVU for Thoracic operations >75: Morbidity for each unit increase in FI 1.25 (95% CI: 1.15 - 1.37)	
Tsiouris A et al 2012 J Surg Res [153]	6373		54.1(17 -91)	Functional status (ADLs)	5 Items	Complications and Mortality	Independent predictor for morbidity (OR: 3.8, $p<0.001$) and mortality (OR: 2.1, $p<0.001$)	14
							For dependent group risk for Pneumonia OR: 2.7, (95% CI: 1.8-3). Risk for intubation OR: 3.1, (95% CI: 2.4-4). Risk for prolong intubation OR: 9.3, (95% CI: 7.5-11.6). Clavien 4 and above complication OR: 5.75, (95% CI: 4.8-6.9). Infectious complication OR: 2.5, (95% CI: 2.1-3.1). Mortality OR: 7.7, (95% CI: 6.1 - 9.8)	
Tsiouris A et al 2013 J Surg Res [154]	1940	944/996	66 ± 11	MFI	11 Items	Mortality and Major Complications	Mfi >0.27 independent predictor of mortality OR: 9.3, (95% CI: 9.4-270)	14
							Mfi >0.27 independent predictor for Clavien 4 complications OR: 4.8, (95% CI: 1.3-230)	
Afilalo J et al 2011 JACC [155]	131	86/45	75.8 ± 4.4	Fried scale, Functional comorbidity, OARS instrumental ADL scales & Katz index of ADL	5 Items	Mortality and Major Morbidity	When adjusted for STS risk score mortality or major morbidity OR: 3.14 (95% CI: 1.02 - 9.68)	13

TR*, Tripod; CAF, Comprehensive Assessment of Frailty; FORECAST, Frailty predicts One year after Elective Cardiac Surgery Test; MFI, Modified Frailty Index; STS, Society of Thoracic Surgeons; OR, Odds Ratio; CSHA, Canadian Study of Health and Aging; CFS, Clinical Frailty Scale; ADL, Activity of Daily Living; HADS, Hospital Anxiety and Depression Scale.

2.3 Mortality

Four studies investigated the relationship between frailty and mortality [111, 149, 151, 154].

These studies utilised 4 different frailty measures (CAF, FORECAST, Katz index of ADL and CSHA) to assess (i) 30-day or in-hospital mortality and (ii) 1-year mortality.

2.3.1 30 day or in-hospital mortality

The odds-ratio for the CAF scoring system to predict 30-day mortality in frail versus non-frail patients was 1.1 (95% CI: 1.06 - 1.2); this was similar to that of FORECAST that demonstrated an odds ratio of 1.3 (95% CI: 1.2, 1.5) [149]. Katz index of ADL was related to in-hospital mortality and reduced mid-term survival with OR of 1.8 (95% CI: 1.1 - 3.0) and HR 1.5 (95% CI: 1.1 - 2.2) respectively [111].

The extended Canadian Study of Health and Ageing Clinical Frailty Scale (CSHA) revealed an OR of 4.7 (95% CI: 1.7 - 1.3) for reduced one month survival after adjusting for CAD index and cardiovascular risk [107]. The final study highlighted the relationship between modified frailty index (Mfi >0.271) and mortality OR: 9.3, (95% CI: 9.4-270) as independent predictors of 30-day mortality in thoracic patients [154].

2.3.2 1-year mortality

The odds-ratio for the CAF scoring system to predict 1-year mortality in frail versus non-frail patients was 1.1 (95% CI: 1.06 - 1.1); this became 1.089 (95% CI 1.045-1.135) when adjusted for EuroSCORE and 1.087 (95% CI 1.037-1.139) when adjusted for STS score [149]. The odds-ratio for FORECAST was 1.3 (95% CI: 1.2 - 1.4); this became 1.271 (95% CI: 1.141 - 1.415) when adjusted for EuroSCORE and 1.264 (95% CI: 1.116 - 1.431) when adjusted for STS [149].

2.3.3 Composite outcome

Five studies reported the relationship between frailty and the combined outcome of major morbidity or mortality [109, 112, 150, 151, 155]. Tools used for this assessment included the Anxiety Depression Scale-Anxiety (HADS-A) scoring system, the Gait Speed Score, the Nagi scale and the extended Canadian Study of Health and Ageing Clinical Frailty Scale (CSHA).

The unadjusted odds-ratio for the Hospital Anxiety Depression Scale-Anxiety (HADS-A) scoring system to predict this composite outcome in frail versus non-frail patients was 4.1 (95% CI: 1.2 - 14.4); this became 5.1 (95% CI: 1.3 - 20.2) when adjusted for mortality and morbidity [150].

The Gait speed score demonstrated an odds-ratio of 2.63 (95% CI: 1.17, 5.90) for this composite outcome, which when added to STS-PROMM became 2.53 (95% CI: 1.15, 5.52) and when added to Parsonnet became OR: 2.28 (95% CI: 1.02, 5.21) [109].

The Nagi scale demonstrated an odds ratio of 1.28 (95% CI: 1.06 - 1.54), which when added to STS-PROMM became 2.66 (95% CI: 1.18 - 5.96) and when added to Parsonnet became 2.17 (95% CI: 0.93 - 5.04) [109].

The extended Canadian Study of Health and Ageing Clinical Frailty Scale (CSHA) revealed an adjusted odds ratio of 2.17 (95% CI: 1.28 - 3.67) [151].

One study from the same group used five items (fried scale, functional comorbidity, OARS instrumental, ADL scales and Katz index of ADL) to assess overall mortality or morbidity demonstrating an odds ratio of 3.14 (95% CI: 1.02 - 9.68) when adjusted for STS risk score [155].

2.3.4 Institutional discharge/Length of stay

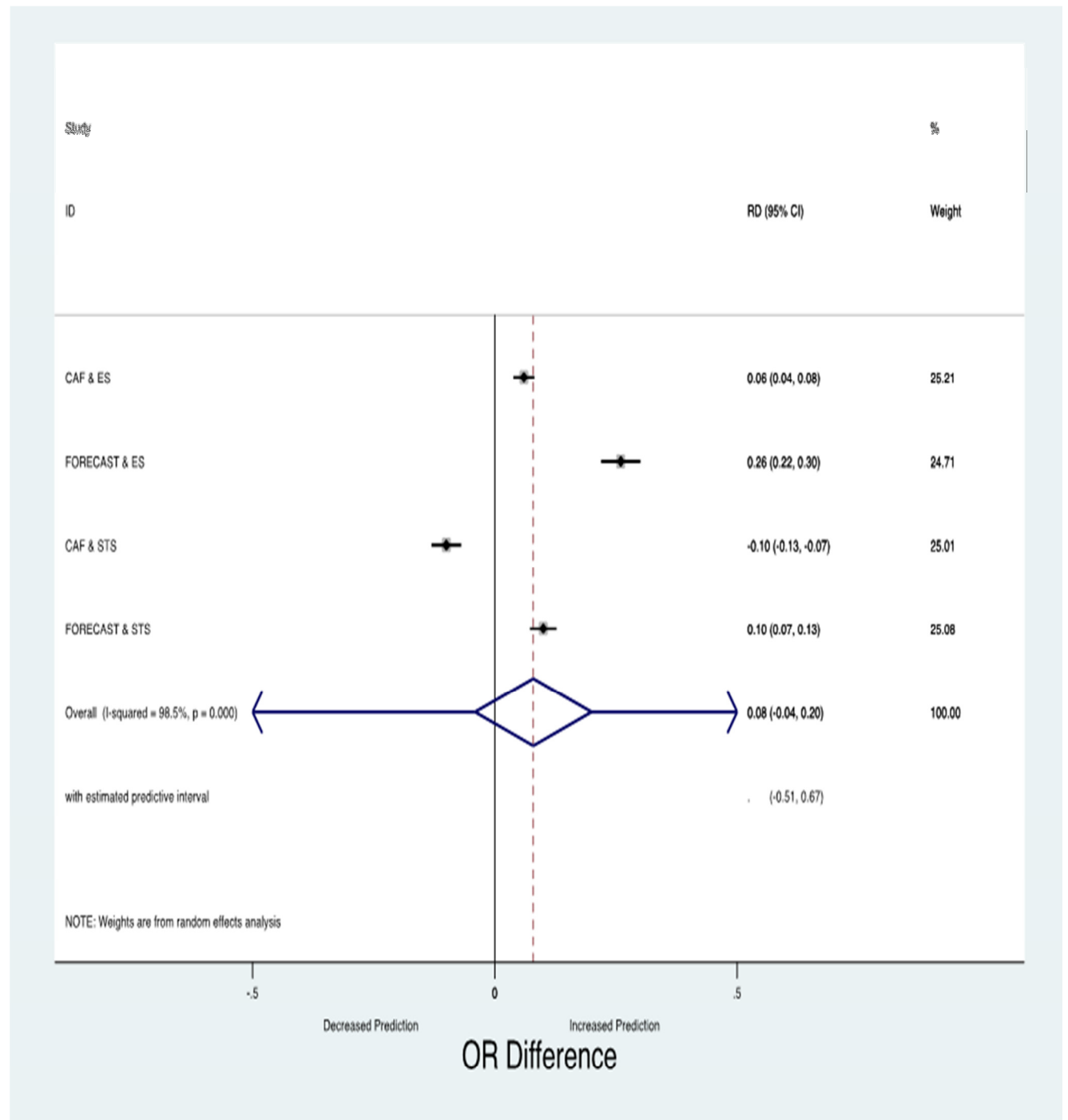
Two studies identified the value of Katz index of ADL and gait speed for predicting discharge from a healthcare facility with an odds ratio of 6.3 (95% CI: 4.2 - 9.4) and 3.19 (95% CI: 1.40 - 8.41) respectively [111, 112]. The study from Afilalo et al [112] also highlighted the relationship between gait speed and prolonged length of hospital stay with OR: 2.32 (95% CI: 0.95 - 5.67).

2.3.5 Pooled Differences between Frailty and Standard Risk Scores on Mortality

(i) Frailty Score Versus Standard Risk Score

Four cohorts compared the odds ratio of mortality between frailty scores and standard risk scores [149]. When compared to established risk scores, frailty scores demonstrated a larger pooled OR of mortality by 0.08 (95% CI -0.04, 0.20), although non-significant (**Figure 2**). However, heterogeneity was high ($I^2 = 98.5\%$) as expected by the usage of different frailty tools.

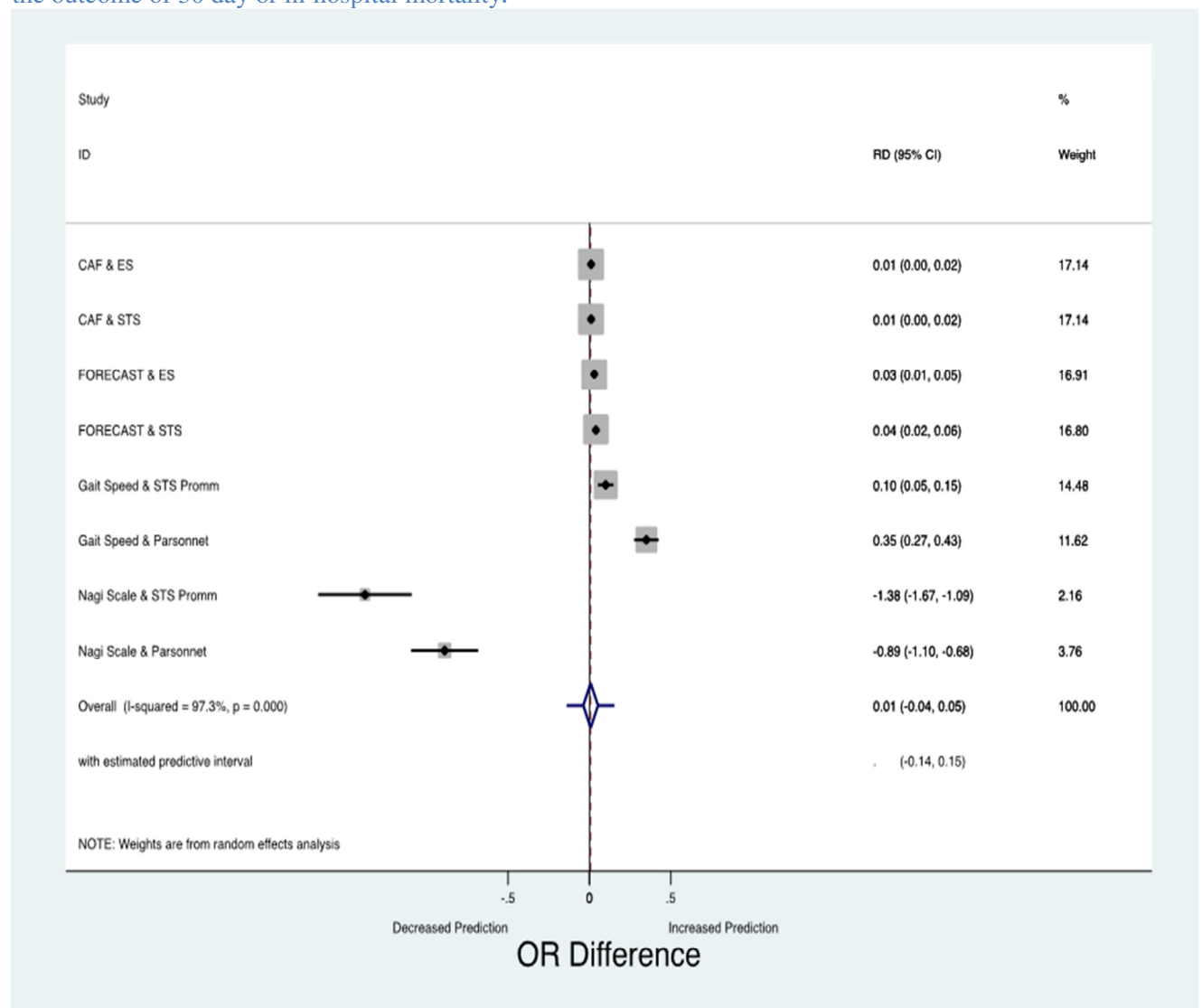
Figure 11 – 2.2 Forrest plot comparing frailty score and standard risk score for the outcome of 30 day or in-hospital mortality.



(ii) Frailty Score Versus Frailty adjusted for Standard Risk Score

Eight cohorts compared the diagnostic odds ratio of mortality between frailty scores and frailty adjusted for standard risk score [109, 149][6, 9]. When compared to adjusted frailty scores, raw frailty scores demonstrated a larger pooled OR of mortality by 0.01 (95% CI - 0.04, 0.05) also non-significant (**Figure 3**). Again inter-study heterogeneity was high ($I^2 = 97.3\%$).

Figure 12 – 2.3 Forrest plot comparing the frailty score and the frailty-adjusted standard risk score for the outcome of 30 day or in-hospital mortality.



2.4 Discussion

This review demonstrates that the pre-operative use of frailty tools can augment the effect size of association for early month mortality (1.8%), morbidity, prolonged length of stay and institutional discharge in patients undergoing cardiac or thoracic surgery; although this increase was not demonstrated to be statistically significant and of unknown clinical impact. The wide variety of independent assessment tools and frailty measures used causes clinical and statistical heterogeneity in the published literature and also demonstrates the growing interest in this cohort of patients whose risk of adverse outcomes cannot be accurately identified by existing scoring systems. There was small change (1%) in the strength of association following adjustment and inclusion of the frailty score in the prediction model and it is very important to note that there is limited information of other measures of model performance and predictive accuracy such as calibration and classification.

Frailty as a risk factor for adverse outcome in cardiac surgical patients has been recognised for many years [111]. It is known that frailty and the onset of dependency in ADLs are strongly related [146], and as a consequence existing measures such as the Katz index of ADLs were initially used as a frailty tool. Lee et al. demonstrated that frail patients were older, had an increased burden of disease and were more likely to undergo more complex operations than non-frail patients [111]. The weak or diminished reserve for mobilisation and ambulation was found to pre-dispose these patients to lung related complications postoperatively, hence resulting in prolonged hospital stay. Blood transfusion, low cardiac output syndrome and sepsis were also more common in these patients. As a result, frailty as measured by Katz index of ADLs is thought to be a better predictor of institutional discharge (OR 6.3) than of in-hospital mortality (OR 1.8) or shortened mid-term survival (OR 1.5) after adjusting for age, gender and other comorbidities. Similarly, Afilalo et al. also demonstrated

[109] slow gait speed and older age to be independent predictors of institutional discharge (OR 3.19) in cardiac surgery patients.

Three studies focused on the relationship between frailty and mortality using different assessment tools. Sundermann et al. identified a slight increase in 30-day and in 1-year mortality with increasing degree of frailty (ORs ranging between 1.1 to 1.3) [149]. Both the CAF and FORECAST tools used to measure frailty in this study continued to be predictive of mortality even after adjusting for age. This remained true with the addition of EuroSCORE and STS score into the developed model, even though there was a small drop in the odds ratios. From all the procedures included in the study, only aortic valve replacement established a significant interaction with CAF and FORECAST scores. None the less, age showed a moderate correlation with both STS and EuroSCORE but it has been inadequately associated with the frailty scores. Lee and team [111] had already shown this weak predictive relationship between frailty and mortality in a previous article whilst in a study by Ekerstad and colleagues [151] utilising the extended Canadian Study of Health and Ageing Clinical Frailty Scale, proved to achieve a higher OR (4.6) after adjusting for CAD index score and cardiovascular risk.

The impact of frailty on mortality and morbidity has been described in 3 studies by Afilalo and team. [109, 112, 155]. In the first study from 2010 [112] they revealed that there is no actual association between gait speed and STS risk score implying that these two cover independently different areas. Also, by pre-selecting 7 core risk factors (age, female gender, previous cardiac operation, low left ventricular ejection fraction, significant stenosis of left main coronary artery, non-elective surgery and type of surgical procedure) and adding slow gait speed, they created a predictive model. There was a very slight difference in the area under the curve when the model was run with or without the addition of the gait speed variable (0.81 vs 0.78 respectively); the Hosmer – Lemeshow Chi-square was 5.70 vs 6.78

respectively. Slow gait speed, previous cardiac surgery and older age were independently predictive of the outcome. In a separate model created by this group slow gait speed conferred a two to three fold increase in risk for any given level of STS predicted mortality or major morbidity compared with normal gait speed. When the model included only STS risk score alone the area under the curve was 0.70 and with the addition of gait speed, it slightly increased to 0.74; indicating that gait speed may augment the information provided by the STS risk score. This outcome corresponded to Hosmer-Lemeshow Chi-squares of 11.53 vs 10.29 respectively. Furthermore, they reported patients with slow gait speed were more likely to be females, to have shorter height, be diabetic and have at least one disability in their ADLs.

In the study from 2012, Afilalo and team [109] investigated patients undergoing CABG and/or valvular surgery, and created a model combining slow gait speed, Parsonnet score and Nagi scale which provided an area under the curve of 0.76. Slow gait speed alone yielded an area under the curve of 0.64 similar to that of the Nagi scale at 0.65. Likewise, when used alone the Parsonnet score revealed a moderate discriminatory ability of 0.72. For a given level of predicted risk, slow gait speed was identified as an incremental predictor of mortality or major morbidity when adjusted for STS-PROMM (Society of Thoracic Surgeons Predicted Risk of Mortality or Major Morbidity) or Parsonnet score (OR: 2.53 vs. 2.28). On the other hand, the Nagi scale also provides an incremental value when adjusted to the above mentioned risk scores (OR: 2.66 vs. 2.17). In the third study by this group frailty as measured by Fried scale was singled out as an independent predictor of composite outcome (OR: 3.14) even after adjusting for STS score [112].

Williams et al [150] studied anxiety and level of depression in patients undergoing cardiac surgery, highlighting preoperative anxiety as an independent predictor of post-operative mortality or major morbidity even after adjusting for STS risk score, age, gender and

depression levels measured by HADS-D score (Hospital Anxiety Depression Scale-Depression). Specifically, a HADS-A score (Hospital Anxiety Depression Scale-Anxiety) of 11 or higher was highly predictive of these two outcomes (unadjusted OR 4.1 vs adjusted OR 5.1).

Finally, Robinson et al [148] identified a sub-group of patients who had the tendency for slow timed up-and-go as having significantly lower survival rate and exhibiting diminished performance in other geriatric characteristics suggestive of frailty (i.e. poor cognition). This group also showed that the higher the frailty scores of the patients the higher the likelihood for postoperative complications, with infection being the most common. An interaction between age and frailty was highlighted; for every one year increase in age, frail patients were 6.7 times more likely to have one or more complications when compared to the 3.3 times for the pre-frail individuals. In terms of predictive accuracy time frailty as measured by the seven different traits performed moderately (AUC:0.711; 95%CI: 0.606 – 0.817).

For thoracic operations, data were much more limited. Tsiouris et al [153] investigated patients undergoing non-cardiac thoracic procedures and divided the patients into groups on the basis of functional status. Patients in the dependent group had a higher likelihood of major postoperative complications, in particular chest complications, and as a result had a longer length of hospital stay and higher mortality. Multivariate analysis highlighted preoperative dependent functional status as an independent predictor for both mortality and morbidity, along with the urgency of the procedure and an open thoracotomy approach. In their more recent publication [154] the modified frailty index (MFI) was applied in patients undergoing thoracic procedures emphasizing a strong relationship between MFI and morbidity and mortality outcomes. When comparing patients with MFI 0.27 to those with an MFI of 0, Tsiouris and colleagues, also noted a greater likelihood of lung related complications (pneumonia, slow respiratory wean), renal failure and clavien 4 and above

complications in the former group. In their multivariate analysis, an MFI greater than 0.27, wound class 3, ASA score 4 and dependent functional status were all predictors of Clavien 4 and above complications.

Velanovich et al [152] showed that frailty as measured by the modified frailty index (MFI) is not only a characteristic of older people, but in fact high indexes can also be found in young patients. They further outlined an increase of both mortality and morbidity for every unit of increase of MFI and level of operation complexity. The effect of frailty seems to be more important for postoperative mortality than morbidity as shown by the higher ORs for mortality outcomes. It is particularly interesting that both in cardiac and thoracic operations the difference in mortality ORs with regards to operation complexity was not as great as expected. The authors however pointed out that in cardiac cases with moderate complexity, the mortality OR for each unit increase in MFI failed to reach statistical significance. Therefore, frailty seems to have more impact on mortality in operations considered as lower risk. However, it is notable that the level of the complexity of the operations did not seem to have great impact on the effect of FI in relation to the incidence of postoperative complications.

2.5 Clinical prediction models

Clinical prediction models may use multiple predictors to analyse their relative effects in the model performance and may also provide personalised outright risk estimation. Logistic regression analysis is most commonly used for the prediction of binary events and cox regression is most common for time-to-event data. In recent years significant developments have been made in the application of a methodological framework for more robust

development, validation and clinical usefulness of prediction models [156-158]. Metrics and several other methods can be used to assess the performance of prediction models.

Old measures for binary and survival outcomes include the Brier score as an indicator of overall model performance, the concordance (or c) statistic for discriminative ability (or area under the receiver operating characteristic (ROC) curve), and the goodness-of-fit statistics for calibration [144]

Our systematic review showed that these measures of performance are poorly reported which constitutes a significant limitation of the currently available literature, consequently hindering any conclusion about the effect on predictive accuracy of adding the variable of frailty score in the established stratification tools.

Recently different measures have recently been proposed that can be seen as refinements of discrimination measures, including variants of the c statistic for survival, reclassification tables, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). In addition to that decision-analytic measures have been proposed, including decision curves to plot the net benefit achieved by making decisions based on model predictions [147, 159]. It has been recommended by the methodological literature that reporting discrimination and calibration is critically mandatory for a prediction model. Decision-analytic measures should be reported if the predictive model is going to be used to making clinical decisions. Other measures of performance may be warranted in specific applications, such as reclassification metrics to gain insight into the value of adding a novel predictor to an established model. Quantifying the predictive ability of a model on the same data from which the model was developed will result in an optimistic estimate of performance, owing firstly to over fitting (which implies that there are too few outcome events relative to the number of predictors included in the model) and secondly to the use of predictor selection strategies.

Studies developing new prediction models should therefore always include some form of internal validation to quantify any risk of optimism in the predictive performance (such as calibration and discrimination) of the developed model. Internal validation techniques use only the original study sample and include methods as bootstrapping or cross-validation. Internal validation is a necessary part of model development. Over-fitting, optimism, and miscalibration may also be addressed and accounted for during the model development by applying shrinkage (for example, heuristic or based on bootstrapping techniques) or penalisation procedures (such as ridge regression or lasso) [160].

After developing a prediction model, it is strongly recommended to evaluate the performance of the model in data from other participant. Such external validation requires that for each individual in the new data set, outcome predictions are made using the original model (that is, the published regression formula) and compared with the observed outcomes [159]. External validation may use participant data collected by the same investigators, typically using the same predictor and outcome definitions and measurements, but sampled from a later period (temporal or narrow validation); by other investigators in another hospital or country, sometimes using different definitions and measurements (geographic or broad validation); in similar participants but from an intentionally different setting or even in other types of participants or developed for predicting fatal events and assessed for predicting non-fatal events). In case of poor performance, the model can be updated or adjusted on the basis of the validation data set. This sort of external validation of the frailty scores is limited by the fact that there is so big variety of frailty scores tested and fragmental information of different outcomes that we can state that future work needs to address these important issues of validity [160].

The absence of consensus on which method should be utilized to measure frailty is attributed to several factors. Firstly, there is no clear universally accepted definition to allow for the

precise identification and measurement of frailty. Secondly, measurement of frailty in these studies is often for different objectives, including assessment, screening, case finding and predicting patient prognosis. Thirdly, the objective of the instruments used to measure frailty depends upon the target group (clinician or researcher). Finally, the objective use of tools to measure frailty in clinical studies is only beginning to develop and thus the application of these tools in the clinical environment remains in its infancy.

2.6 Limitations

This study benefits from systematic analysis of the largest number of studies of frailty in cardiothoracic surgical patients. However, overall some weaknesses were noticed. (i) the definition of frail vs. non-frail was not consistent, (ii) there was variability in study design and none was randomised. (iii) power analysis was not stated clearly across studies. (iv) the comparison between frailty vs. standard risk stratification scores was only reported in a few studies and (v) data was not fully available for standard cardiothoracic outcomes in all studies. Additionally many of these studies failed to report on common endpoints which limited formal meta-analysis for these outcomes thereby limiting our interpretation of the best predictive value of each frailty tool.

Despite these limitations, the growing economic constraints on the UK NHS and other national healthcare systems necessitates an improvement in our ability to assess and predict the risk associated with medical and surgical interventions. Through careful refinement and accurate selection of frailty assessment tools it is possible that we may be able to in future cultivate an improved estimation of risk in our ever-aging patient population. In this way, we may optimise patient selection and subsequently guide patients towards personalised treatment plans that will maximize the unmet need to optimize resource distribution and to avoid costly but ineffective interventions.

2.7 Conclusions

This review highlights there is limited evidence on the ability of frailty scores to augment conventional risk stratification models in predicting adverse morbidity and mortality outcomes after cardiothoracic surgical procedures. A range of available frailty tools were alone able to act as independent predictors of adverse outcomes and prolonged length of stay emphasising the importance of frailty in this ever-aging patient cohort but the statistical modelling of the published studies is inadequate to conclude on calibration and classification measures of predictive accuracy.

Future work should now consider whether an updated version of the EuroSCORE or STS score should include frailty as one of its variables. Additionally, we should now strive to utilize a more targeted, multicenter approach comparing frailty tools across a standardized set of outcomes that would allow us to determine which tool could best be used to provide a single more homogeneous assessment of frailty for future studies.

Main Points and Recommendation.

- Clinical prediction models may combine multiple predictors to assess their relative effects on how the models perform.
- Only 1 study presented calibration analysis data (Hosmer–Lemeshow test) for their predictive model whilst 4 reported discriminative analysis data (AUC)
- Four studies found that the addition of frailty increased the predictive power of conventional risk scores, but this requires further validation
- The assessment of frailty may enhance the preoperative workup and offer an optimized risk stratification measure in patients undergoing cardiothoracic procedures even though the reporting standards of calibration and classification measures have been relatively poor. The sizes of the association of these tools with morbidity and mortality outcomes report varied.
- None of the studies mentioned Brier scoring, which is a measure of the accuracy of probabilistic predictions.
- It is imperative updated version of EuroSCORE II & STS should include frailty score using validated frailty measuring tools such as REFS.

3.0 Chapter 3

3.0 Hypotheses, objectives, and general methodology

In the light of the introduction and literature review in the preceding chapters, chapter 3 will focus on explaining in detail the hypotheses of this project, the objectives we aim to accomplish, and the approach utilised to conduct this study.

3.1 Hypotheses and Overview

The principal hypotheses of this study expose the frailty syndrome and prove it is strongly and independently associated with combined outcome of unevaluated and unplanned hospitalisation. Hence it can be deduced frailty impacts on physical and mental component of patients is a predictor of poor quality of life, cardiac function and recovery.

As outlined in previous chapter's cardiac surgery carry immediate, early and late risk of complication. This risk increases with age however over the past decade with the advancement of technology, intelligent surgical tools combined with improved surgeon's skills, more and more older age persons are defying the old tradition and are braving to undergo more complex procedures.

In addition, little objective data exists on how patients recover physically from surgery or the impact on their quality of life. Such information can help to determine surgical or medical course of treatment for patients. Objective mobility data can be used as a measure of health and to evaluate the relevance of certain medical treatments and to estimate the quality of life of an elderly patient. Slow gait speed is a reliable measure of frailty and resiliency to stressors, increased risk of cardiovascular mortality, and a simple and effective indicator of an individual's recovery after cardiac surgery. It can help identify vulnerable elderly patients with increasing risk of mortality and major morbidity undergoing cardiac surgery.

The most reliable mobility information of the patients can be achieved via a long-term monitoring that is performed in patients' own environment as compared to a short period of monitoring in unnatural clinical environment. Long-term activity monitoring at home provides clinically useful trend data enabling clinicians to monitor the patients' health (e.g., urgent care would receive it in a more timely fashion) and their response to treatments and, overall, make informed decisions.

A large body of research associates frailty with poor outcome; however, what constitutes frailty and the predictive value of frailty in cardiac surgery patient's quality of life and recovery is yet to be explored in detailed. Therefore, we hypothesise that:

1. Frailty is associated with a high rate of poor outcome after cardiac surgery.
2. Patients with frailty (by Edmonton frail scale ≥ 7) have worse QoL postoperatively, more complications and slower recovery.
3. Patients that have less invasive surgery have fewer complications, better QoL, recovery of physical activity compared to open surgery. This effect is preserved even in frail patients.
4. Patients undergoing surgery can have their activity level monitored before and after surgery by an accelerometer.
5. Patients with frailty have lower pre-operative physical activity score.
6. MDT personal wants additional frailty data and addition of Edmonton Frail Score data changes MDT decision making.

3.2 Rationale for Current Study

Clinicians need accurate data to risk stratify patients during preoperative assessment in order to optimise them for surgery, in order to predict outcomes with or without surgery and in order to support decision-making.

Frail patients have reduced physiological reserves to tolerate major surgery and, in some cases, their life expectancy may be greater and quality of life preserved with non-operative management. Frailty is not currently routinely measured in surgical patients, but interest in this area is rapidly growing. In addition, there is a cohort of patients who may benefit from deferring surgery until after a period of focused physiotherapy.

To this end we intend to perform a prospective observation study of patients undergoing cardiac surgery, evaluating their preoperative risks using validated measurement tools, and then follow-up patients over a period of one year.

3.3 Study Objectives

To see if we can determine how adult patients who are undergoing cardiac surgery recover and whether patients can be better stratified into groups at higher perioperative risk, which ultimately can be targeted with healthcare resources to minimise complications and risk of dying.

To study the outcomes of patients aged 65 years or older who undergo cardiac surgery up to one year. Outcomes of interest are mortality, morbidity, readmission, composite complication, reoperation, physical activity, and quality of life.

3.3.1 Measurable objectives

To test the above mentioned hypotheses we conducted the following measurable objectives.

- A) Measure QoL pre- and post-cardiac surgery and evaluate its relationship with pre-operative frailty score.
- B) Quantify habitual physical activity levels in high risk patients undergoing cardiac surgery pre- and post-operatively comparing these measures with disease activity and frailty scores.
- C) Examine the success of implementing accelerometer in real world setting and to objectively measure PA in cardiac surgery patients in pre and post-operatively.
- D) Define the strength of association between PA level and cardiac surgery outcomes.
- E) Identify which frailty measurement tool is most accurate in predicting poor outcome in frail patients undergoing cardiac surgery.

3.4 Research themes

The study will focus analysing 3 key cases.

1. Frailty risk factors & Recovery.
2. Quality of life of frail patient's pre and post cardiac surgery.
3. Evaluation of the influence of frailty factor in cardiovascular meeting and MDT performance.

3.5 General Methodology

This section elaborates the methodology followed in accomplishing this project and offers an overview of the pre-requisite protocol embarked. However for simplicity of reading and understanding chapter specific methodology is omitted in this section and elaborated in-depth in chapter 6.

3.5.1 Study design and strategy

Prospective observational study whereby adult patients facing cardiac surgery were invited to participate in the study by their Consultant or registrar after evaluating patient's medical notes and referral letters and were deemed potential participant in the project. Then at the time of the pre-assessment clinic visit they were approached by the researcher- PhD candidate (YA) and given further information on the study and asked if they would like to take part. Signed consent was taken at this juncture (Appendix 1).

Patients were asked to complete a simple questionnaire including a basic standardised frailty score the Reported Edmonton Frail Scale (Appendix 2) and QoL questionnaires; RAND 36, EQ5-3DL (Appendix 3), taking about 20 minutes. Further data was obtained from patient's records and during their preoperative assessment. This did not interfere or influence the patients planned treatment.

Patients were also shown and asked to wear a non-invasive monitor (a wristband) containing a triaxial accelerometer which will record their level of physical activity in their homes and in hospital before and after surgery.

Participants then underwent surgery and received standard intraoperative and postoperative treatment. At 30 days from discharge from hospital, the proforma was updated with regards to type of surgery performed, duration of operation, blood loss, any readmissions to ITU/HDU, postoperative complications, discharge to home/rehabilitation/nursing home. This information was obtained from their medical notes and dendrite clinical system application- (standard data collection as part of national audit).

Participants were contacted at 90 days, 6 months and 1 year by telephone to assess further postoperative complications, current residence (home/nursing facility), and quality of life.

Alternatively, if more convenient, patients may undergo these assessments by post, while attending follow-up clinic appointments. This was confirmed at pre-assessment prior to surgery which approach the patient prefers to gather follow-up information.

3.5.2 Recruitment, withdrawal and consent

Participation of the study was voluntary and participants had the right to withdraw at any time without prejudice to their treatment or care. Researcher went through in-detail the Patient Information Sheet (PIS) with the participants explaining what the study involves. Prior to study enrolment, Informed consent was obtained voluntary (Appendix 1).

3.5.3 Exclusion criteria

The following quality criteria were applied to minimise the confounding influence of particular variables on the selected research outcome.

- a) Participants under the age of 18 years of age were excluded from the study.
- b) Participants who are unable to consent to surgery or research (e.g. severe cognitive impairment, emotional distress, unconscious).
- c) Wheelchair bound or patients with compromised mobility.
- d) Emergency and urgent admission due to lack of sufficient time to take consent as well as pre-operative evaluation and measurement.

3.5.4 Study Environment

This research project focused on the patient in the department of cardiothoracic surgery, Hammersmith hospital. The hospital is one of the five hospitals that make up Imperial college healthcare NHS Trust. The cardiothoracic unit provides surgical service to mostly west London population, regional area and private patients from all over the world.

The division of cardiac surgery performed 859 cardiac cases and a further 549 thoracic surgery in the financial year 2011-2012 (theatre log book and SCTS data).

It has three full time dedicated operating rooms that can function simultaneously. From the operating room patients are taken to a recovery unit that has a capacity of 8 beds, from recovery, patients are taken to CICU ward with bed capacity of 16, the patients are planned to stay in this ward for a period of between 2-3 days depending on the individual patients needs ie lack of any complication means they will proceed to another cardiac surgery ward with a bed capacity of 20. It's from this ward that their discharge destination is planned as well as their next appointment and the rehabilitation regime that they will need to undergo.

3.5.5 Study outcomes

Primary outcome: Change in quality of life.

Secondary outcomes: Re-admission, Re-operation, Mortality and Complications at 30 days, 90 days, 6 months & 1 year postoperatively. Length of hospital stays (LoS), Post-hospital discharge destination, and Physical activity before surgery and following surgery.

The analysis of the 3 cases has been structured to answer the following research objectives:

1. Is there a reliable pre-operative risk assessment way that might increase the predictive power of existing cardiac risk prediction models in the elderly population and can help facilitate clinical decision-making?
2. Demonstrate potential improvement in quality, safety, efficiency and motivation as a result of the changes in patients QoL perception.
3. Can the underlying process of MDT decision making for the selection of patient for cardiac surgery influenced by frailty scores and patient outcome reports.

3.6 Frailty and QoL Score Tools

3.6.1 Reported Edmonton Frail Scale

The Reported Edmonton Frail Scale (REFS) is the upgraded version of the old (EFS) and is by far most robust tool in screening frailty in a clinical setting. It has been validated in surgical assessment of patients undergoing surgery hence we utilised REFS in this study due to the following reasons:

- (i) REFS are a reliable tool that has been validated [161] and used by a body of different research studies [162]
- (ii) It associates moderately well with the Geriatrician's Clinical Impression of Frailty (GCIF), cognitive impairment, increasing comorbidity and functional impairment,
- (iii) It has been proven to have excellent inter-rater reliability when administered by researchers without medical training and takes about 5 minutes to complete the assessment.

The REFS samples 9 main domains with a maximum frailty score of 18. One domain – the clock test for cognitive impairment is used to test performance-based items. The other domains are general health status, mood, functional independence, medication use, social support, nutrition, continence, self-reported performance measuring physical activity, burden of medical illness and quality of life which are all standard historical items in geriatric assessment.

It further categorises patients based on their score (between 0 and 18) into different groups as shown below.

Domain	Item	Score 0	Score 1	Score 2
Cognition	Please imagine that this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions then place the hands to indicate a time of 'ten after eleven'	No errors	Minor spacing errors	Other errors
General health	In the past year, how many times have you been admitted to a hospital?	0	1-2	2 or more
	In general, how would you describe your health?	Excellent/ very good/ good	Fair	Poor
Functional independence	With how many of the following activities do you require help? (meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications)	0 -1	2 - 4	5-8
Social Support	When you need help, can you count on someone who is willing and able to meet your needs?	Always	Sometimes	Never
Medication	Do you use five or more different prescription medications on a regular basis	No	Yes	
	At times, do you forget to take your prescription medications?	No	Yes	
Nutrition	Have you recently lost weight such that your clothing has become looser?	No	Yes	
Mood	Do you often feel sad or depressed?	No	Yes	
Continence	Do you have a problem with losing control of urine when you don't want to?	No	Yes	
Self-reported Performance	Two weeks ago were you able to:			
	(1) Do heavy work around the house like washing windows, walls or floors without help?	Yes	No	
	(2) Walk up and down stairs to the second floor without help?	Yes	No	
	(3) Walk 1 km without help?	Yes	No	

Table 3 - 3.1 Scoring for the REFS (/18)

Not Frail: 0 - 5 Apparently Vulnerable: 6 - 7 Mild Frail: 8 – 9 Moderate Frail: 10 -11 Severe Frail: 12 – 1

3.6.2 EQ-5D-3L

The European Quality of Life Group trademarks EQ-5D™ was founded in 1987 by multilingual international researchers from Europe across different learning fields. The goal was to develop an easy to use, patterned, non-disease specific tool that could assist in the description and evaluation of health -related QoL [163].

The EQ-5D questionnaire is quite simple making it uncomplicated for the participants to answer and understand the questions. It allows it to be administered either individually or in an interview to generate a descriptive profile and a single index value that can be useful in medical studies. The questionnaire is divided into 2 main parts

The descriptive system is made up of 5 questions which reflect the 5 different dimensions. This include: ‘Mobility, self-care, usual activity, pain/discomfort and anxiety/depression’. The parties answering the questionnaires are expected to choose one answer out of 3 likely levels provided. They could tick no problem, some problem or extreme problem based on the one they consider to be most comparable to their health.

The score of the EQ-5D is calculated by adding the five dimension scores to create a 5 digit number which enables the state of the health of the respondents to be explained. For each dimension the response results in a one-digit number that is from 1-3.

Using the Visual Analogue Scale (EQ-VAS), participants are requested to rate the state of their health using a 20-cm vertical graph of analogue scale which ranges from 0-100, zero representing the worst imaginable health status and 100 representing the best imaginable health status. They are required to draw a line from the box marked “Your health state today” to the point on the scale they deem to be appropriate. Therefore, the results will give an image of the overall self-rating health status. All around the world especially in Europe the

use of EQ-5D has been approved in hundreds of studies both economically and clinically on an extensive array of health conditions [163].

3.6.3 Medical Rand 36-Item health survey

It was in 1948 when the World Health Organisation officially adopted the concept of health in a society and defined as a “state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.”[164]. It is interesting to note at that time there were no tools to measure health and it was not until decades later that interest to utilise a comprehensive set of tools to measure physical, mental, and social vitality of an individual health has grown.

Among the foremost and most widely used tools developed to measure health-related quality of health (HRQoL) is the Medical RAND-36, which is a profile based measurement tool that consist of 36 items that scores eight health concepts figure 1 namely: (1) physical functioning (PF) that assess 10 items stretching from vigorous activities such as running, lifting heavy objects, strenuous sports or walking to moderate activities such moving table, bowling or playing golf bathing, as well as dressing, bending and bathing. This captures and scores both the existence and the degree of any physical limitation; (2) role limitation due to physical health (RPL) consist of 4 items, signifying the extent of physical role limitations in relation to his/her age and perceived social activity participation, with low scores indicating difficulties with work and other related social activities; (3) bodily pain (BP) measure two items that highlights the intensity of bodily pain and the magnitude that instigates hindrance with daily activities, including work or walking alone outside of residence or home; (4) general health (GH) scores for four items that reflects patients own rating and self-awareness of perceived general health as well as the patient’s opinion, attitude, and expectations toward their health status; (5) vitality (VT) on the other hand consist of four items that evaluates energy levels

and fatigue; (6) social functioning (SF) measures two items that assess the effect of physical or emotional problems on social activities and interactions with family, friends, and neighbours); (7) role limitations due to emotional problem (RLE) consist of three items and evaluates the impact of emotional problems and individual spirit or interest on accomplishing specific task or other daily activities; and finally (8) Emotional well-being (EW) scores for 5 items assessing incidence of mental health problem and in particular the major mental health dimensions such as depression and anxiety, psychological well-being and the ability to self-control emotional distress.

RAND-36 is a robust tool that gives scale scores and two summary scores (physical and mental); with its eight score dimensions formulated from the RAND 36-item which was originally modified and selected from a larger pool of instruments participated by patients recruited to RAND Medical Outcome Study (MOS) [165, 166].

The RAND-36 takes about 7-10 minutes and it can either be self-administered or a trained researcher can easily administer via telephone or face to face.

Several studies has utilised RAND-36 as a generic profile HRQoL measures, comparing the relative burden of disease for patients with diverse chronic illness [165, 166].

3.6.3.1 Scoring RAND-36

When scoring RAND-36 for health survey two principles are followed: (1) the pre-recorded values are documented in accordance with the scoring key developed. Furthermore each item score is converted to between 0 to 100 ranges. Scores represent percentage of total possible score attained. This way premature overlap of score in item 20 and 32 is avoided and both item are scored in the same direction. (2) Items in the same scale are averaged together to create the 8 scale score as shown in the figure below.

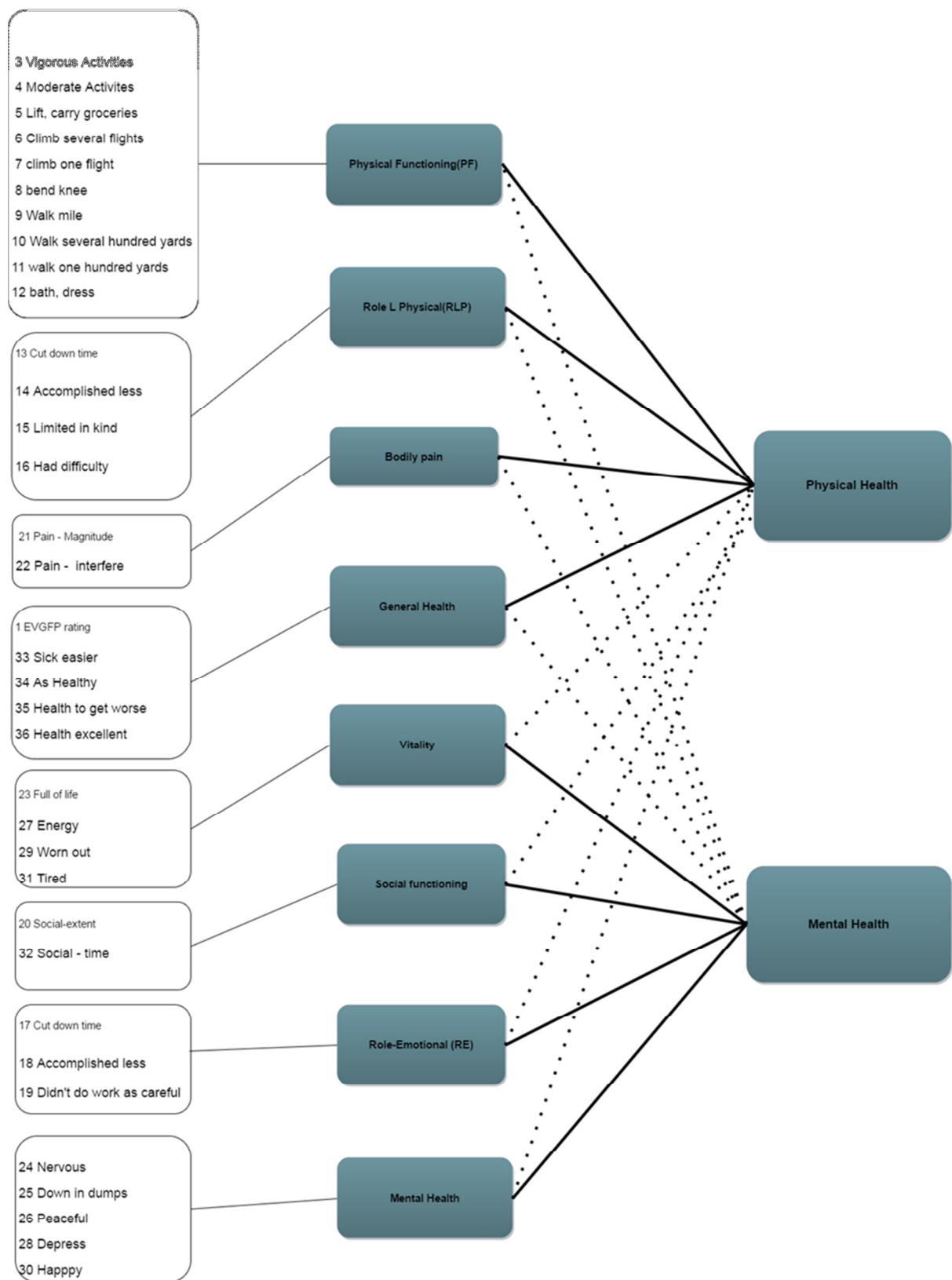


Figure 13 - 3.1 shows RAND-36 with its multi-item, multi-domain health survey, with a measurement model that has three levels: items, domains, and component summary.

3.7 Regulatory issues

3.7.1 Ethics approval

Our overall assessment of this project was that it is a low-risk one, which does not raise any serious ethical issues whatsoever and needs only local (ICL & ICHNT) ethic review. Specifically, we were performing this project and it does not involve biopsy or sample extraction. No individual will be put at risk given the complete anonymity and non-invasiveness of the project. Despite this, we felt it is important to get ethical review for two reasons:

1. It is accepted good research practice to ensure some form of ethical review is required
2. In order to publish in a reputable peer reviewed journal some form of ethical review will be required.
3. To comply with national and international guidelines such as the statement below:

“The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that “every clinical trial must be registered on a publicly accessible database before recruitment of the first subject”; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry”[167]

Initial application to NRES Committee South Central Hampshire (Bristol) did not find the application suitable for Proportionate Review. Please see attached letter. Also study application was judged invalid and in need of resubmission on grounds the application form had been completed incorrectly:

1. The study needed to be 'Basic science study involving procedures with human participants'
2. Providing the checklist and full supporting documentation
3. Clarification that Chief Investigator in section A22 is Mr Yusuf Abdullahi (PhD student)
4. The signature of the Lead Sponsor (C. Buicke).
5. The signature of the Educational Supervisor (T. Athanasiou).
6. Electronic authorisations or wet ink on the hard copy form.

This submission has been amended accordingly and all requirement achieved leading to the start of the recruitment.

Joint Research Compliance Office
Academic Health Science Centre
Imperial College London and
Imperial College Healthcare NHS Trust
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Christine Bulicke
Research Governance Manager

03/06/2014

Mr Yusuf Abdullahi
Research Fellow
Imperial College London
Hammersmith Hospital
Du Cane Road
W12 0HS

Dear Mr Abdullahi

RE: JRCO Study Approval

Project Title: Using Quality of Life and Frailty as Predictors of Recovery in Cardiac Surgery Patients

Joint Research Compliance Office Reference number: 14HH2016

Ethics reference number: 14/LO/0693

Principal Investigator: Mr Yusuf Abdullahi

I confirm that this project has now been approved by the Joint Research Compliance Office. The project may now start at Imperial College Healthcare NHS Trust sites. Please note that the start date of the project is the date of this letter and the duration is the same as that provided in your application form.

The list of documents reviewed and approved by the Joint Research Compliance Office under requirements of the Research Governance Framework are as follows:

Document	Version	Date
Participant Consent Form	2	27 May 2014
Participant Information Sheet	2	27 May 2014
REC Application Form		07 April 2014
Protocol	1	15 November 2013
Non-validated questionnaire (Medical RAND)		
Validated questionnaire (Revised Edmonton Frail Scale)		
Validated questionnaire (EQ5D)		
SSI form		07 April 2014
REC Approval Letter		02 June 2014

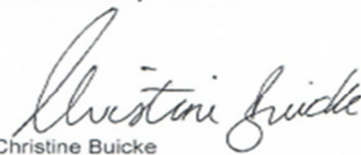
Before you commence your research, please note that you must be aware of your obligations to comply with the minimum requirements for compliance with the Research Governance indicators 17 (Data Protection); 25 (Health and Safety) and 22 (Financial Probity). Details of the requirements to be met can be found in the Research Governance Framework available on www.dh.gov.uk.

Under the Research Governance regulations, Serious Adverse Event Reports, Adverse Reactions and amendments to the protocol or other supporting documents must be forwarded to the Joint Research Compliance Office and Ethics Committee.

In accordance with the Research Governance Framework, research projects carried out in the Trust will be randomly chosen by the Joint Research Compliance Office for auditing. Please see the attached checklist for documentation that will be required during the audit.

I wish you well in your research.

Yours sincerely


Christine Bulicke
Research Governance Manager

4.0 Chapter 4

Systematic Review: Accelerometer applications in elderly patients with cardiovascular disease.

4.1 Objectives

The objective of this review is to investigate accelerometers applicability in elderly adults with cardiovascular disease undergoing surgery and evaluate focusing on the validity, reliability and feasibility of their use.

4.2 The measurement of activity level

Measuring activity levels on older institutionalised people especially outside of a laboratory environment is a demanding task [114]. In hospitalised elderly patients monitoring the activity levels may contribute to implementation of changes towards improved mobility and functional independence. Different methods have been tried in the past for estimation of activity levels and these include: questionnaires, energy expenditure measurements and activity monitors (AM), the latter being amongst the oldest tools used [115]. AM have evolved over time from pedometers to uni-, bi- and tri-axial accelerometers [116]. It has been reported that pedometers were first invented by Leonardo da Vinci in the 1500s [114], but it wasn't until the 1980s that accelerometers, providing an integrated method of measuring PA, were developed [117].

Accelerometers are electronic motion sensors which later evolved with the capacity to detect any mechanical force and thus any bodily acceleration. The acceleration measured is represented as a voltage which is then converted into counts; the greater the count, the greater the intensity of physical activity (PA) [118]. Accelerometers have been authenticated in labelled water techniques (indirect calorimetry) [168], and their measurements have been

found to be directly proportional to energy expenditure [120]. Algorithms which are inbuilt into the devices are used to convert energy expenditure into the counts which can then be categorized into light, moderate, or vigorous intensity levels depending on the degree of energy expenditure. The threshold for the intensity of exercise was described by Esliger et al [121]. Thus, accelerometers allow the determination of both the quantity and intensity of any activity and can be used to describe the sum and distribution of PA [114, 116]. The past few decade's accelerometers have further evolved into small, lightweight instruments, which can measure acceleration in one, two or even three axes and store data minute by minute [116].

Studies have revealed that the most popular accelerometers in PA research are the Actigraph uniaxial GT1M accelerometer and the triaxial GT3X accelerometer which was developed and released much later [121, 122]. Whilst the GT1M measures both static and dynamic accelerations, the GT3X measures accelerations in three planes of motion and provides an overall value of PA [123]. Apart from this a biaxial accelerometer also exists which measures PA in two axes [116].

As the GT3X measures PA in more axes it should in theory also provide a more reliable assessment of PA. Originally the ActiGraph uniaxial accelerometer, worn on the hip, was the most used accelerometer. It was used in the 2003-2006 National Health and Nutrition Examination Survey (NHANES) to give the largest database of monitored PA. However, the 2011-2014 NHANES used the ActiGraph GT3X+ accelerometer which was worn on the wrists [124]. It was shown that wearing an accelerometer on the wrist instead of hip increased compliance and also allowed for the examination during sleep; with triaxial they were able to measure a wider range of movements. In terms of analysis although linear regression models for the uniaxial accelerometers have been shown in studies to be effective in analysing the data, there is limited research validating the algorithms used for the analysis of data collected by triaxial accelerometers [121].

Accelerometers have many advantages when compared to alternative methods of PA measurement. These include being able to track intensity, duration and frequency of an activity [125]. Some accelerometers, such as GeneActive can detect different levels of activity in many planes (triaxial) [120]. This characteristic makes them applicable for use in the measurement of PA in patients with cardiovascular disease. Patients with such disease are increasingly inactive and their low intensity PA may be picked up by accelerometers and would not be accurately measured otherwise.

Why do we need to measure PA in patients with cardiovascular disease?

PA is described as any bodily movement, produced by skeletal muscles, which results in energy expenditure [126], and has been shown to be fundamental for optimal health and wellbeing [125]. It has also been shown to both improve the quality of life, readiness for discharge reducing the mortality of patients with cardiovascular disease [128, 129, 169]. However, there is no routine practice to quantify activity level in a clinical setting, showing a gap in the overall assessment of a patient before discharge.

Scientific evidence has repeatedly linked PA to cardiovascular health outcomes, with the overall view being that individuals who partake in PA regularly are less likely to develop coronary heart disease (CHD) and heart failure (HF) [130] PA is not only one of the major risk factors for the development of cardiovascular disease, but also has a favourable effect on many of the other risk factors. Regular PA and exercise can help reduce blood pressure, the LDL and total cholesterol levels and can increase glucose control in diabetics [130] PA is therefore one of the core focuses for the prevention of cardiovascular illness via cardiac rehabilitation [131]. With a lack of PA being a modifiable risk factor for cardiovascular

disease [116], PA and it's monitoring, becomes crucial in the management of cardiac patients [132]

Our aim is to (i) review studies that validated accelerometer as a reliable activity monitor in patient with cardiovascular diseases. (ii) Verify accelerometers validity, feasibility and the adherence to physical activity recommendations when using it; (iii) identify the accelerometer type with the strongest predictive value test in relation to reported outcomes.

4.3 Methods

4.3.1 Literature Search Strategy

Data was sourced from EMBASE, CINAHL, MEDLINE, Cochrane, PubMed and other web based science electronic database for the period from 1980 to 2015. The following search terms were used to retrieve potential published articles for inclusion: ('Older', 'Frail', 'Elderly') AND ('Cardiac surgery', 'Thoracic surgery', 'Cardiovascular disease',) AND ('accelerometer', 'accelerometry',) ('Risk', 'Risk stratification', 'outcome',).

4.3.2 Study Inclusion Criteria

Selection criteria included (i) studies defining accelerometer as a measuring instrument, validating its reliability, validity and feasibility in assessing physical activity (ii) studies based on a patient population with known cardiovascular diseases and or in rehabilitation or under intervention; (iii) studies offering predictive value test on accelerometry tools outcomes (iv) studies that validated the use of accelerometers (+/- pedometers) to define human postural movement and mobility in a medical context.

The review will include as variables: study population, accelerometer type and body position of device, study setting, duration, method, result and limitation of each validated study.

4.4 RESULTS

Our literature search yielded 1461 studies, of which 17 articles fulfilled our inclusion criteria. A flow chart of our search results according to PRISMA guidelines is shown in Figure 4.1. Overall, 4 different accelerometry types were used in cardiovascular intervention or cardiac and thoracic surgery table 4.1. The algorithm performance of these tools was reported by Kaplan Meir analysis, Chi-square, regression, OR and 95% confidence intervals (CI) [Table 4.1.]

Figure 14 - 4.1: Flow diagram of study selection

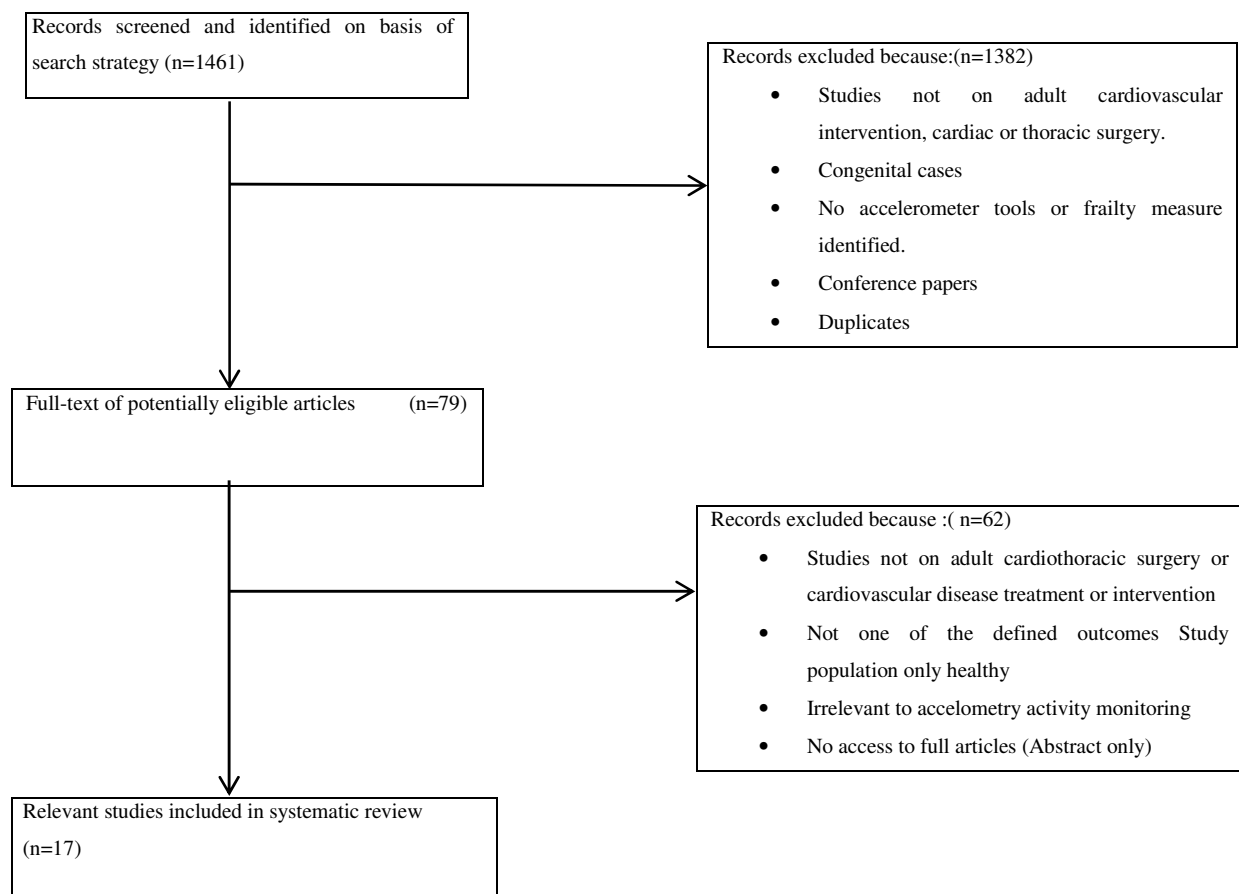


Table 4 - 4.1 Synopsis of current literature on Accelerometer

Reference Publication Year	Subjects	Mean Age (range) (y)	Accelerometer Device(s) (frequency, range)	Device Position(s)	Study Setting	Duration	Experimental Design (validation)	Classification Algorithm	Algorithm Performance	Limitations/Future Work
Wetzler et al, 2003	10 Hypertensive or cardiac disease patients, 16 healthy subjects	50	2 Biaxial (25Hz, $\pm 2g$)	Thigh	NA	30min	Routine: lying, sitting, standing, walking with no predefined order (direct observation)	NA	Misclassification rate: standing (0%), walking (0%), lying (1.37%), sitting (10.71%)	Second sensor required at thorax for accurate detection of lying and sitting
Van den Berg-Emons et al, 2000	10 Patients with stable congestive heart failure	(34–72)	4 Uniaxial (32Hz)	2 on sternum, 1 on left thigh, 1 on right thigh	Home	45min	Daily routine	k-Nearest neighbor	Sensitivity: lying (97%), standing (90%), sitting (89%), walking (86%), walking stairs (49%), cycling (97%)	Slow walking detected as standing, walking stairs detected as walking, lying detected as sitting
Bidargaddi et al, 2007	Cardiac outpatients	NA	1 Triaxial (75Hz)	Waist	Hospital	1hr	Routine: biking, rowing, walking on stairs, arms exercise, walking on treadmill, ball workout (self-report)	NA	Sensitivity and specificity: walking (89%, 90%)	Further validation required to verify accuracy under free-living conditions and with different patient and age groups
Buman et al, 2015	21 women with BMI 29.27 $\pm$ 7.43	30-64	Actigraph GT3X+ - a micro-electromechanical system. GeneActive - microelectromechanical sensor 10-100Hz. SenseWear Mini - triaxial accelerometer.	Actigraph - non dominant hip, Geneactiv- wrist, Sensewear Mini - upper arm.	Home and work	1Wk per sensor	Daily physical activity and sleep behaviour	NA	Wear time was valid on 93.9% (Actigraph), 100% (Geneactiv) and 95.2% (sensewear).	More research is needed across populations and study designs.

Deschamps et al, 2013	149 following cardiac surgery. Procedures included: CABG, CABG with valve surgery, valve surgery.	52-90	Fitbit wireless accelerometers	Ankles	Hospital	5-7 days (LoS)	Daily mobility	NA	Sig-differences in mobility SNF or HHC $p<0.001$ by Kruskal Wallis test. $P<0.05$ b	The first day post ICU was designated as recovery day 1, this is when the accelerometers were fitted. However length of stay included time spent in ICU.
Kolb et al, 2012	73 ICD/CRT recipients	60+/- 20 years	External accelerometer: Aipermotion 440	Trousers in an anterior posterior position.	Home	7 days	5 different modes of PA:	t-test and variance, Spearman's rank correlation, multivariate regression analysis.	A strong sig correlation in 70% of patients, between measurements of ICD/CRT and the external accelerometer $r>0.7$.	ICD/CRT measurements need prior validation with external accelerometry prior to use for prognostic information.
Dendale et al, 2013	80 coronary artery disease patients who completed phase 2 cardiac rehabilitation	NA	Triaxial accelerometer	NA	Home	18 weeks	Daily physical activity	Shapiro Wilk test, Mann-Whitney U test, Chi Square test, Wilcoxon signed ranks test, Spearman, Kaplan Meir curve.	Kaplan Meir analysis showed a trend towards fewer re-hospitalisations for patients in the telemonitoring group.	Larger trials will be necessary in the future to confirm the hypothesis that the physical activity telemonitoring program reduces the number of re-hospitalisations.
Cooper et al, 2003-2006	3370 adults from the NHANES study	20-65	Actigraph model 7164	Right hip	Home	7 days	Daily PA	NA	NA	Access to objective and accurate data of PA are required

Cipriano et al, 2013	16 male patients with heart failure	NA	Actigraph GT3X - triaxial accelerometer. 0.25-0.5 Hz	Right hip	Home	7 days	Steps per day, total light, moderate and vigorous physical activity	Pearson correlation, p<0.05 was considered significant	NA	Small dataset, only male subjects with ischemic HF included (limiting the applicability of the findings to female subjects and those with other forms of HF). Future research should address these issues.
Karunanithi et al, 2007	Patients undergoing cardiac rehabilitation	NA	triaxial accelerometer	Waist	Hospital	One hour, twice a week, for six weeks	Biking, rowing, walking, arms exercises, walking on a treadmill, ball workout.		Signal vector magnitude (SVM) based measure was the most efficient (89.14% sensitivity and 89.97% specificity)	Future work will include integration of the current algorithm into a care assessment platform.
Pathak et al, 2012	80 stable cardiac patients at 2 months/1 year after a cardiac rehabilitation program	NA	Uniaxial accelerometer	Waist	Hospital	3hrs/day,	Ergocycle, treadmill, outdoor walking	Chi squared test, ANOVA	NA	Most subjects were men, marital status, educational level, employment status and household income were not indicated and could have influenced PA.
Dalman et al, 2014	24 patients with AAA disease	71+/-3 years	Uniaxial accelerometer	Anterior superior iliac spine along the anterior axillary line	Home	3 days	Daily PA	ANOVA, linear correlation and intraclass correlation coefficients.	Difference in HRs accelerometer p<0.001 and 3-DR questionnaire) p<0.1. Acc and 3-DR had the highest agreement with a coefficient of variation of 7.9% and r=0.86.	Oxygen uptake not assessed. Adult patients from the AAA-STOP trial and the results may differ in younger patients with other conditions participating in the cardiac rehabilitation program.

Koehler et al, 2013	155 patients with chronic heart failure (NYHA class 2-3)	>18	Triaxial accelerometer	Hip	Home	Monthly 6MWT	6 minute walk test	NA	Accelerometer accuracy within 99th percentile. Sig. correlation between step count, walking speed and measured 6MWT distance $r=0.80$, $p<0.001$.	All patients walked on flat surfaces; however accelerometry is not limited to flat surfaces.
Hager et al, 2009	57 patients with congenital heart disease following TCPC	Aug-52	Triaxial accelerometer	Waist	Home	3 days	Daily physical activity	NA	NA	Measurement of daily activity was affected by weekday and weekend alteration. Recording of daily activity over one week should be aspired.
Tu et al, 2009	55 patients with high disease burden following CABG	>65 years	Triaxial accelerometer	NA	Home	3 days	Daily physical activity	NA	NA	The interventions were not tailored to CABG patients with a high disease burden. In the future more tailored interventions should be used to the needs of the subjects.
Paul D.Loprinzi et al, 2015	377 adults, at an elevated risk of CVD within 10 years.	48-79	Actigraph 7164 accelerometer							
van den Berg-Emons et al, 2000	24 patients with AAA disease	34-72	4Uniaxial (32Hz)	2 on sternum, 1 on left thigh, 1 on right thigh	Home	45min	Routine: sleeping, watching TV, standing, dressing, washing dishes, walking stairs etc (video camera)	k-Nearest neighbor	Sensitivity: Lying (97%), standing (90%), sitting (89%), walking (86%), walking stairs (49%), cycling (97%)	Slow walking detected as standing, walking stairs detected as walking, lying detected as sitting

4.5 Discussion

Validity and reliability

The experimental design dictating the parameters used to assess the validity of the accelerometers differed between the studies. The steps taken per day, the intensity of exercise (light, moderate or vigorous) and daily PA and energy expenditure were amongst the most frequently used parameters.

Da Silva et al [133] measured steps per day as well as the intensity of exercise using a triaxial accelerometer. They concluded that PA assessed by accelerometers is significantly associated with key cardiopulmonary exercise testing variables ($p < 0.05$), indicating that accelerometers are valuable in their measure of PA. In addition, another study by Cook and colleagues [134] evaluated the number of steps using a triaxial accelerometer and reported the mobility data from the accelerometry in patients who had cardiac surgery following their procedures has great potential and is effective in the assessment of surgical recovery. Likewise Sato and team [135] also measured the number of steps and energy expenditure using a uniaxial accelerometer and concluded that both parameters correlated with oxygen consumption ($p < 0.01$ and $p < 0.05$ respectively).

Two studies [170, 171] evaluated intensity of exercise using a biaxial accelerometer and uniaxial accelerometer respectively worn by patients with cardiopulmonary disease or CAD; Nguyen concluded PA monitoring using accelerometry provided fundamental information, which is not captured by other investigations in patients with cardiopulmonary disease whilst Karjalainen reported that the validity of the accelerometer was confirmed by Bidargaddi and team [172] and as the device allowed the measurement of PA at up to 5 different intensities it provides invaluable information and new perspectives in the study of PA

Furthermore, Pressler et al [132] analysed steps as well as intensity of activity when comparing the use of an implantable cardiac defibrillator (ICD) to accelerometry in the measurement of PA in patients with ICDs. This study found that data from ICD differs substantially from accelerometers and is not as precise when measuring the amount of PA. Overall the findings from these studies suggest that the number of steps and intensity of exercise are accurate measures of PA, indifferent to the type of accelerometer used (uniaxial, biaxial or triaxial). Daily PA was also one of the commonly used parameters amongst the studies.

Luke et al [173] investigated daily PA and analysed the activity counts per minute as well as the number of minutes in 1-minute bouts of exercise in adults from the NHANES study using a triaxial accelerometer. They found that both measures were significantly negatively associated with diabetes and hypertension, the odds was 20% lower for hypertension and 35% lower for diabetes with one standard deviation increase in PA. However, the estimates of activity measured by accelerometry differed to the patients' objective quantification of PA in self-report. This led to the conclusion that there is either a bias in the self-reporting by patients or an inaccuracy in the measurement by accelerometry and further studies are needed to confirm this.

On the other hand, Myers et al [174] who also measured daily PA in patients with abdominal aortic aneurysm disease using a uniaxial accelerometer, found a high agreement between accelerometry and a 3-day recall questionnaire (coefficient of variation of 7.9% and $r=0.86$). It was therefore concluded that accelerometry provides a valid reflection of energy expenditure and PA. However, this study included only 24 patients, therefore a larger sample would be needed to confirm the findings. Barnason and colleagues [175] measured daily PA in patients with a high disease burden following cardiac bypass surgery. The measurement of PA was carried out using accelerometry as well as an activity diary, both methods yielded

similar results suggesting that accelerometry is a reliable and accurate measure of PA. Contrastingly, Bidargaddi and team [172] used accelerometers to assess the PA in patients undergoing cardiac rehabilitation. The patients wore the accelerometers for one hour twice a week for a period of six weeks whilst carrying out various activities including: biking, rowing, and walking on a treadmill and a ball workout. They concluded that using a signal vector magnitude based measure; accelerometry had 89.14% sensitivity and 89.97% specificity. This shows that accelerometers are valid tools of the assessment of strenuous PA as well as daily PA.

In addition, Guiraud et al [176] used a uniaxial accelerometer to assess PA patients, following their cardiac rehabilitation, carrying out activities such as ergocycle, treadmill and outdoor walking. They found that knowledge on how to improve adherence to rehabilitation exercise and psychological motivation for patients is under researched but the instrument is valid for rehab programs. Jehn et al (31) used a triaxial accelerometer to assess the PA of patients with NYHA class 2 heart failure and asked them to perform a 6-minute walk test. In their study they found a significant correlation between step count, walking speed and distance ($r=0.8$, $p<0.001$) and determined that the accuracy of accelerometry was within the 99th percentile.

Feasibility

Feasibility refers to the application of the device by professionals as it also defines many aspects of the tool itself. The choice and the precise positioning of the device plays a crucial role. The accelerometer device was positioned in differing places and for different amounts of time in each of the studies. The device positions included: waist, wrist and hip. The accelerometers were either worn whilst the patients were in hospital during exercises or for a fixed period of time at home. Continuing, we will check the feasibility of the different methods.

The most frequent device position used in the studies was the accelerometer worn on the hip. Da Silva (n=16) patients found that the use of a triaxial accelerometer worn on the hip for 7 days was a reliable way to measure PA in patients. The study by Luke (n=3370) [173] patients applied accelerometers worn on the hip and reported no limitations of accelerometry recording in this way. Similarly, another three studies [132, 174, 177] all positioned accelerometers in the hip and reported similar reliability outcome.

On a related note, one study by Huberty et al [178] highlighted the validity and feasibility of three different types of triaxial accelerometers positioned in different places. The three devices were: the actigraph GT3X+ worn on the non-dominant hip, the GeneActive worn on the wrist, and the Sensewear Mini worn on the upper arm. It was determined that the GeneActive accelerometer was more valid than the Sensewear Mini or the Actigraph accelerometers (validity: 100%, 95.2% and 93.9% respectively). Furthermore, they concluded that not only was the GeneActive more reliable, the position of the device (wrist) was also preferred by patients' comparative to the Actigraph (hip). The patients found that the accelerometers worn on the upper arm and wrist were easier to wear and preferable to the device worn on the hip (satisfaction: 68.4%, 80% and 47.6% respectively).

In the study by Karjalainen et al [171] the accelerometers were also worn on the wrist by patients. This was a new technique in which a uniaxial accelerometer device was integrated into a wrist watch. He noted the composition of the device makes it very easy to use comparative to alternative accelerometers. The device was used to measure PA over 5 days, highlighting the feasibility of the wrist position of the device.

Two studies by Bidargaddi et al [172] and Guiraud et al [176] used accelerometers which were worn on the patients' waists. Bidargaddi describes that this conferred an accurate measurement as this accelerometer placement is close to the patients' centre of mass. In both

studies the device was worn for a set period of time when the patients were in hospital, or as outpatients whilst carrying out activities such as biking, rowing, treadmill etc. Even though different devices were used in the studies, triaxial and uniaxial respectively, both studies concluded that the use of the devices in this way was a reliable method of measuring PA.

Limitations

This study benefits from systematic analysis of the largest number of studies of accelerometry use in patients with cardiovascular disease. The studies used included not only different accelerometer devices, but also different tools to validate the accuracy and reliability of the devices. However, overall some weaknesses were noticed. (i) in the initial phase of the review, studies were used if their titles included (elderly, frail, validity, reliability, cardiovascular, outcome etc), if studies didn't include these phrases in their titles it is possible that they may have been missed, (ii) most of the studies sample size was small, and the majority of the patients were male, limiting the applicability of their findings to female patients in some cases, (iii) there was also variability in study design and very few were randomised, (iv) power analysis was not stated clearly across studies and data was not fully available for standard cardiovascular outcomes in all studies, (v) additionally many of these studies failed to report on common endpoints which limited formal meta-analysis. Finally, the studies included different patient groups. Therefore, it was not always possible to compare the studies and effectively conclude on the validity, reliability and feasibility of the use of accelerometers in patients with cardiovascular disease.

Conclusions

Through our review on the use of accelerometers to measure PA in patients with cardiovascular disease we aimed to assess the validity, reliability and feasibility of different accelerometer devices. Our search yielded 17 papers specific to patients with cardiovascular disease +/- risk factors. We assessed the feasibility of the devices based on where they were worn by the patients. All studies confirmed that the placement of the accelerometers on the hip, waist or wrist conferred reliable measurements, however a comparison showed that placement on the wrist was not only more accurate but also more comfortable for the patients. With respect to the validity and reliability of the devices, no significant difference was found between the devices and it was highlighted that further studies will be needed to confirm the reliability of these devices in all patient groups.

Main Points

- Studies are required to investigate in depth their interrater reliability, test-retest when quantifying reliability of the accelerometer type used.
- Overall the sensitivity of this review instruments used was good when measuring their feasibility.
- All studies confirmed that the placement of the accelerometers on the hip, waist or wrist conferred reliable measurements.
- The review highlights the usefulness of screening tools in inpatients hospital care for the identification of frail patients.
- Future studies should report reproducible criteria on how to improve adherence to rehabilitation exercise and psychological factors that hampers patient's motivation to stringently follow prescribed rehab programs.

5.0 Chapter 5

The Impact of Valve Surgery on the Quality of Life of Elderly Patients: Systematic Review.

5.1 Aim: To investigate the impact of valvular heart surgery on the quality of life of elderly patients and highlight the predictors of poor quality of life post-operatively.

5.2 Introduction

The world health organisation (WHO) defines Quality of Life as “individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”[179]

One of the measures of quality of life (QOL) is the Health Related Quality of Life (HRQOL). Interest in HRQOL has significantly increased over the last decade amongst healthcare benefactors. Similarly, patient reported outcomes are also seen as an effective approach to measure QOL.

Furthermore, demographic trends show an undeniable increase in the average population age, particularly the ‘very old’ age group is growing at an unprecedented rate – a prominent phenomenon perhaps best seen in Europe [180]. Understandably, as the general population becomes older, age-related disease such as coronary artery disease and valvular heart disease become increasingly prevalent [181]. To address these problems, the field of cardiothoracic surgery has evolved in ways that see increasingly more complex operations carried out in a plethora of innovative ways to address the needs of an older population.

Some argue that a bygone golden era of cardiothoracic surgery has now been over-run by advances in interventional cardiology such as percutaneous coronary stents displacing coronary artery bypass grafts (CABG) as the new norm. Additionally, newer technologies such as transcatheter aortic and mitral valve replacements are on the rise, being utilized in an

increasingly larger number of patients. While these options may provide an alternative to cardiac surgery, newer surgical techniques coupled with technological advances have demonstrated superior results for many patients groups [182].

To ascertain the benefits of undergoing cardiac surgery, many studies have been published on perioperative mortality and morbidity. Typically, these figures compare surgical intervention to conservative treatment or catheter-based intervention. Statistics on valvular haemodynamic, blood loss and ICU stay are typically lauded when decisions are made whether to operate on patients or not [183]. However, while it must be acknowledged that these outcomes are indeed important, there is an increasing body of interest, particularly in older patient groups that advocates the incompleteness of these measures alone when assessing appropriateness of surgical intervention. Instead, some authors advocate a holistic approach to choosing guiding intervention – that is to say, the likely improvement of QOL[184].

Quality of life is a term which generally encompasses the well-being of individuals, observing life satisfaction, and multiple domains including but not limited to physical wellbeing [185]. Multiple scales exist to measure and quantify well-being, perhaps one of the most commonly used is the Short Form-36 (SF36) which measures well-being (as its name suggests) on a 36 item, 5-point Likert scale short form survey [186]. This survey is also unique in that it has been translated to multiple languages such as German and Arabic [187] to capture data from a variety of population groups. Once all items have been completed, scoring is sub-classified under one of eight domains [186].

From the research already conducted in QOL within a cardiothoracic context, there has been evidence that QOL is generally improve post-operatively compared to baseline levels [188]. Similarly, a large percentage – two-third of octogenarians were able to live independently one

year following cardiac surgery [189]. However, in saying this, a paucity of data remains in certain areas – for example, when assessing QOL following valvular surgery in elderly populations.

Based on the above, it becomes evident that measuring and quantifying QOL for patients undergoing valvular heart surgery is of the utmost importance. As such, this paper will attempt to focus primarily on how QOL is affected by these operations. Furthermore, given the relevance of an aging population in the field of cardiac surgery – this paper will have a focus on this particular age group.

5.3 Method

This systematic review study benefits from the protocol developed based on the preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) [190].

5.3.1 Data sources and search

Data was sourced from EMBASE, CINAHL, MEDLINE, Cochrane, PubMed and other web based science electronic database for the period from 1980 to 2017. The following search terms were used to retrieve potential published articles for inclusion: ('Old', 'Frail', 'Elderly') AND "(Quality of life, HRQOL, PRO, QoL) AND ('Well-being, Physical health, Health status,) AND ('Risk', 'Risk score', 'Risk stratification', 'outcome',). AND (Mini, minimal invasive, minimally) AND (AVR, MVR, Valve surgery, CABG, Cardiac surgery)". Other relevant articles were manually added and referenced.

5.3.2 Study Inclusion Criteria

Researcher (YA) independently retrieved potential articles using the aforementioned search terms. Cross-sectional or prospective studies evaluating the relationship between quality of life and elderly patients undergoing cardiac surgery were sourced. Abstract was reviewed and screened for inclusion. Selection criteria included (i) studies defining frailty and QoL as a multidimensional tool (ii) studies based on a patient population undergoing either cardiac or

valve surgery; (iii) studies offering post cardiac surgery outcome data of elderly patients in relation to quality of life; (iv) articles written in English. Excluded studies were review articles, dissertations, and conference papers.

5.3.3 Evaluation of Quality and Risk of Bias

Quality assessment of each study was performed by attributing a quality assessment score using a modified Newcastle–Ottawa scale [191]. The scale was modified to include all 17 EuroSCORE II cardiac risk factors as well as baseline physical, social and mental health function for comparability. See table 1 for the analysis results. The scoring criteria are shown in Table 2.

5.4 RESULTS

Our literature search yielded 2359 studies, of which 27 articles with a patient population of 5,457 fulfilled our inclusion criteria. A total of nine different quality of life measurement tools were applied in almost all of the articles individually with the exception of two studies that combined one or more tools (Table 5.3). Eighteen studies utilised FS-36 to assess and measure quality of life, Four studies equally used EQ-5D and Nottingham health profile whilst the remaining studies each applied separately the following tools; short form (SF 12), Minnesota Living with Heart Failure (MLHF), Seattle Angina, FPI-R, EBF-24 and SVF-66. Patient aged ranged from 34 to 85 years and included studies sample size ranged from 34 to 762. The procedures undergone by these patients varied in terms of incision method and operation type; open sternotomy was noted as the preferred choice over minimal access. All studies had a follow-up period ranged from 3 months to 8 years (Table 5.3).

Most of the studies reported outcomes including in-hospital mortality, composite outcome and prolonged length of stay along with quality of life, however, studies failed to report on common endpoints which limited formal meta-analysis for these outcomes thereby limiting

our interpretation of the best predictive value or score for quality of life tool to accurately measure valve surgery consequences on frail elderly patients.

Table 5 - 5.1: Quality analysis

Author (no of patients)	Selection			Comparability			Outcome		Total
	1	2	3	4	5	8	6	7	
Detter (140)	-	-	-	**	***	-	*	*	7
Aicher (166)	-	-	-	**	**	-	*	*	6
Grady (370)	-	-	-	*	-	**	*	*	5
Goldsmith (61)	-	-	-	*	***		*	*	6
Notzgold (80)	-	-	-	*	*	-	*	*	4
Zhao (267)	-	-	-	*	***	**	*	*	8
Aboud (136)	-	-	-	-	-	-	*	*	2
Van Geldorp (132)	-	-	-	-	-	***	*	*	5
Tseng (247)	-	-	-	-	-	-	-	*	1
Casali (36)	-	-	-	-	-	-	*	*	2
Machaalany (43)	-	-	-	-	-	-	*	*	2
Markou (415)	-	-	-	***	*	***	*	*	9
Vicchio (520)	-	-	-	***	***	-	*	*	8
Whitlow (78)	-	-	-	*****	***	-	-	*	10
Ussia (39)	-	-	-	-	-	-	*	*	2
Maliwa (312)	-	-	-	-	-	-	*	*	2
Sedrakyan (148)	-	-	-	****	***	-	*	*	9
Florath (392)	-	-	-	*	***	***	*	*	9
Jokinen (184)	-	-	-	****	**		*	*	8
Lam (58)	-	-	-	-	-	-	-	*	1
Zacek (139)	-	-	-	**	***	-	*	*	7
Maisano (225)	-	-	-	-	-	-	*	*	2
Folkmann (154)	-	-	-	-	-	-	-	*	1
Klomp (762)	-	-	-	****	**	-	*	*	8
Vicchio (160)	-	-	-	****	*****	-	*	*	11
Aoyagi (60)	-	-	-	-	-	-	*	*	2
Oliveira (114)	-	-	-	-	-	-	*	*	2

Table 6 - 5.2 Newcastle scoring system

Criteria for quality assessment. Modified Newcastle–Ottawa scoring criteria
Quality checklist
Selection 1. Assignment for treatment – any criteria reported? (If yes, 1-star) 2. How representative was the reference group in relation to the general population for aortic / mitral surgery (If yes, 1 star, no star if the patients were selected or selection of group was not described) 3. How representative was the comparison group in relation to the general population for aortic/mitral surgery? (If drawn from the same community as the reference group, 1-star, no star if drawn from a different source or selection of group was not described. Comparability Comparability variables: (1) age; (2) gender; (3) renal function; (4) extracardiac arteriopathy; (5) poor mobility; (6) previous cardiac surgery; (7) chronic lung disease; (8) active endocarditis; (9) critical preoperative state; (10) IDDM; (11) NYHA; (12) CCS IV; (13) LV function; (14) recent MI; (15) pulmonary hypertension; (16) urgency; (17) combined; (18) physical function score; (19) mental function score; (20) social function score 4. Groups comparable for 1, 2, 3, 4, 5, 6, 7, 8, 9 (If yes, 1-star was assigned for each of these. No star was assigned if the groups differed) 5. Groups comparable for 10, 11, 12, 13, 14, 15, 16, 17 (If yes, 1-star was assigned for each of these. No star was assigned if the two groups differed). 6. Groups comparable for 18, 19, 20 (If yes, 1-star assigned for each of these. No star was assigned if the groups differed) Outcome assessment 6. Clearly defined outcome of interest (If yes, 1-star). 7. Follow-up (1-star if described)
IDDM=insulin dependent diabetes mellitus; MIVS=minimally invasive valve surgery; NYHA=New York Heart Association; ST= standard sternotomy. Comparability includes all the EuroSCORE II risk-factors

Figure 15 - 5.1: Flow diagram of valve QoL study selection

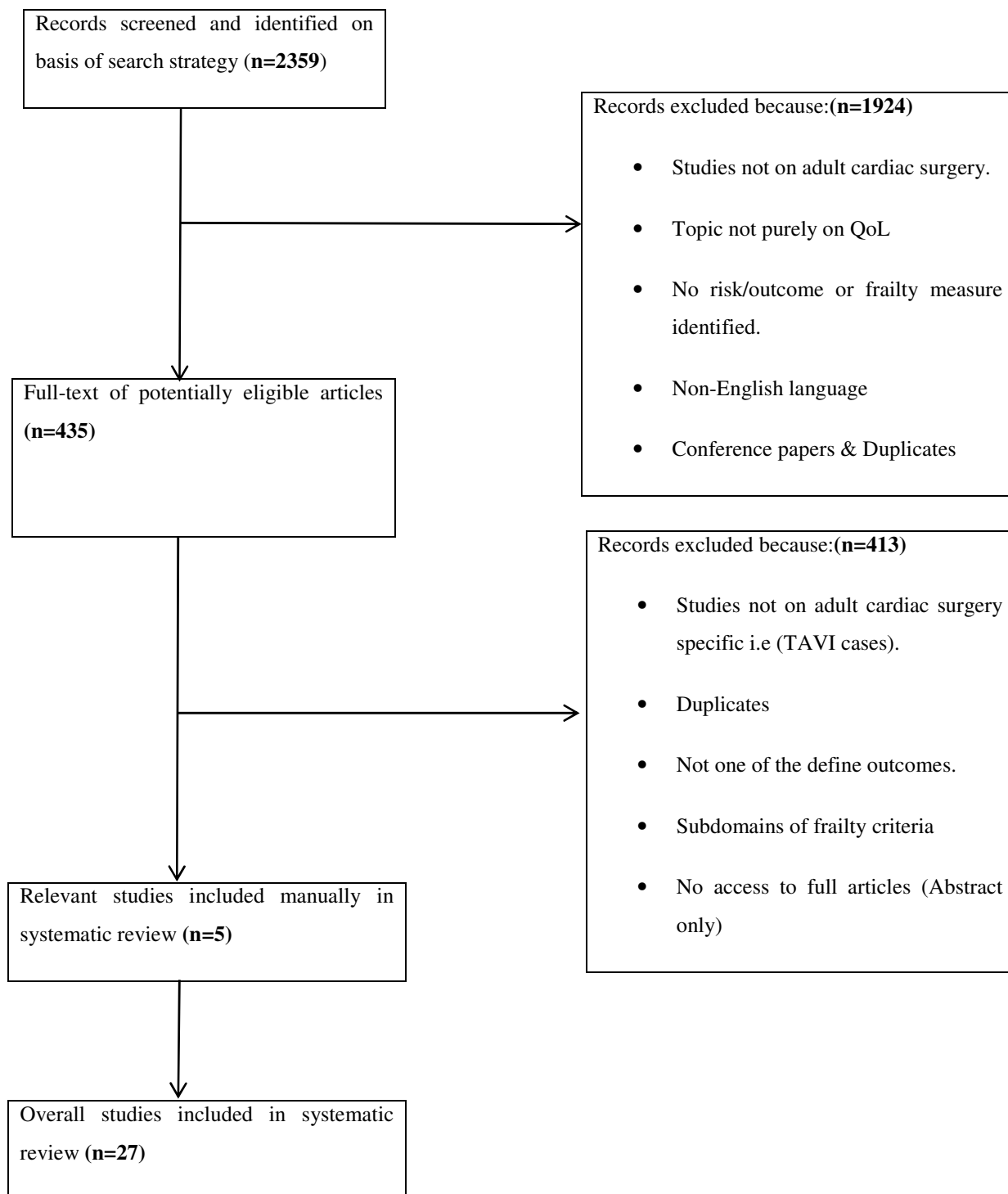


Table 7 - 5.3 - Synopsis of current literature on QoL of valve surgery

Author, year, Ref	Type of cardiac valve procedure	Study type	No. of patients at baseline	Age of patients	Follow-up duration (mean)	QoL Instruments	Conclusion	Physical component improved	Quality score
Detter, 2002 [192]	AVR: Minimally invasive (n = 70) vs. conventional replacement (n = 70)	Retrospective cohort	140	Mean 64.3 years Range 34–83 years	34 months (minimally invasive) 33.1 months (conventional)	SF-36	No significant differences in QoL between the groups at the end of the follow-up	N/A-No comparison with pre or norms	7
Aicher, 2001 [193]	AVR; repair (n= 86), mechanical replacement (n=41), pulmonary autograft (n=39)	Cross sectional study	166	40 +/- 6 (repair) 46 +/- 7 (mechanical replacement) 46 +/- 7 (pulmonary autograft)	3-7 years	SF-36	Aortic valve repair and pulmonary autograft lead to less long term alteration from normal	N/A-No comparison with pre or norms	6
Grady, 2011 [194]	coronary artery bypass grafting, 136; aortic valve repair or replacement, 96; mitral valve repair or replacement, 92; Maze procedures, 46	Single-site prospective, longitudinal observational study	370	61.5 +/- 11.9 years old,	3 Years	SF-36	Health-related quality of life improves early after operations and remains constant long-term independent of procedure	N/A-No comparison with pre or norms	5
Goldsmith, 2001 [195]	Mitral Valve replacement (n=21), Mitral Valve repair (n=40)	Prospective cohort	61	65.9 +/- 12.6 (MV repair) 65.6 +/- 8.4 (MV replacement)	3 Months	SF-36	Significant improvement in QOL following mitral valve surgery, especially in repair. Impaired LV function/high end-systolic dimensions less likely to show improvement in QOL	Significant change in follow up from pre-op in QOL for almost all parameters in repair group, improvement in some parameters for replacement group	6

Notzold, 2001 [196]	Aortic Valve replacement; autograft (n=40), mechanical (n=40)	Retrospective cohort	80	57.58 +/- 10.27 (Ross procedure) 59.18 +/- 10.39 (mechanical)	2.21 +/- 1.29 years (Ross procedure) 1.86 +/- 0.69 years (mechanical)	SF-36 FPI-R EBF-24 SVF-66	Patients with pulmonary autograft have greater benefits in QOL compared to mechanical valve substitutes	N/A-No comparison with pre or norms	4
Zhao, 2007 [197]	Mitral valve repair (n=163), mitral valve replacement (n=104)	Multi-centre Prospective cohort	267	58.1 +/- 12.2 (repair) 61.6 +/- 12.9 (replacement)	12 months	SF-36	After mitral valve surgery, especially mitral valve repair, there is a significant improvement in NYHF class and health status	Scores for PCS were depressed at 1 month for both groups, but they showed marked improvements at 3 and 12 months after surgery for both groups (P .0001).	8
Aboud, 2009 [198]	Aortic valve replacement, mechanical (n=83) vs bioprosthetic (n=53)	Retrospective cohort	136	74 (52-87) (mechanical prosthesis) 64 (44-81) (Bioprosthetic)	21.4 +/- 4.6 months	SF-36	Physical function scores were significantly better in patients with a mechanical prosthesis. Mental health indices were identical in both groups. Younger patients with mechanical valves and older patients with biological valves had significantly better item scores.	Physical functioning index was significantly better in patients with mechanical prosthesis	2
Van Geldorp, 2012 [199]	Conservative management (n=84) vs aortic valve replacement (48) for aortic stenosis ** 22 patients crossed over	Multi-centre prospective cohort study	132	73.2 +/- 10.9 (Conservative) 67.8 +/- 12.2 (AVR)	18 months	SF-36v2TM	s Aortic valve replacement improves physical quality of life, general health and vitality in patients with symptomatic severe aortic stenosis.	Physical functioning, improved significantly 1 year after aortic valve replacement. In conservatively treated patients physical quality	5

	from conservative to surgical							of life deteriorated over time	
Tseng, 1997 [200]	Isolated AVR (n=247)	Retrospective cohort study	247	76.2 ± 4.8 years.	4.1 ± 3.1 years	SF-36	Patients undergoing AVR scored better than those who were 75 and older who did not (age adjusted norm), however, quality of life was similar between AVR group and those 65-74 who did not undergo AVR (age adjusted norm)	In areas of physical function, patients who underwent AVR scored better than did patients in the 75 years of age and older group and comparably with patients in the 65-74 year age group (age adjusted norm)	1
Casali, 2008 [201]	Aortic valve replacement with 17mm St Jude Medical regent mechanical prosthesis (n=36)	Retrospective cohort study	36	66.9 +/- 12.1	4.1 ± 1.8	SF-36	Scores obtained in 7 of the 8 domains of the test were significantly higher than preoperative values.	Post-operative physical function was improved compared to pre-operative physical functioning	2
Machaalany, 2013 [202]	Patients implantated with PTMA device (n=30)	Muti-center prospective cohort study	43	72 ± 11	5.8 +/- 3 months	Minnesota Living with Heart Failure Questionnaire EQ-5D questionnaires	Overall, PTMA had mild impact on MR reduction, left ventricular remodeling, QOL, and exercise capacity.	N/A-No comparison with pre or norms	2
Markou, 2011 [203]	Isolated AVR (n=200) vs AVR+CABG (n=215)	Retrospective cohort study	415	71.7 ± 7.3 (55–88)	1 year (only 239 patients)	EQ-5D	Postoperatively, all patients Experienced significantly better health-related QOL. However, the patients	N/A-No comparison with pre or norms	9

							undergoing combined surgery experienced more benefit from their operation.		
Vicchio, 2012 [204]	Isolated AVR (n=406) vs AVR + CABG (n=112)	Retrospective cohort study	520	74.2 ± 3.6 years 74.3 ± 3.6 (AVR) 74 ± 3.3 in (AVR+CABG)	4.2 ± 3.3 years	SF-36	The scores obtained in the SF-36 test were similar in the two groups and significantly higher than those of the general population matched for country, age and sex (p < 0.001 in all domains).	Physical functioning score was higher in both groups compared to the elderly Italian population	8
Whitlow, 2011 [205]	Underwent MitraClip procedure (n=78)	Prospective cohort study	78	77	1 year	SF36	The MitraClip device reduced MR in a majority of patients deemed at high risk of surgery, resulting in improvement in clinical symptoms and quality of life	The physical component of SF36 improved from 31.6 ± 9.1 to 36.5 ± 10.6	10
Ussia, 2012 [206]	Mitral valve repair with the MitraClip (n=39)	?Prospective cohort	39	72±11	6 months	SF12 (v2)	early marked improvement in functional status and physical and mental health in patients underwent percutaneous mitral valve repair with the MitraClip System	At 6 month follow up point, a drastic improvement in PCS was observed (PCS 35.44 vs 44.67, P<0.0001)	2
Maliwa, 2003 [207]	Underwent mechanical AVR (n=312)	Retrospective cohort	312	41 +/- 12	30 +/- 1.8 years	SF36 EuroQol (EQ-5D)	At long term follow-up (mean 30 years) of patients who had mAVR. QoL was relatively high	Physical functioning QOL subscale was lower than that of other populations e.g. Dutch population	2

Sedrakyan, 2003 [208]	Aortic Valve replacement (n=72) Mitral Valve repair (n=72)	Prospective cohort	148 *220 initially sampled, but only 148 had complete data	66.5 +/- 14.4	18 Months	SF36	Age does not appear to limit the QOL benefits of surgery.	Physical functioning improved significantly for all age groups	9
Florath, 2005 [209]	Bioprosthetic AVR (n=247) Mechanical AVR (n=145)	Retrospective cohort	392	Bioprosthetic: 76 +/- 5 Mechanical: 71 +/- 4	3 to 66 months	Nottingham health profile	Elderly people receiving stentless bioprostheses benefit emotionally because of the avoidance of coumarin.	Physical functioning comparable to general German population, females in the study scored higher	9
Jokinen, 2007 [210]	MV Repair: (n=85) MV Replacement: (n=99)	Prospective cohort	184	MV Repair: 62.2 +/- 9.2 MV Replacement : 61.3 +/- 9.4	7.3 +/- 1.4	Nottingham Health Profile	Survival is longer after MV repair than after MV replacement. The quality of life of not differ from each other.	Physical activity was statistically significantly worse in the MV replacement and repair groups than in the reference population	8
Lam, 2004 [211]	Aortic Valve replacement in >80 years age (n=58)	Prospective Cohort	58	83.7±3.4	35.3±25.3	SF36	Despite higher operative risk and greater morbidity, QOL indicators in patients ≥80 years were equivalent to or better than their counterparts.	N/A-No comparison with pre or norms	1
Zacek, 2016 [212]	aortic valve-sparing procedure, age <50 (n=36) aortic valve-sparing procedure, age >50 (n=52)	Cross sectional study	139	aortic valve-sparing procedure, age <50 36.3 ± 6.1 aortic valve-sparing procedure, age >50 59.2 ± 7.7	median 26.9 months	SF36	Postoperative quality of life is influenced by the type of aortic valve procedure and is negatively linked with mechanical prosthesis implantation and long-term anticoagulation	younger valve repair patients and Ross patients scored significantly better than the patients after mechanical valve replacement in all four physical	7

	Ross procedure (n=22) mechanical aortic valve replacement (n=29)			Ross procedure 37.8 ± 11.9 Mechanical aortic valve replacement 39.7 ± 7.3				subscales	
Maisano, 2009 [213]	Isolated mitral valve surgery (n=) Combination aortic/mitral valve surgery (n	Retrospective Cohort	225	77 +/-3.2 years.	2.8 +/- 1.2 years	Minnesota Living with Heart Failure (MLHF) questionn aire	Quality of life following mitral valve surgery is suboptimal in more than half of elderly patients. MLHF score at follow-up is mostly related to preoperative conditions. Type of surgery does not influence MLHF score, however, quality of life is worse in patients with recurrent/residual MR following repair.		2
Folkmann, 2010 [189]	AvR with CABG (n=80) AvR without CABG (n=74)	Retrospective Cohort	154	82.9 +/- 2.5	1 year	Seattle Angina Questionn aire	Surgery in the aortic valve without CABG is associated with a good outcome. The improvement in QoL after one year supports the decision to operate on patients older than 80 years of age	Assessment of QoL revealed a substantial improvement of physical fitness in all 126 patients (who survived to be followed up at 1 year)	1

Klomp, 2016 [214]	Age <80 N=597 Age >80 N=163	Prospective single-center cohort study	762	Age <80 71 (66-75) Age >80 82 (81-83)	1 year	SF-36	surgical aortic valve replacement in octogenarians could be performed with very low mortality, and with a relevant and significant increase of the quality of life towards normal values	PCS increased from baseline for both group at 1 year follow up	8
Vicchio, 2007 [215]	Bioprosthetic AVR N = 62 Mechanical AVR N= 98	Retrospective cohort	160	Bioprosthetic group: 82.9 +/- 2.7 Mechanical group: 81.8 +/- 1.8	3.4 +/- 2.8	SF-36	Long-term survival after AVR in selected octogenarians was similar to that of the general elderly population. The device type exerted no influence on QOL.	N/A-No comparison with pre or norms	11
Aoyagi, 2010 [216]			60	82.3 ± 1.9	3.4 +/- 3.1 years		Some 97.6% of late survivors reported that their activity level was equal to or better than the preoperative level;	N/A-No comparison with pre or norms	2
Oliveira, 2011 [217]	>75 year old patients that underwent AVR (n=114)	Retrospective cohort	114	78.5 ± 2.5 years	47.2 ± 23.4 months		At follow-up, most achieved improvement of QoL and remained autonomous.		2

5.5 Discussion

The growing elderly population worldwide places demands on health care providers and policy makers to formulate strategies in improving and maintaining quality of life during the extended years of life. Valvular surgery is increasingly becoming a common procedure in the elderly group. While the aforementioned demand for these procedures is driving the increase, improvements in surgical skills and advances in prosthesis models make these procedures safe and feasible.

This review aims to answer the question around whether improvements in QoL can be observed post valve related cardiac surgery and more specifically – highlight predictors of poor QoL post-operatively. To answer this question, one must first acknowledge that due to the nature of cardiac surgery – there are some inherent risks. These risks are well documented and can be both short and long term [218]. These risks are compounded in elderly patient who have a greater set of co-morbidities often placing them in the ‘high risk’ category [219]. Because of this – much focus is directed towards traditional markers of operative success. However, an increasing body of evidence informs us that elderly patients value regaining their independence and ability to enjoy improved quality of life post-operatively over and above the traditional markers of operative success [220].

Frailty Factor

Phenotype is often used a measure of frailty to aid clinicians in decision making on appropriate intervention for patients. Kojima et al. (2016) applied 36-item Short Form Health Survey instrument and demonstrated that patients rated as frail or intermediate frail according to the Phenotype Frailty score have been shown to correlate to have lower physical and

mental quality of life scores [221] but a numerous body of evidence challenges this conclusion..

Studies presented age alone should not be a precluding factor of worsening QoL post-surgery [198, 199, 208]. In fact, Sedrakyan et al. (2003) show that not only is age not correlated with QoL post-surgery, but that benefits reaped from valvular surgery seem to be prominent regardless of age. Additionally, Lam and Hendry [211] found that in octogenarians undergoing aortic valve replacement, quality of life post-operatively was equivalent to, or better than their counterparts

HRQOL outcome: PCS vs. MCS

A significant improvement in QoL following valve surgery was overwhelmingly reported regardless of the different QoL tools used, even for the studies that pre-selected baseline characteristics, or grouped patients into cohorts of middle and advanced age. Similarly articles that compared their study to country specific age matched population norms noted overall improvement in quality of life. However majority of the articles 25 reported improvement in PCS and general health compared to 8 articles for marked improvement in MCS. Four studies reported MCS did not improve while Van Geldorp and Tseng added MCS score was lower than population norms and didn't benefit from surgery concurring with the study by Maliwa and colleagues.

Given that the overwhelming majority of literature indicated QoL is generally improved by surgical intervention, this study aimed to assess predictors of poor quality of life post valvular surgery.

Predictors of Quality of life.

Assessing predictors of QoL was a difficult task as data on the subject matter is extremely limited; in fact of the 14 prospective studies that had both pre and post-op data and the 5 retrospective studies that matched their study population with age and population norms, only 10 studies evaluated any predictors of QoL post-surgery. The predictors identified in the studies are briefly discussed below.

Female Gender.

Goldsmith et al. (2001) reported female gender as an independent predictor of lower QoL following an open Mitral valve repair or replacement. This was previously reported in a large study of 741 patients that also included concomitant procedure with (212 MVP and MVR patients) by Flameng and colleagues [222]. The decline in general health for female gender in the first 3 months post-surgery is not yet well known.

Mitral Regurgitation.

Two studies [195, 223] investigated the impact of mitral regurgitation/residual following MR on the QoL. They noted non-significant improvement in QoL 3 months post-surgery when compared to baseline data in both open MV repair and replacement, with patients presenting etiology of mitral regurgitation (MR) with end systolic dimensions of more than 45 mm disadvantaged. Conversely patients with functional MR had improved their QoL post-surgery compared to those presenting degenerative MR in minimal invasive based MV repair.

Coronary artery disease.

Four studies [189, 194, 203, 204] focused on the impact of coronary artery disease on the quality of life of patients undergoing aortic valve replacement. Studies reported previous myocardial infarction (MI) was predictive of rapid improvement in the physical component of QoL shortly after cardiac surgery. They however indicated non-significant mental health component improvement regardless of patient's history of coronary artery disease, acute MI, previous PCI intervention or repeat CABG surgery. Interestingly one study reported that

concomitant CABG and AVR is associated with poor QoL, precipitating higher mortality rates compared to sole AVR, however, on regression analysis – CABG alone was not significantly responsible for this increase [204]. This was further challenged by Markou and colleagues who reported in their prospective study of 215 concomitant (CABG+AVR) and 200 isolated valve that patients undergoing combined surgery exhibited greater benefit from their surgery than their counterpart.

Ejection Fraction, NYHA and LV function.

Three studies pre-selected ejection fraction, LV function and NYHA class to evaluate any improvement in QoL post-surgery. Work by Goldsmith et al. (2001) revealed significant improvement in QoL following mitral valve repair but noted impaired LV function or end-systolic dimension is less likely to aid improvement in QoL. Likewise he presented higher NYHA functional score being independent predictor of low improvement in QoL and general health status post mitral valve surgery. Conversely Zhao et al [16] reported significant improvement in NYHA class and health status for mitral repair patients.

Other determinants of Quality of life.

Type of Prosthesis.

Prosthesis type was reported as another important indicator of QoL post-operatively. Some studies have pointed out that even though surgery improves QoL, certain prosthesis result in better gains than others. One example is the research done by Florath et al (2005) who have concluded that elderly patients receiving a stentless bio-prosthetic aortic valve had a greater gain in the emotional QoL component due to the avoidance of warfarin [209]. This point was further supported by Zacek et al. [212] who stated QoL post-operatively is influenced by the specific type of aortic valve and greater quality of life and freedom is preserved by procedures that avoid lifelong anticoagulation.

On the other hand Vicchio et al. [215] found that while survival in selected octogenarians was similar to the general elderly population, quality of life was not influenced by the type of aortic valve used – that is to say, there was no difference in quality of life between patients with bio-prosthetic or mechanical valves.

Type of Surgery

QoL following mitral valve surgery has been a closely followed topic. Much of the literature suggests that patients undergoing mitral repair experiencing a greater QoL improvement whereas mitral valve replacement yield inferior QoL gains [197]. Interestingly, Jokinen et al. (2007) assert that their research indicated quality-of life post-operatively was not significantly different between mitral valve replacement or repair, whereas survival was longer after mitral valve replacement as compared to repair. Furthermore, when compared to an age- and sex- matched population, scores around energy and mobility were lower. Juxtaposed to this, Maisano et al. [213] found that quality of life following mitral valve surgery is suboptimal in almost half of all elderly patients, particularly those with residual mitral regurgitation.

Incision factor

The impact of full sternotomy on patient's postoperative quality of life and the perceived benefit of minimally invasive approach were investigated by Detter and colleagues [224] in their study of 140 patients that were separated equally to their respective cohort (minimal vs. conventional) group, and with a mean age 64.3 years and 34 months follow-up.

Interestingly they presented the absence of any significant difference between the two groups in any of the 8 domains of the quality of life tool used (SF 36). Furthermore they reported patient's satisfaction and scar judgement after the operation was not influenced by the incision style. None the less their study has few limitations and to begin with their postop follow-up was not done at 3 months or at 12 months, hence they haven't reported early mobilisation or

the stability of the sternum at any given point. Similarly their post-op complication list didn't not account for surgical site infection on which case if considered and reported it may have influence the patient's satisfaction and quality of life results.

5.6 Limitation.

In conducting this review, multiple limitations must be acknowledged. While some of the studies reviewed were prospective in nature, many were retrospective (see table of studies above). Similarly, many studies were single centre, which can affect the generalisability of results. Quality analysis demonstrated some of the most common flaws in the studies – namely patient selection, which must be acknowledge is largely due to ethical and technical consideration rather than poor selection.

One of our search criteria was to look at all literature on this subject from the year 1980 onward. Since this point, many advances have been made. Such advances in the field of valvular repair and replacement include transcatheter aortic valve replacement and transcatheter mitral valve replacement. Comparing the efficacy of these newer technologies is beyond the scope of this paper, however, it should be acknowledged that they will have a role, especially in the years to come, on impacting QoL in elderly patients undergoing valvular intervention.

We were specifically interested in identifying predictors of poor QoL gains post-operatively, and given the paucity of data around the subject, this was particularly difficult. In all of the literature identified, only five studies directly broached this topic. This provides a bottleneck in terms of validating the findings of these articles as well as limiting the scope of other potential factors which can negatively affect QoL post-operatively.

5.7 Conclusion

Increases in average population age across developed countries means there is a greater prevalence of valvular heart disease. Elderly patients can safely undergo valvular surgery with excellent post-operative outcomes. While mortality and morbidity are both important measures of operative success, it is imperative that a quality of life measure be included when evaluating the success of valvular surgery in elderly patients. Our literature review identified that quality of life gains post-operatively for elderly patients undergoing valvular heart surgery are both evident and significant when compared to pre-operative state. In saying that, we identified certain factors which can be correlated to limited QoL improvement – these included prosthetic type, valve dimensions, higher NYHA score and replacement as compared to repair in mitral valve surgery.

6.0 Chapters 6

Systematic Review on Quality of Life of Patients after isolated Coronary Artery Bypass Grafts (CABG).

6.1 Aim: To investigate the impact of isolated CABG surgery on the quality of life of elderly patients and highlight predictors of poor quality of life post-operatively.

6.2 Introduction.

Coronary artery disease (CAD) has a significant population prevalence in the developed world and is considered to be one of the leading causes of premature death worldwide [225], with new strategies being consistently formulated to combat this epidemic. While it remains a key contributor to the global burden of disease, patterns show that mortality rates have directly declined in the past two decades [225]. This decline has been attributed to several factors – namely that the issue has been targeted holistically from a biopsychosocial perspective which has yielded this reduction [226].

Two of the leading treatments of coronary artery disease are myocardial revascularisation by means of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) [227]. PCI involves arterial puncture, wire insertion and stent utilization for arterial revascularisation [228] whereas CABG is a surgical option that involves the use of autologous blood vessels (venous or arterial) to bypass distal to points of stenosis [227].

Despite being effective at relieving symptoms as well as improving survival, in recent years, there has been a shift away from CABG, with nearly half as many operations being performed in 2012 compared to 2006 [227]. In saying this it should be noted that, according to the AHA/ACC guidelines, there continues to be good evidence supporting the use of CABG, particularly in the case of left main coronary artery stenosis as well as triple vessel disease [229]. Additionally, improved perioperative care as well as surgical technique over

the past 20 years has allowed this operation to be performed with an ever decreasing mortality and morbidity [227].

As the main protagonists of treatment options for this disease, clinicians treating CAD ought to approach the condition from a holistic standpoint. Indeed, the World Health Organisation's (WHO) definition of health states that health is not merely the absence of disease but encompasses domains of physical, mental and social wellbeing [230] or in other words quality of life.

Quality of life can be defined as an "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [179]. Given the subjective measure of QoL, many scales exist which attempt to provide an objective numerical number to assign QoL. An example of a popular scale is the Short-Form 36 (SF-36) [231]

None the less, perhaps not unexpectedly, most of the current evidence base assesses CABG from a technical standpoint, with outcomes more-often-than not being mortality as well as traditional measures of morbidity. This is juxtaposition to the amount of literature available on the quality of life (QoL) outcomes following CABG, which is sparse; our initial search identified only 40 articles. Comparatively a crude PubMed search for 'outcomes' and 'coronary artery bypass grafts' identified thousands of articles.

To better appreciate the importance of this discovery one only needs to turn to the World Health Organisation's (WHO) definition of health. Broadly speaking, research previously conducted on QoL in a cardiothoracic context has generally shown that it improves post-operatively compared to baseline levels [188].

In the modern era, the rise of percutaneous revascularisation over surgery makes the issue of QoL ever more important, and raises several questions of the overall risk gain benefit ratio, other than mortality as a mere single objective end point. The impact of the surgical burdens

of a median sternotomy, cardiopulmonary bypass and intensive care unit stay on patients' QoL post-surgery in the short and longer term and compared to PCI requires further evaluation. Furthermore, do surgical specific complications, particularly wound infection, amongst others, render patients worse off despite the survival benefit from managing their CAD?

Due to the sparse amount of information available, as well as the importance of QoL and on-going place of CABG in myocardial revascularisation, this study aims to explore this topic in more detail. This will be done by firstly identifying all appropriate studies in the area, which for our purpose will include and focus older patients, studies focusing on isolated CABG. Secondly, a variety of factors including demographics as well as operative technique will be analysed to determine their effect on QoL. Of particular interest is the physical and mental component in QoL measures. Finally, all of this information will be discussed in-depth and limitations identified.

6.3 RESULTS:

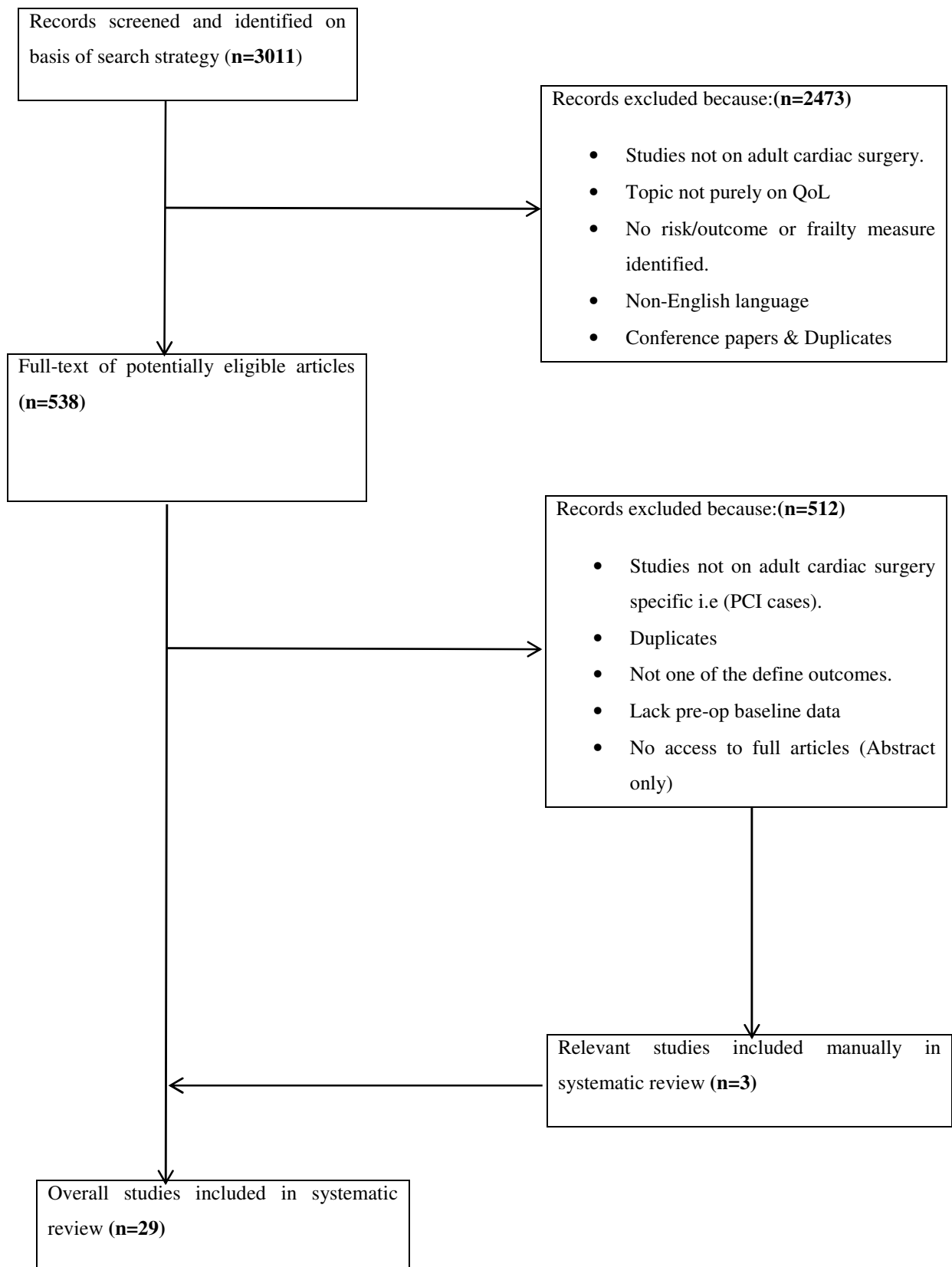
Evaluation of Quality

Quality assessment of each study was performed by attributing a quality assessment score using a modified Newcastle–Ottawa scale [191]. The scale was modified to include all 17 EuroSCORE II cardiac risk factors as well as baseline physical, social and mental health function for comparability. See table 1 for the analysis results. The scoring criteria are shown in Table 2.

Table 8 - 6.1. Criteria for quality assessment. Modified Newcastle–Ottawa scoring criteria

Quality checklist
<i>Selection</i>
1. Assignment for treatment – any criteria reported? (If yes, 1-star)
2. How representative was the reference group in relation to the general population undergoing CABG (If yes, 1 star, no star if the patients were selected or selection of group was not described)
3. How representative was the comparison group in relation to the general population for CABG? (If drawn from the same community as the reference group, 1-star, no star if drawn from a different source or selection of group was not described)
<i>Comparability</i>
Comparability variables: (1) age; (2) gender; (3) renal function; (4) extracardiac arteriopathy; (5) poor mobility; (6) previous cardiac surgery; (7) chronic lung disease; (8) active endocarditis; (9) critical preoperative state; (10) IDDM; (11) NYHA; (12) CCS IV; (13) LV function; (14) recent MI; (15) pulmonary hypertension; (16) urgency; (17) combined; (18) physical function score; (19) mental function score; (20) social function score
4. Groups comparable for 1, 2, 3, 4, 5, 6, 7, 8, 9 (If yes, 1-star was assigned for each of these. No star was assigned if the groups differed)
5. Groups comparable for 10, 11, 12, 13, 14, 15, 16, 17 (If yes, 1-star was assigned for each of these. No star was assigned if the two groups differed).
6. Groups comparable for 18, 19, 20 (If yes, 1-star assigned for each of these. No star was assigned if the groups differed)
<i>Outcome assessment</i>
6. Clearly defined outcome of interest (If yes, 1-star).
7. Follow-up (1-star if described).
IDDM=insulin dependent diabetes mellitus; MIVS=minimally invasive valve surgery; NYHA=New York Heart Comparability includes all the EuroSCORE II risk-factors.

Figure 16 - 6.1- Flow diagram of CABG QoL study selection



6.1 RESULTS

Our literature search yielded 3011 studies, of which 29 articles with a total patient population of 11,506 fulfilled our inclusion criteria. A total of 20 different health related quality of life measurement tools was applied in almost all the articles individually apart from 4 studies that co-applied two or more tools in their study group (Table 6.2). Fifteen studies utilised SF-36 to assess and measure quality of life, four studies applied EQ-5D, six studies equally applied SF-12 and Rand 36, two studies utilised Nottingham health profile, whilst the remaining studies each used separately the remaining tools (Table 6.2).

Patient ages ranged from 39 to 88.8 years and the included studies sample size ranged between 48 to 2000. The procedures undergone by these patients varied in terms of incision method and operation type; open sternotomy was noted as the preferred choice over minimal access. All studies had a follow-up period ranged from 3 months to 15 years (Table 6.2).

Most of the studies reported outcomes including in-hospital mortality, composite outcome and prolonged length of stay along with quality of life improvements or decline, however, studies failed to report on common endpoints which limited formal meta-analysis for these outcomes thereby limiting our interpretation of a baseline predictors for quality of life and a cut-off value that accurately measures valve surgery consequences in frail elderly patients.

Table 9 - 6.2. Synopsis of current literature on QoL CABG surgery

Author, year, Ref	Intervention	Study type	No. of patients at baseline	Age of patients	Follow-up duration (mean)	QoL Instruments	Conclusion	Physical component improved	Quality score
Azzopardi, 2009 [232]	CABG (n=48)	Retrospective cohort	48	66.6 (SD 9.9)	2 years	SF-36	Statistically significant improvement in 5 of the SF-36 health domains and in the physical component summary (P<05).	Improvement in mean score of physical component from 35.2 to 43.3	**
Bjessmo, 2010 [233]	Patients undergoing CABG with ACS N=62 Patients undergoing CABG with stable angina N=51	Retrospective cohort study	113	Acute Coronary Syndrome: 61.7 +/- 10.2 Stable Angina: 65.6 +/- 8.63	10 years	SF-36	Surgical revascularization offers excellent long term QOL, comparable to that of a matched control population. No difference was found between patients with ACS or stable angina pectoris.	There was no clinical significant difference in PCS after CABG for ACS or stable angina. The ACS group had a statistically significant lower PCS score than a reference population	*****
Bonaros, 2009 [234]	Robot-assisted CABG. Endoscopic (n=55) vs Sternotomy (n=56)	Prospective cohort	120	Sternotomy 64.28 +/- 7.3 Totally endo 60.28 +/- 6.0	6 Months	SF-36	Endoscopic CAGs leads to improved physical health, shorter hospital stay and a more rapid restoration of daily activities. Conversion does not lead to QOL impairment as compared to primary sternotomy.	Physical function was significantly improved following CABG surgery for the total study population. Most prominently in the endoscopic group.	***** **

Covinsky, 2008 [235]	Females undergoing CAGs (n=137) No Procedure (n= 2263)	Prospective cohort	2400	CABG 66.6 +/- 6.9 No-Op 66.6 +/- 6.8	11.5±3.5 months	Duke Activity Status Index (DASI) and RAND	Following CABG surgery in postmenopausal women, on average, HRQOL is virtually identical to the pre-operative baseline. However, there is significant variability, as substantial numbers of women are significantly better or significantly worse.	Difference in physical function pre vs post CABG: -0.4 (-2.2, +1.5) Statistical significance not calculated	****
Damgaard, 2011 [236]	Single/Double ITA + Radial grafts: 161 vs Conventional revascularisation using left ITA/SVGs 170	Prospective cohort	329	Single/Double ITA + Radial grafts: 59 +/- 8 Conventional revascularisation using left ITA/SVGs: 59 +/- 8	1 year	SF-36	Health-related quality of life up to 1 year after total arterial revascularization is equal or slightly better than results after conventional coronary surgery	For total arterial revascularization, there were not statistically significant improvements for 'physical component summary' (P = 0.09),	*****
El Baz, 2009 [237]	198 patients -> patient split between care pathway group and conventional care group not stated	Prospective cohort	198	Pathway Group: 64.93 +/- 9.60 Conventional Care: 64.83 +/- 10.53	6 Months	SF-36	The aims of clinical pathways – reducing LOS and costs, was not fulfilled in the study	Both groups had an improved physical function score compared to baseline, the conventional care group had a higher improvement of	*****

								physical function when compared to baseline	
Herlitz, 2009 [238]	Patients undergoing isolated CABG N=2000	Prospective cohort	2000	62.7 (SD not stated)	15 years	The Nottingham Health Profile, the Psychological General Well-Being Index, and the Physical Activity Score	Despite an ongoing decline in QoL over the years, there was still an improvement in most aspects of QoL 15 years after CABG compared with that before surgery	A significant improvement in physical function still existed 15 years post CABG compared to baseline, despite ongoing deterioration of overall physical function	**
Hokkanen, 2014 [239]	Patients undergoing isolated CABG N=508	Prospective cohort	508	62.3 +/- 9.3	11.8 years +/- 0.48	RAND-36	Despite an ongoing deterioration 12 years after the CABG, there was significant improvement in most dimensions of the QoL and functional capacity in comparison with the preoperative values.	Physical function significantly improved post CABG, even at 12 year follow up time point. Physical function was better than that reported for general population	**
Jidéus, 2009 [240]	Sternal wound Infection n=84 CABG group N=42	Retrospective cohort	126	Sternal wound infection: 68.27 (46.72-81.43) CABG group 65.71 (48.58 - 78.83)	20 months (range 740).	SF-36	Results confirm that if the patients survive, sternal wound infection is a very serious complication concerning QoL. At follow up the SWI patients did not improve their QoL, with no	Physical function for patients with sternal wound infections was below that of population normals	****

							difference in surgical technique used, although they had undergone open heart surgery.		
Jrvinen, 2014 [241]	Patients undergoing CABG with perioperative myocardial infarction (PMI) N=8 Patients undergoing CABG without PMI N=493	Prospective cohort	501	PMI: 65.4 +/- 9 Non-PMI: 61.7 +/- 9.3	1 year survey: Mean follow up 12.6 +/- 1.2 months 12 year survey: mean follow up time 11.8 +/- 0.48 years	RAND-36	Although PMI has a negative impact on health-related QOL 1 year after CABG, this effect is only minor in the long term. PMI increases 30-day mortality but shows no effect on later mortality.	Patients in both the PMI and non-PMI groups had significantly improved physical function post CABG	*****
Juergens, 2010 [242]	patients undergoing elective cardiac surgery (coronary artery bypass grafting (CABG), heart valve surgery, or a combined procedure n=56	Prospective cohort	56	63.6 +/- 11.6	3 months	SF-12	Patients' beliefs about their illness before surgery strongly influence recovery from cardiac surgery. The results suggest that patients could benefit from pre-surgery cognitive interventions aimed at changing maladaptive illness beliefs to improve physical functioning and disability following cardiac surgery.	Patients reported higher physical functioning 3 months after surgery compared to presurgery	**

Kapetanakis, 2011 [243]	Off-pump CABG N=116 On-pump CABG N=75	Prospective cohort	191	Off-pump CABG 68.5 (42.0 to 85.0) On-pump CABG 66.0 (39.0 to 87.0)	6 months	SF-36	no significant differences in the expected QOL at six months after either on-pump or off-pump CABG	nil	***** *
Khoueiry, 2011 [244]	Patients undergoing Off-pump CABG N=50	Prospective cohort	50	63.28 +/- 11.20	9 months	Beck Depression Index (BDI) Beck Anxiety Index (BAI) Sheehan Disability Scale (SDS) Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)	despite that all scores returned to or below baseline at 9 months, a high percentage of patients still had depressive symptoms and overall poor quality of life (QOL)	nil	**
Kołowski, 2011 [245]	Patients undergoing isolated CABG N=86	Prospective cohort	86	63.3 +/- 8.93	5 months	EQ-5D	The quality of life significantly improves in the first 4 weeks after cardiac surgery. There is a relation between the patient's age and their reported QoL	nil	**
Lee, 2009 [246]	Patients undergoing CABG N=128	Retrospective cohort (not formally stated)	162	Not stated	5 years	SF-36	study demonstrates that both anxiety and depressive	nil	*

							symptoms are strongly implicated in determining PCS and MCS 5 years post-CABG using the SF-36.		
Lie, 2009 [247]	Isolated CABG patients receiving home based intervention program and controls N = 93 Control group N=92	Randomised controlled trial	203	Intervention group 62 (range 39–77) Control group 62 (range 42–78)	6 months	SF-36	HRQoL after CABG improved markedly over time, but no significant or clinically important differences were found between patients receiving a home based intervention program and controls	PCS in both groups improved from baseline to 6 months following surgery, however there was no difference in PCS between intervention and control group 6 months post operation	*****
Mark, 2014 [248]	Assignment to medical therapy N=602 Medical therapy + CABG N=610	Randomised trial	1212	Median age of medical therapy group: 59 (53–67) Median age of CABG + medical therapy group: 60 (54–68)	36 months	The Kansas City Cardiomyopathy Questionnaire SF12 SF36 Cardiac Self-Efficacy Questionnaire EuroQol-5D	In a cohort of symptomatic high-risk patients with ischemic left ventricular dysfunction and multivessel coronary artery disease, CABG plus medical therapy produced clinically important improvements in several health status domains compared with medical therapy alone over 36 months	nil	*****

Markou, 2008 [249]	Group A, primary isolated CABG patients age <65 years: n=285 group B, primary isolated CABG patients age 65—74 years: n=210 group C, primary isolated CABG patients age 75 years: n=73	Retrospective cohort study	568	Group A 56.9 +/- 5.8 Group B 69.5 +/- 2.8 Group C 77.7 +/- 1.9	1 year	EuroQoL questionnaire	Elderly patients have the same improvement of their symptomatic status as younger patients. However despite this improvement they have less benefit from CABG regarding to their quality of life and physical activity.	For physical activity there is a statistical significant improvement for groups A and B, but the improvement is lesser in group B (mean change 0.2 vs 0.5 in group A). The improvement in PA in group C does not result in a significantly higher follow-up PA (p = 0.744).	*****
Merkouris, 2009 [250]	Elderly patients (age >65) undergoing CABG N= 63	Prospective cohort study	63	72.9±3.7	12 months	theMacNew Heart disease health-related quality of life questionnaire	A high proportion of the patients experienced improvement while a substantial number had exacerbations related to self confidence and dependence to others	67.9% percent of patients improved in the category 'physically restricted or limited', improvement is statistically significant, p<0.001.	**
Middel, 2014 [251]	Patients scheduled for CABG N=256	Prospective cohort study	256	64.89 +/- 9.95	6 months	SF-36	There is evidence that increased symptoms of psychological	Patients with and without a Type D personality	**

							distress is a strong predictor of no change-deterioration trajectories in HRQoL and that this relationship is influenced by personality trait Type D. Concluded that mediating factors, especially increased anxiety and depression, should be treated adequately in post-CABG clinical routine	showed significant improvements in PCS post CABGs, however patients with type D personality scored lower than their counterparts (both pre and post-op).	
Najafi, 2012 [252]	Diabetics undergoing isolated CABG N=113 Non-Diabetics undergoing isolated CABG N=155	Cross-sectional study	268	Diabetics: 60.3±8.4 Non-diabetics: 59.2±9.4	24 hours post-operatively	SF-36	An adverse relationship was found Between pre-op mental summary score and the mean of plasma glucose concentrations during 24 h after surgery. No significant association was found between pre-op physical summary score and mean of plasma glucose concentration during this time.	nil	**

Najafi, 2009 [253]	Patients undergoing isolated CABG N=283	Not formerly stated – but likely prospective cohort	283	59.8 ± 9.0	Not stated	WHOQOL-BREF questionnaire 13, 14	The study found that the independent physical component predictors for higher QoL included male gender and diabetes mellitus, while the independent psychological component predictors were male gender and high ejection fraction. Males, diabetics and patients with low education levels had higher social well-being than others	nil	*
Østergaard, 2016 [254]	Elderly patients undergoing off-pump CABG n=61 Elderly patients undergoing on-pump CABG n=59	Prospective cohort study	120	All patients: 75 +/- 4.5 Off-pump CABG 76 +/- 4.8 On-pump CABG 75 +/- 4.2	8 years	SF-36	HRQoL SF-36 scores improved significantly in both groups post-operatively compared to pre-operatively. On-Pump patients had a greater social function score compared to off-pump counterparts.	Physical function improved significantly between baseline and all points of follow up (3 months, 12 months, 8 years) across both groups.	*****
Peovska, 2008 [255]	Patients with ischaemic cardiomyopathy undergoing CABG more than four viable	Prospective cohort study	65	56 ± 15	14 ± 4 months	Minnesota Living with Heart Failure (MLHF) scale	The presence of more than four viable segments (24% of the left ventricle) on MPI in patients	nil	**

	segments N = 39 Patients with ischaemic cardiomyopathy undergoing CABG less than four viable segments N=26						with ischaemic heart failure before CABG surgery is significantly correlated with the improvement in LVEF, heart failure symptoms and quality of life post-operatively.		
Peric, 2008 [256]	Patients undergoing elective CABG n=208	Prospective cohort study	208	Male 58.2 +/- 8. Females, 61.5 +/- 5.6	6 months	The Nottingham Health Profile Questionnaire	The predictive factors for quality of life worsening six months after CABG are female gender, diabetes mellitus, low ejection fraction, and the presence of postoperative complications.	Physical mobility significantly improved post- operatively (70% of patients improved)	**
Sandau, 2008 [257]	Consecutive patients undergoing CABG n=64	Prospective cohort study	64	65.2 +/- 9.3	3 months	SF-12	Patients reported improvements in HRQL measures, including two of three subjective neurocognitive measures	PCS improved from baseline (40) to 42.2 post-operatively which was statistically significant	**
Tully, 2009 [258]	Elective CABG patients n=226	Prospective cohort study	226	62.9 +/- 9.5	6 months	SF-36	Elevated depression symptoms before and after surgery showed an association with lower and worse HRQOL for vitality and social role functioning and physical and	Nil	**

							general health		
Van Mastrigt, 2010 [259]	CABG patients undergoing short-stay intensive care (8 hours intensive care) n=201 CABG patients control subjects (overnight intensive care stay) n= 207	Randomised clinical equivalence trial	410	Control group: 62.0 ± 13.77 Short-stay intensive care group: 61.8 ± 10.67	1 year	Multidimensional index of life quality (MILQ) EQ-5D Beck Depression Inventory State-Trait Anxiety Inventory	the HRQoL of SSIC patients is similar to patients receiving care as usual.	Nil	*****
Wagner, 2011 [260]	Patients undergoing isolated CABG, radial artery group n=366 Patients undergoing isolated CABG, saphenous vein group n=367	Multicentre randomised control trial	733	Saphenous Vein Group: 62 +/- 8 Radial Artery group: 61 +/- 8	1 year	Seattle Angina Questionnaire and Health Utility Index	Coronary artery bypass grafting with the radial artery lasts approximately 31 minutes longer than with the saphenous vein. However, costs and the quality of life were not statistically different.	Nil	*****

Figure 17 - 6.2. Describes quality score of all the studies included.



6.4 DISCUSSION.

In our present analysis, we conducted a systematic review of 29 studies assessing quality of life after coronary artery bypass graft (CABG) surgery. Whilst there was notable variability amongst the studies, our review has found that, overall, CABG surgery confers not only an improved long-term survival, but an improved physical and mental well-being as seen from a variety of scoring tools indicating a better quality of life (QoL) after CABG surgery.

Patient requiring CABG undergo a significant amount of physical and psychological stress in the perioperative process and the rehabilitation post-surgery. The impact on physical competency post sternotomy, post-surgical pain, and the psychosocial stresses associated with the recovery process, impedes gains in quality of life perceived by patients or, worse, a decline in quality of life post CABG. Yet what our study findings suggest is that the surgical treatment of ischaemic heart disease, its symptomatic improvement and relief of myocardial ischaemia, are factors significant enough to nullify the perioperative stresses and provide an improved physical and psychosocial state for the patient owing to improved cardiopulmonary reserve. This is not without mentioning the patients' intrinsic healing potential that also makes this possible. The studies analysed cover a wide time frame, some showing improvement in QOL as early as 3 months, and lasting for up to 15 years.

Whilst our study is crucial in assessing patients' functionality after life-prolonging surgery, reviews of this nature have some important difficulties to mention. First, there is heterogeneity in the tools used for measuring quality of life amongst the studies. A large portion of the studies used the short-form-36 (SF-36), which uses 36 generic questions in a number of specific domains, and a handful of studies used the EQ5D/EuroQOL. There were a few studies that used specific cardiac symptoms related questionnaires which, although

different to other study tools, evaluated variables that were directly taken from validated HRQOL tools. Whilst some differences exist between these tools, the main QOL factors they assess are very similar. The second issue is the difficulty in taking the baseline deterioration in human QOL, especially in the elderly, into account. Two studies from our cohort, Hokkanen and Herlitz, use methods to take into account the baseline average deterioration in QoL in the elderly. It is also notable that these two studies provided the longest follow up period (11.8 years and 15 years).

A very notable study by Mark et al randomised 1212 patients to either CABG or medical therapy alone and found that the surgical option conferred a more significant improvement in QOL. This was the only study to compare CABG with such a clear control group to demonstrate significant QOL improvement. Being one of the three largest studies in our analysis, Mark and colleagues used multiple QOL assessment tools to validate many of their findings and at several time points between 4 months and 3 years post-surgery. Interestingly, the authors focus on high-risk patients with impaired left ventricular function and multivessel coronary disease: patients who would be deemed higher risk for surgery, who yet still go on to have a more improved QOL compared to patients being offered medical therapy alone.

However, it may be that certain disease factors limit the QOL improvement. Peovska and colleagues highlighted that choosing patients with revascularisation of viable myocardial segments (measured using myocardial perfusion scans) compared to those with more non-viable segments can confer a greater improvement in QOL. This was directly related to patients having a more improved LVEF, which indicates that measured success of myocardial revascularisation is crucial in ensuring patients experiences a better QOL after surgery.

A recent myocardial infarction (MI), which is a common indication for revascularisation, may also confound the QOL after surgery. This was seen in the study by Järiven et al who, using the RAND-36 questionnaire, found that the improvement in QOL 1 year after surgery

was significantly less in patients who had a recent MI compared to those who did not. However, 12 years after surgery, there were no differences between the two groups, both of which showed a generalised decline in QOL. The study also found operative mortality to be higher in the MI group of patients, although long-term survival at 10 years was similar when compared to non-MI patients. The study by Bjessmo et al reported no difference in QOL outcomes between MI and non-MI groups, however, the study was retrospective and patients were only assessed 10 years post-surgery, which therefore does not disagree with the Järiven study.

6.4.1 Surgical factors

In a prospective cohort study, Kapetanakis et al compared QOL after on-pump CABG with QOL after off-pump CABG and not only found that neither surgical strategy was more beneficial than the other, but also found pre-procedure QOL to be similar to reported QOL post-surgery (time period = 6 months) between groups, adding no benefit exerted by any particular surgical strategy over the other. This compared to the randomized study by Ostergaard and colleagues, who found a more significant improvement in the social functioning subscale of the SF-36 questionnaire in on-pump patients compared to off-pump patients. They also found an improvement in only five of the eight domains of SF-36 in the off-pump group, compared to eight out of the eight domains in the on-pump group.

Bonaros and colleagues found that robot assisted CABG confers an even greater improvement in QoL when compared to conventional CABG via sternotomy. A subgroup analysis also found that, in patients planned to have robot assisted surgery that go on to have a conversion sternotomy, they do not have an impaired quality of life compared to planned conventional sternotomy patients.

In a Scandinavian prospective study by Damgaard et al, total arterial revascularisation (TAR) was compared with conventional CABG (mammary artery and vein grafts) and found a significantly greater improvement in the social functioning element of QOL compared to conventional surgery, as well as a non-significantly greater improvement in the physical component at one year post surgery.

6.4.2 Patient factors

Many of the studies analysed patient-related predictors of poorer QOL performance after CABG surgery. A notable study by Peric et al followed 208 patients and through the use of multivariate logistic regression, identified a number of factors significantly associated with worse QOL 6 months after surgery, including diabetes mellitus, low preoperative ejection fraction, and the female gender. This was found to influence a number of QOL domains, including physical, social and reports of pain. The two studies by Kapetanakis and Najafi, respectively, also found diabetes to be an independent positive predictive factor for patients reporting a better QOL following CABG.

In the study by Markou and colleagues, the researchers split patients into three age groups and found the most significant improvement in QoL in the youngest group (age < 65) followed by the middle group (age 65 – 75) and an even lesser improvement in QoL in the third group (age >75). This was most markedly seen in the domain of physical activity, where no significant improvement was seen in the second and third groups.

Najafi and colleagues also found gender to play a role, with male patients being more likely to have better physical and psychological component scores after isolated CABG than females. However, Covinsky and colleagues focused on postmenopausal females undergoing CABG surgery and found no significant change compared to the preoperative baseline.

6.4.3 Post-surgical complications

Specific attention should also be given to the impact of complications on the QOL outcome following surgery. Jideus and colleagues found that sternal wound infection was significant negative influence on improvement in QOL following surgery. Peric et al found that the occurrence of postoperative complications worsened physical and mental components of reported QOL outcomes 6 months after surgery. Whilst this study was not designed to assess each specific complication, significant complications affecting postoperative QOL included prolonged ventilation, reoperation for bleeding, sternal wound infection, pericardial effusion, arrhythmia and perioperative MI amongst others.

A protracted ICU stay after CABG surgery occurs when serious complications arise or patients have a poor baseline, leading to the need for prolonged critical care support. Some cases can remain in ICU up to a few days or even weeks. Undoubtedly this will affect the recovery period and impact the physical strength of the patient as well as the psychosocial well-being, through factors such as critical care neuropathy, malnutrition, pain, and sepsis.

6.4.4 Patient health perceptions

A small number of studies in our analysis found a crucial impact of patients' baseline mental and psychological state as well as personality traits in affecting the QOL outcome after cardiac surgery, albeit all studies finding an overall positive impact of CABG on QOL post-surgery.

In a study by Juergens et al, patients received an illness perception questionnaire prior to surgery, the results of which were found to impact the variance of the QOL outcome post-surgery. In other words, patients' beliefs about a negative impact of their illness pre-surgery was related to poorer physical and mental component scores 3 months after surgery, suggesting a potential role for cognitive intervention prior to surgery.

The study by Khoueiry et al in off-pump CABG patients used the Beck Depression Index to identify that depression and disability initially worsen one month post-surgery but that this remarkably improves by 9 months after surgery.

Lee and colleagues found that anxiety and depression symptoms had a significantly negative impact on QOL improvement after surgery. A study by Middel et al took this further to identify that intrinsic personality traits possessed by patients, conferring negative affectivity and social inhibition (Type D personality), predicted failure of improvement in the physical and mental domains of the SF-36 tool 6 months after surgery. Moreover, the study concluded these findings despite patients achieving an objective improvement in known biomedical variables, including ejection fraction and relief of angina.

6.5 CONCLUSIONS

There is significant evidence demonstrating that CABG improves the quality of life in physical and mental domains, as well as its established efficacy in treating angina and increasing life expectancy. Whilst factors such as minimally invasive surgery and total arterial revascularisation are positive predictors of QOL, post-surgical complications can worsen QOL outcomes. Due attention should be given to certain patient factors, and especially to patient mood and health perception, where pre-operative cognitive intervention may play a role in influencing their outcome.

7.0 Chapter 7

Predictors of early outcome in high risk frail patients undergoing cardiac surgery using accelerometers and its clinical significance

7.1 Hypothesis:

Pre and post-surgery activity can be monitored using an accelerometer for patients undergoing cardiac surgery. This technique allows prediction of adverse early outcome in frail patients undergoing cardiac surgery.

7.2 Introduction:

Physical activity (PA), as a functional assessment of physiological reserves is critically important for predicting the ability to tolerate a major operation that might increase the possibility of greater occurrence of postoperative complications. In advancing age low PA has been linked with reduced physical functioning that compromise mobility [261], a backbone for any individual to maintain self-independence [262]. Sustained PA over an individual lifespan has been shown to improve quality of life, and increases independence and social activity even in those who begin to take part in PA at a later stage in life [263, 264]. This is particularly true in patients with chronic obstructive pulmonary disease or other cardiovascular diseases [265]. Strength training is also a known factor in reducing sleep apnea [266].

The effect of PA intensity level on cardiovascular/cardiovalvular disease as a frailty marker and its relation to advancing age is not clear understood as much of the evidence comes from self-reported data on PA. This has necessitated the development and introduction of frailty measuring tools such as Edmonton Frailty Scale in clinical practice and the need to use technology to objectively capture patient's real time habitual activity level in real world setting is becoming an emerging concept. Accurately recording PA levels and patterns, using lightweight, unobtrusive and comfortable activity monitors such as pedometers and accelerometers have been shown to be sensitive and logistically feasible for measuring

general activity patterns in older adults [180]. However, the use of an accelerometer has been sparsely utilised in these cohort of high risk patients with advancing age although it has been extensively used to assess PA in other age groups and healthy populations [117, 267]

Accelerometers have been validated in calorimetry and especially labeled water techniques [168] and it's believed to be directly proportional to the generated muscle forces and hence to energy expenditure [120]. Coupling this with the inbuilt algorithm enables the conversion of energy expenditure into activity counts, which are generated every 60 seconds. These counts can be classified into thresholds, signifying sedentary to light, light to moderate or moderate to vigorous intensity levels [120]. The cut-point threshold for each of the aforementioned was achieved in a comparable manner to that described by Esliger et al [121].

The use of accelerometers have established benefits over self-reported measures, they are able to objectively track intensity, duration and frequency of an activity without relying on patient recall [125]. GeneActive in particular can detect varying levels of activity and movement in multiple planes (tri-axial) [120] enabling them to be potentially suitable for measuring physical activity in patients with cardiovascular or cardiovalvular diseases, these are largely sedentary population and most functional movement is of low frequency and intensity. Consequently it is implausible to accurately report using self-report measures.

It is widely acknowledged that it is possible to predict adverse effect, morbidity or prolonged length of hospital stay and highlight a cohort of patients requiring additional post-operative rehabilitation or residential care by incorporating frailty scores and physical activity levels into risk assessment preoperatively. Patient frailty is a known factor in contributing to post-operative outcomes in cardiac surgery. Frailty is currently present in approximately 15% of people over 75 years old which further increases to 40% by 85 years [142].

Frailty can be defined as a biologic syndrome of reduced reserve and resistance to stressors, resulting from cumulative declines across several physiologic systems causing eventually increased potential for adverse outcomes [80].

Evidently, there is no current literature simultaneously encompassing a comprehensive study on a set of clinical markers, with self-reported data and frailty measure for validating accelerometer output be that in pre-and or postoperative among patients undergoing cardiac surgery. This study is the first, as it also further validates the output from GeneActive.

GeneActive; a seismic based acceleration sensor established by Unilever Discover (Colworth, United Kingdom UK) and manufactured and disseminated by Activinsights Limited (Kimbolton, Cambridgeshire, UK). The study aims to (i) examine the success of implementing accelerometer in real world setting and to objectively measure PA in cardiac surgery patients. (ii) to assess habitual physical activity levels in high risk patients undergoing cardiac surgery and to compare these measures with disease activity and frailty scores. (iii) to validate whether existing risk models can be significantly improved by incorporating real-time and accurate measurement of individuals' level of PA using accelerometer. (iv) to explore whether high frailty scores can predict adverse outcome. (v) to define the strength of association between PA level and cardiac surgery outcomes; and (vi) to identify relationship between frailty score and acceleration output in predicting post-operative outcome.

7.3 METHOD:

7.3.1 Instrument: GeneActive watch

Light weight tri-axial accelerometer with seismic acceleration sensor of +/-6g at 7.8mg resolution housed in a small (43 × 40 × 13), with a robust water resistant design called GeneActive (Activinsights Ltd) was used in this study as a measuring device. The additional benefit of being able to be worn at different body locations (waist, wrist & ankle) makes

GeneActive, the most appropriate device. In this study patients were able to choose to wear GeneActive at their preferred wrist (right or left). Movement is measured in three dimensions by three accelerometers oriented at right angles to one another.

The sampling frequency of GeneActive ranges from 10 to 160 Hz, similarly the battery can last up to 10d when recording data at 80Hz, hence 10Hz sampling frequency was applied to this study in order to optimize long term monitoring and data collection without the need to re-charge or premature run of data storage capacity.



Figure 18 - 7.1 GeneActive wrist watch

7.3.2 Participant and protocol

The sample consisted of 80 patients undergoing cardiac surgery with no contraindications (not allergic to plastic or metal) who satisfied the following inclusion criteria: (i) age ≥ 65 years, (ii) agree to wear a wrist band (GeneActive) that contains a tri-axial accelerometer in order to objectively measure their PA levels both preoperatively for a period of 14 days (24/7) and postoperatively for a period of 30 days (24/7) including while sleeping and bathing, (iii) agreed and signed the content in the consent form. (iv) were able to walk freely

(not wheelchair bound). The study protocol was approved by NRES Committee London - Harrow Research Ethics Committee (14/LO/0693).

7.3.2 Outcome measure

7.3.2.1 Physical activity

PA was evaluated using GeneActive accelerometer calibrated with sampling frequency of 10Hz which allows data collection for up to 60 days without the need to re-charge or run out of data storage capacity. Recording start mode was set as “On button press”, once activated the GeneActive continuously tracks activity and stores raw data whether or not it’s worn. This enables the end user to have greater control over the raw accelerometry data processing and measure skin surface temperature. Converted data is recorded every second and summed to produce 60 seconds epochs of activity. The inbuilt three accelerometers oriented at 45° to each other captures movement in three dimensions (X, Y and Z) vectors. The resultant vector was achieved by integrating data from the three dimensions into a single-dimensional signal magnitude vector as shown below [121].

$$SMV = \sqrt{X^2 + Y^2 + Z^2}$$

Data was then uploaded using GeneActive supplied PC software from the wrist band accelerometer, The extracted raw data is done so as a .bin file; however the GeneActive software enables the user to convert this into .csv (compressed epoch files), which can be loaded in to excel sheets. Epoch period of 60 seconds was selected and the temperature compensation box enabled. The .csv files were then uploaded to GeneActive supplied Macros [268]. Data reduction was implemented by removing all non-wear periods at the end of the file, non-wear algorithm was define by looking at no movement for over a period of 1 hour.

The activity patterns and intensity was further classified into sedentary, light, moderate and vigorous physical activity for each patient after having the results from the accelerometer activity. The threshold cut-point to define each of the activity intensity was calculated using

the higher of Eslinger et al [121] scaled appropriately and according to the activity counts recorded and the analysis of the inbuilt algorithm calculated by GeneActive macros [268].

7.3.2.1 Frailty score

In this study we applied the Reported Edmonton Frail Scale (REFS) as a tool to measure frailty due to the following reasons. (i) REFS are a reliable tool that has been validated and used by different studies [161, 269](ii) It associates moderately well with the Geriatrician's Clinical Impression of Frailty (GCIF), cognitive impairment, increasing comorbidity and functional impairment; (iii) It has been proven to have excellent inter-rater reliability when administered by researchers without medical training.

The REFS samples 9 main domains with a maximum frailty score of 18. One domain – the clock test for cognitive impairment is used to test performance-based items. The other domains are general health status, mood, functional independence, medication use, social support, nutrition, continence, self-reported performance measuring physical activity, burden of medical illness and quality of life which are all standard historical items in geriatric assessment.

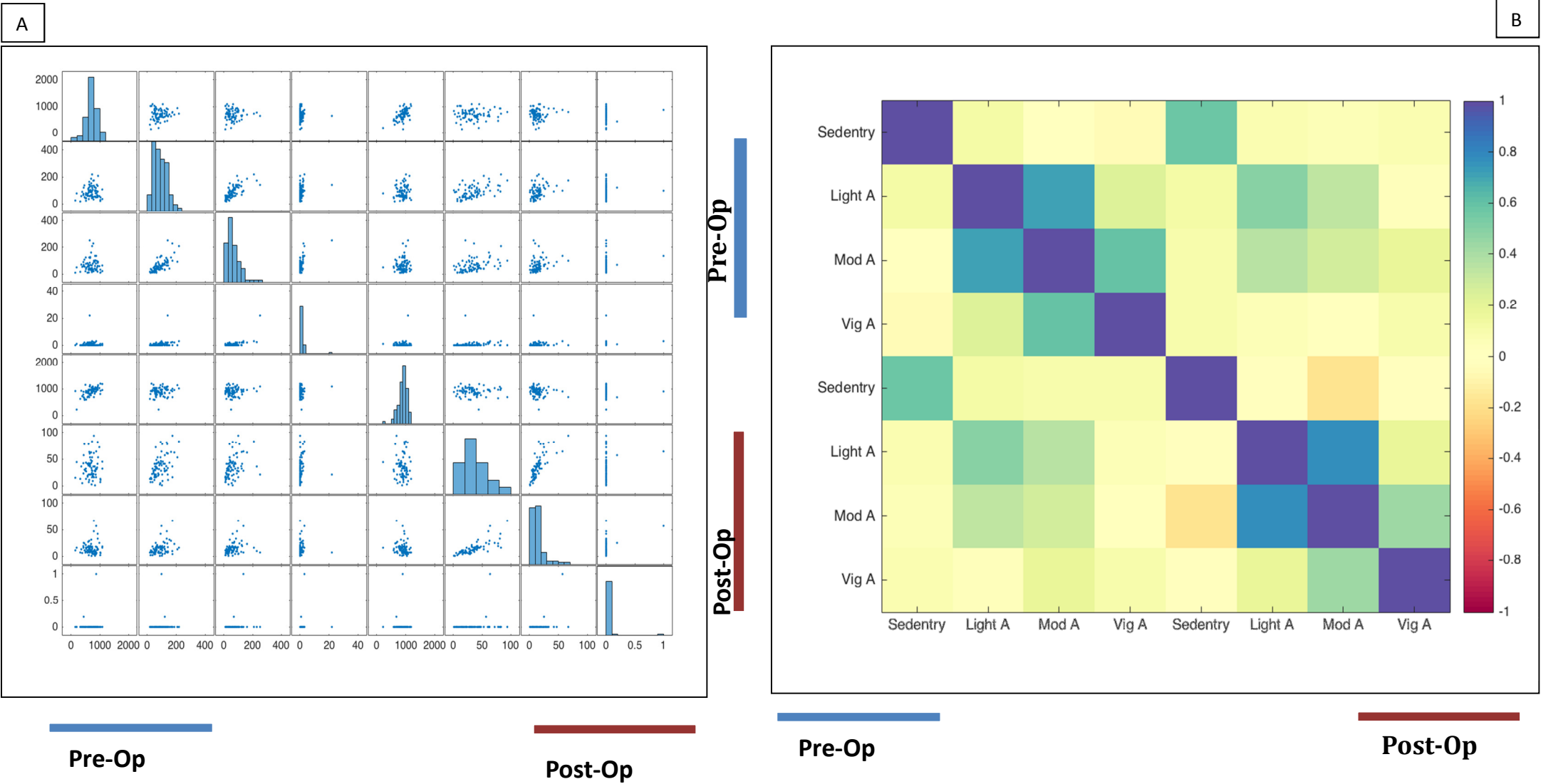
7.4 Results.

Table 10 - 7.1: Demonstrate the general change with respect to pre-op vs. post-op in PA level.

N=80	Pre-Op Mean	Post-Op Mean	t-test P-value	MW test P-value	KS test P-value
Sedentary (mean +/- SD)	703 +/- 191.1	895.9 +/- 156.2	0.0	0.0	0.0
Light A (mean +/- SD)	90.2 +/- 45.1	35.4 +/- 20.6	0.0	0.0	0.0
Mod A (mean +/- SD)	64.1 +/- 48.0	14.6 +/- 11.5	0.0	0.0	0.0
Vig A (mean +/- SD)	0.8 +/- 2.5	0.0 +/- 0.1	0.0	0.0	0.0

Pre-op=pre-operative, Post-op= post-operative

Graph 5.1. Scatter graph (A) and Heat map (B) highlighting the correlation between the pre-op vs post-op PA level.



Graph 5.2. Heat map (A) and scatter graph (B) highlighting the difference of pre-op vs post-op PA level

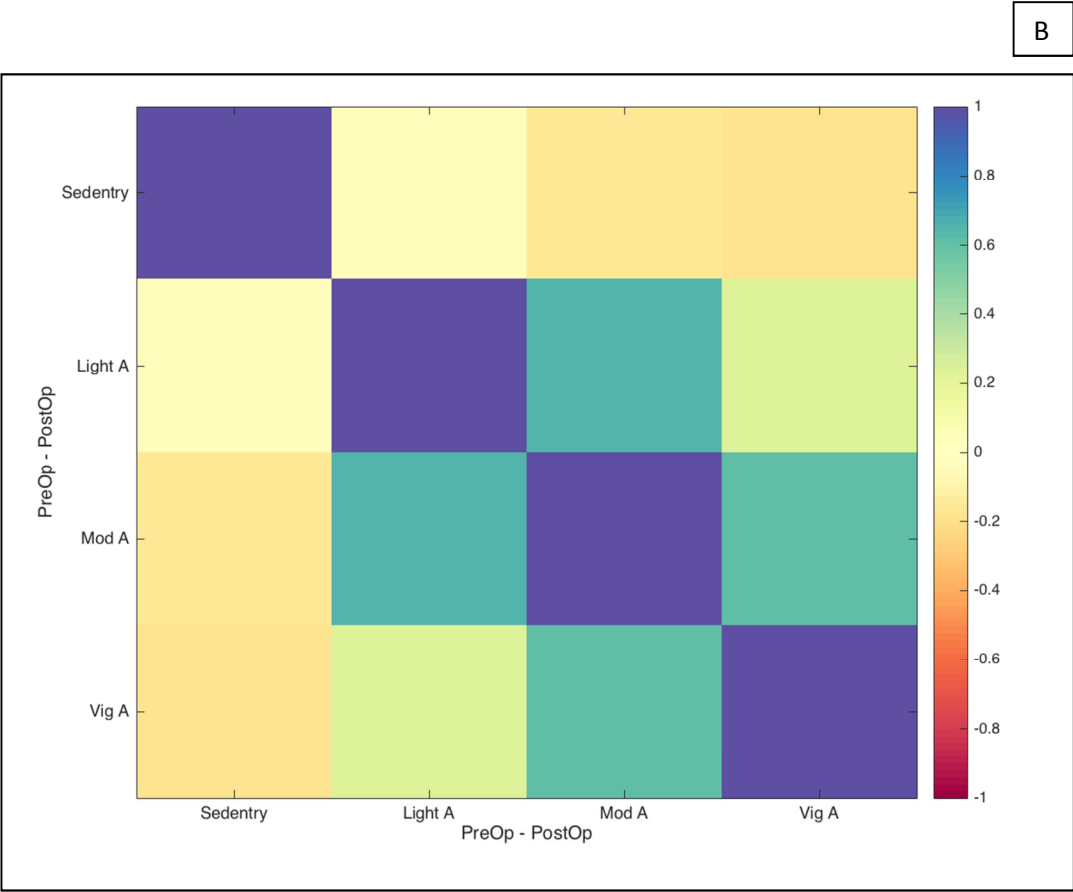
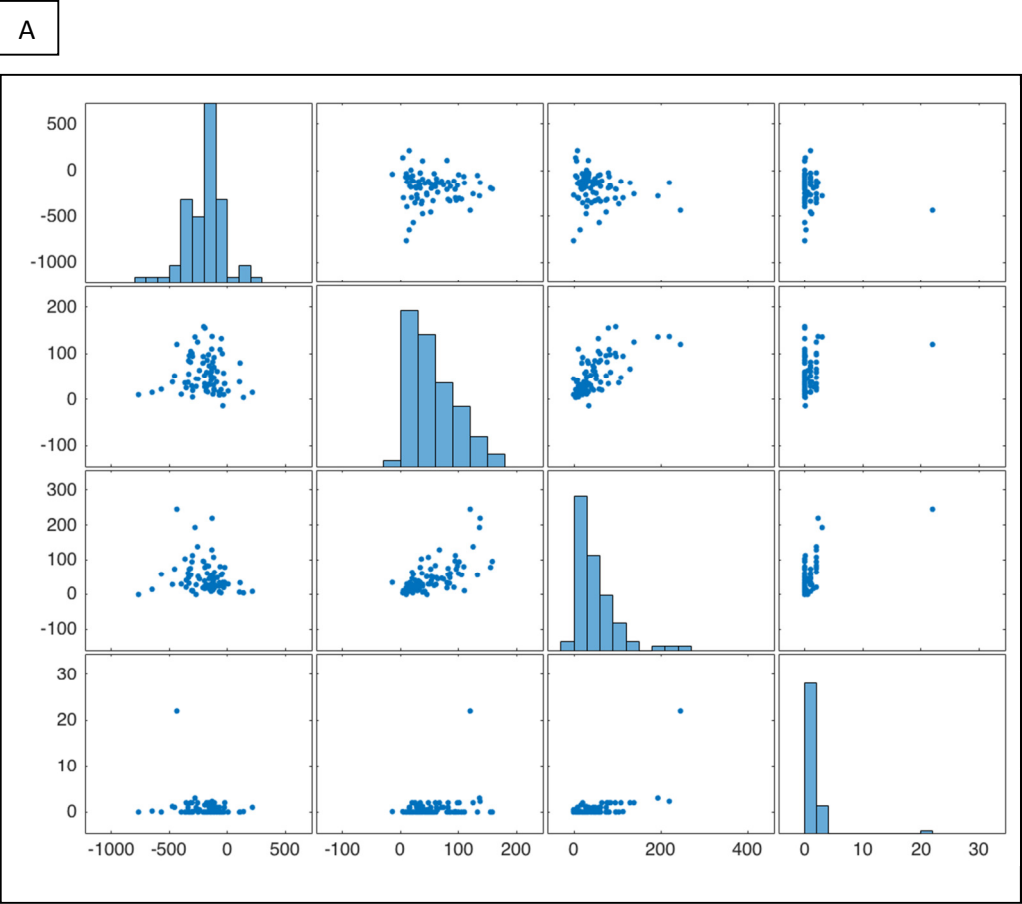


Table 11 - 7.2: PA level classified into the two groups: Low Frailty (≤ 9) vs. High Frailty (>9) and in relation to pre-op vs. post-op intensity.

N=80	Activity Type	Low Frail	High frail	T-test P-value	MW test P-value	KS test P-value
Pre-Op	Sedentary (mean +/- SD)	715.5 +/- 201.5	667.7 +/- 157.5	0.328	0.1682	0.1294
	Light A (mean +/- SD)	99.7 +/- 46.9	63.5 +/- 26.2	0.001	0.0007	0.0005
	Mod A (mean +/- SD)	72.6 +/- 52.2	40.2 +/- 19.4	0.007	0.0052	0.0015
	Vig A (mean +/- SD)	0.9 +/- 2.9	0.3 +/- 0.7	0.358	0.2282	0.9086
Post-Op	Sedentary (mean +/- SD)	899.7 +/- 163.1	885.4 +/- 137.9	0.722	0.6304	0.7513
	Light A (mean +/- SD)	37.4 +/- 21.4	30.1 +/- 17.8	0.164	0.1269	0.1124
	Mod A (mean +/- SD)	16.2 +/- 12.7	10.2 +/- 5.2	0.04	0.0488	0.1055
	Vig A (mean +/- SD)	0.0 +/- 0.1	0.0 +/- 0.0	0.488	0.4072	1

Table 12 - Table 7.3. PA level classified into the two groups: Low Frailty (≤ 9) vs. High Frailty (>9) and in relation to Difference between pre-op vs. post-op intensity.

N=80	Low Frailty (≤ 9)	High Frailty (>9)
Sedentary Activity (mean +/- SD)	-184.1 +/- 161.3	-217.7 +/- 166.2
Light Activity (mean +/- SD)	62.3 +/- 42.4	33.4 +/- 17.4
Moderate Activity (mean +/- SD)	56.5 +/- 51.2	29.9 +/- 17.2
Vigorous Activity (mean +/- SD)	0.92 +/- 2.9	0.3 +/- 0.7

Table 13 - 7.4. PA level classified into the two groups: Low Frailty (≤ 9) vs. High Frailty (>9) and in its relation with frailty score (pre-op vs. post-op intensity)

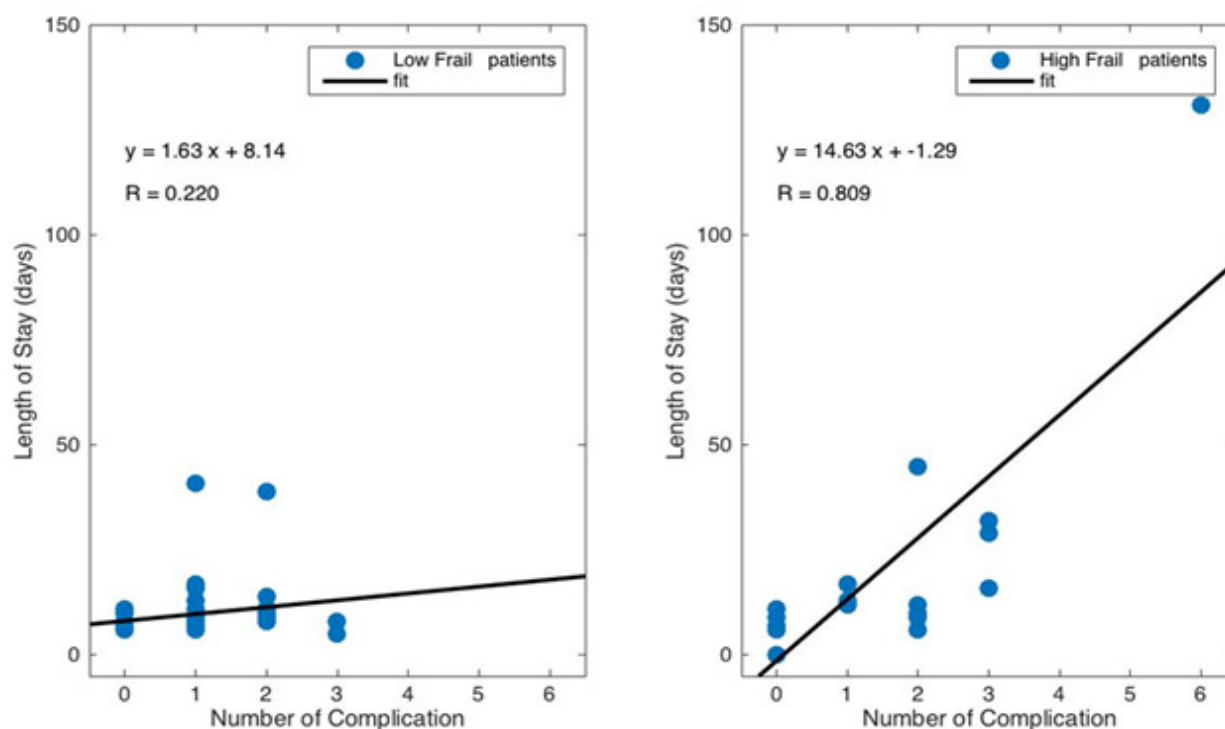
	Pre-Op				Post-Op			
Frailty vs. PA correlation	Sedentary Activity	Light Activity	Moderate Activity	Vigorous Activity	Sedentary Activity	Light Activity	Moderate Activity	Vigorous Activity
Correlation Coefficients	-0.2669	-0.4290	-0.3900	-0.2806	-0.1667	-0.3093	-0.3548	-0.1539
P-value	0.0167	0.0001	0.0003	0.0117	0.1395	0.0052	0.0012	0.1728

Pre-op=pre-operative, Post-op= post-operative

Table 14 - 7.5: Compares complication rate for the two groups: Low Frailty (≤ 9) vs. High frailty (>9)

	Low Frail (Control)	High Frail (exposed)	<i>P-value</i>
Composite Complication	2	4	0.019
Renal Failure	3	5	0.014
Re-operation	4	5	0.033

Graph 5.3: Presents LoS against complication for the two groups: Low Frailty (≤ 9) vs. High frailty (>9) and Kaplan Meyer Plot.



7.5 Discussion.

Tri-axial accelerometer was used to assess the habitual physical activity level of high risk frail patients undergoing cardiac surgery. Our results support the clinical utility of accelerometry as an outcome measure to accurately quantify different levels of habitual physical activity; this was highlighted as such in patients undergoing cardiac surgery and frailty (validated by its association with the Reported Edmonton frail scale (REFS)).

Predictive validity

This study has demonstrated distinct patterns of quantifiable differences in physical activity levels and intensity over the course of the day (for the two groups). Furthermore, Patients with high frailty scores were more sedentary with fewer habitual physical activities compared to those who were not frail or with mild frailty. Previous studies have shown that an average American adult spends 60% of their day in sedentary activities [270].

Evidently, the cardiac group that identified higher count of physically active patients scored better in almost every domain of the REFS, as a result patients with greater intensity of habitual physical activities reported feeling better than those patients with lower intensity level of physical activities. These findings are supported by earlier studies highlighting direct relationship between exercise capabilities improving the sense of well-being in older patients [263, 264]. Although not having an effect on disease activity with certainty, greater intensity of habitual or ambulatory physical activity levels are clearly associated with markedly improved quality of life and sense of well-being as along with potentially enabling the patients to fairly cope with the disease activity.

Previous studies have reported energy expenditure indexes of total or activity calories as a measure of accelerometer output, however in our study we opted to report raw index of physical movement (vector magnitude) when measuring accelerometer output. Offsetting the probability of those patients with cardiovascular disease will be underrated by energy

expenditure prediction formula. This is supported by a recent study [271] that reports the proprietary Tritrac formula underestimated energy expenditure when compared to indirect calorimetry in older adults. Using vector magnitude to quantify activity instead of activity calories has been recommended for physically impaired persons, elderly patients or those with insufficient energy use during walking and on routine habitual activities [272]

The correlation coefficient presented relationship between accelerometer output and REFS results suggesting that tri-axial accelerometer is a valid tool to measure physical activity level in this cohort of functionally-limited patients. Even-though the most significant differences were noted before the operation ($P=0.0464$) rather than the post procedures; this can be explained by the fact that all patients were made to wear the wrist band five days post operatively for a month. We believe the result would have been very different if we had applied the wrist bands at 3 or 6 month post-operatively. Furthermore the patients under investigation ($n=80$) could have had a larger number ($n=150$) which could be a factor and would have significantly increased diversity and hence improved pooled result post-operatively.

Implications of key findings.

This study highlights the lack of screening tools in cardiac outpatient's clinics to determine which cardiac patients are at high risk of poor outcome and unplanned longer in-hospital stay. The combined use of (REFS and Tri-axial accelerometer) tools to measure frailty proved to strongly and independently associate with combined outcome of unevaluated and unplanned hospitalisation and death in one case. Furthermore the distinct differences in complication rates between high frail patients versus low frail signifies excellent prognostic utility of the frailty tools used which hold a potential promise as a user friendly tools to identify high risk patients. The study has shown low frail patients are less likely to have one or more complication with relative risk of 0.4421 when compared to high frail patients. The odds ratio

were (OR: 0.2716) with significant P value of ($p=0.0287$). In addition, high frail patients were twice more likely to have longer in-hospital stay than non-frail (Mean 21.2 vs. 9.6 days) respectively with significant t-test value ($p=0.016$).

None the less it can be argued tri-axial accelerometer has good simultaneous validity in relation to its fairly robust association with exercise propensity tolerance and level of disease activity and is by far superior to currently used self-report methods that rely on memory. This makes accelerometer a potentially valuable tool in risk stratification and modification as it enables the researcher to detect a cohort of patients whose sedentary lifestyle pose great risk to their general health and well-being. Furthermore it acts as an outcome measure in interventions to improve mobility as it highlights the needs of patients with either neuromuscular or cognitive impairment or frailty that require additional pre-operative exercise prescription as well as post-operative planned rehabilitation and residential care.

Benefits of tri-axial accelerometer application in cardiac patients.

Benefits of accelerometer use in this study included patients reporting the device being comfortable to wear and not overly intrusive. The study also benefits from being a novel strategy to measure an important dimension of functional status and quality of life not formerly well-reckoned.

The use of raw acceleration data permits for more transparent data analysis than proprietary movement counts. However some weaknesses were noticed. (i) Larger study sample with diverse degree of frailty (high, mild frailty as well as very fit participants etc) are needed to evaluate whether these dynamics might modify our findings better. (ii) Vibration and movement from riding cars and other moving vehicles could contribute potential acceleration error. (iii) Older patients with cognitive impairment and some kind of memory loss were excluded from the study.

Despite these limitations, the growing economic constraints on the UK NHS and other national healthcare systems necessitate the use of technology in order to enhance in our ability to assess and predict the risk associated with medical and surgical interventions. Through careful refinement and accurate selection of frailty assessment tools it is possible that we may be able to in future inculcate an improved estimation of risk in our ever-aging patient population. In this way, we may optimise patient selection and subsequently guide patients towards personalised treatment plans that will maximize the unmet need to optimize resource distribution and to avoid costly but ineffective interventions. Further studies are needed to examine the generalizability of our findings across different populations and accelerometer types.

Conclusion.

A difference has been identified in the preoperative activity; this was measured by the accelerometer between highly frail and less frail patients. The operation affected the activity level of both groups with no significant difference noted postoperatively between them. Complication aggregation and length of hospital stay were higher in the highly frail group.

Main Points

- Tri-axial accelerometer has good simultaneous validity in relation to its fairly robust association with exercise propensity tolerance and level of disease activity and is by far superior to currently used self-report methods that rely on memory.
- Accelerometers are potentially valuable tools in risk stratification and modification as it enables the researcher to detect a cohort of patients whose sedentary lifestyle pose great risk to their general health and well-being.
- The combined use of REFS and Tri-axial accelerometer tools to measure frailty proofed to strongly and independently associate with combined outcome of unevaluated and unplanned hospitalisation.
- High frail patients were twice more likely to have longer in-hospital stay than non-frail (Mean 21.2 vs. 9.6 days) respectively with significant t-test value ($p=0.016$).
- Distinct differences in complication rates between high frail versus low frail patients signifies excellent prognostic utility of the frailty tools used which hold a potential promise as a user friendly tools to identify high risk patients.
- Using vector magnitude to quantify activity level instead of activity calories has been recommended for physically impaired persons, elderly patients or those with insufficient energy use during walking and on routine habitual activities.

8.0 Chapter 8

National Survey of Frailty consideration in Cardiovascular MDT.

Aim: 1.To assess frailty factor and influence in heart team meeting.

2. Measuring the quality of MDT Process.

8.1Introduction.

Since the publication of the SYNTAX trial [273] and National Service Framework (NSF) for coronary artery disease (CAD) [274] a new concept of decision making between cardiologists and surgeons has emerged. There has been an increase interest for implementing a new strategy to integrate multidisciplinary teams (MDTs) for heart failure further [275]. The ACCF/AHF Guidelines identify a Heart Team as a multidisciplinary team composed of an interventional cardiologist and cardiac surgeon that reviews the patient's medical condition, and agrees that either PCI or CABG procedure is technically suitable and communicates the shared decision outcome with the patients or duly appointed surrogates before commencing any treatment [276].

The Heart Team Multidisciplinary meeting (MDT), normally comprising of a surgeon, an interventional and non-interventional cardiologist, radiologist, nurse practitioners, geriatricians, cardiac anaesthetist as well as other non-clinical staffs (MDT coordinator) and allied health professionals, became central to the management of heart failure patients. MDT is normally chaired by a cardiac surgeon and the outcome and decision is populated into an MDT proforma by the MDT co-ordinator - hence an MDT proforma is filled for each patient.

The perception of Heart Team managing patients with complex coronary artery disease is now a Class 1C recommendation in guidelines issued by American and European professionals [277, 278]. In addition the 2014 European Association of Cardiothoracic Surgery (EACTS) and the European Society of Cardiology (ESC) guidelines provide auxiliary interpretation on a cohort of patient group that must be discussed by Heart Team

[278]. This necessitated the thought of expanding of Heart Team initiatives into routine clinical care and has since become established across the National Health Service (NHS) [275].

8.2 Advanced heart failure and mutual decision making: Why?

The legal and ethical mandate empowers service providers to lead the prerequisite to involve patients in each stage of their treatment plan. Shared decision making also covers consenting to treatment after fully informing the patients of the risks and benefits involved [279].

Managing heart failure patients can take several years, their treatment and interventional procedures vary at individual level. In addition the complexity of the presented clinical conditions largely due to frailty, the presences of significant co-morbidities, and polypharmacy merits a shared decision making [280]. Furthermore, the continuous technological advancement and therapeutic procedures can augment important benefits and carry complications such as hospital bed retention, re-admissions and diminished quality of life for a cohort of frail patients not identified in the pre-assessment clinics [281].

MDT meetings are believed to encourage better teamwork with the sole purpose of improving patients' safety and care [282]; such prolific meetings should also offer an environment for education and training even though it is currently under-developed. MDT meetings are characterised by an evidence based approach to decision-making [283, 284]. However shared decision-making for advanced heart failure has become increasingly challenging and more crucial as a result of longer life expectancy, disease duration and an increase in treatment options.

Reports suggest heart failure affects 2.4% of the adult population, and this number increases to 11% for adults over the age of >80 years with predicted economic implications of 44.6 billion by the year 2050 in USA alone [285]. Furthermore given the extensive use of Heart

Team MDTs, unnecessary disparities in team membership and processes and the consequences for patients of inequitable care can have an impact on the opportunity costs for the NHS. Thus it is crucial to investigate what constitutes quality improvement or acts as a proven backup for quality of care.

A study by Hannan et al [137] and Lee et al [138] reported that both patients and cardiologists, when asked why CABG was carried out, respectively responded showing a lack of consistent targets and aims. It is therefore necessary to have reproducible transparency in MDT decision-making. The information must be presented to the MDT in a comprehensive manner to ensure an all-inclusive assessment of each patient and frailty factors must be considered.

In the light of the above; shared decision making is ultimately beyond informed consent, explanation of risk and benefits or reasonable alternatives but rather involves clinicians working with patients to uphold patient values, goals, and preference that should guide informed decision [138]. Shared decision incorporates clinician perspective in his/her responsibility to refine the diagnosis and treatment types to those that are clinically sensible. Shared decision also entails clinicians and patients sharing information and working towards patients-centered decisions about treatment. Hence an integrated team approach with diverse medical expertise may be able to provide a personalized and more robust treatment plan for a particular patient.

Furthermore, other factors compelled by the Bristol enquiry [286] and the publication of named surgeon specific mortality outcome by the Society of Cardiothoracic Surgeons in Great Britain and Ireland (SCTS) [287], reported outcomes from 10 other specialities in myNHS website [288] exacerbated the want for transparency in decision-making. This coupled with media attention which may or may never help patients to determine which

course of treatment to follow, and patients or duly appointed surrogates expectations being greater than ever before instigate an urgent need for MDT process re-evaluation and frailty influence considerations in the meeting [289].

None the less, basic questions, such as the importance of MDT in practice, have not been addressed. Even though observational studies from other medical specialities such as the well-established cancer MDT have already demonstrated the benefit of MDT methodology in terms of optimum treatment [290, 291] ambiguity about what constitutes effective MDT meeting structure and process has resulted considerable diversity in the recommended guidelines and there is no randomised trial on survival and quality of life regarding follow-up on MDT decisions or even its reducibility.

8.3 Heart Failure: Prognosis, Risk Appraisal and Quality of Life.

Cardiac procedures carry immediate, early and delayed risks of complications. Little objective data exists on how patients recover physically from surgery or the impact surgery has on their quality of life. The diversity of the reported heart failure variables associated with mortality and re-admission in the literature is well over 100 [292]. Examples of these prognostic factors include demographics, functional status, exercise capacity, cardiac structure and function, biomarkers, filling pressure, comorbidities, renal and liver dysfunction, mental and physical health status component and finally interest in frailty as a predictor of adverse outcome in cardiac surgery is growing [111].

During this time, a greater focus on developing a variety of multivariable models has been established in order to narrow predictions of prognosis in patients with heart failure. A further study highlighted a group of heart failure patient at risk for unfavourable quality of life [293]. The application of these models in advance heart failure have been shown to either overrate preoperative risk in healthy elderly patients or underrate the risk posed by surgery in higher risk frail patients with similar morbidities. For instance EuroSCORE II tends to overrate

preoperative risk in healthy elderly patients, whereas STS underrates the risk posed by surgery in higher risk frail patients with similar morbidities [109]. Before developing a clinical prediction model, certain factors are lacking in the current models, which needs to be incorporated into the new model; adequate discriminatory ability (ability of a model to accurately distinguish between a patient at adverse risk versus one who is not) [294, 295] and calibration (ability of the model to accurately predict the observed probability of an event across levels of risk) [296] should be applied after validating it in broader population and targeted clinical trials.

Given the nature of the clinical course of heart failure patients which fluctuates radically across the spectrum of disease cruelty and unpredictability for an individual patients figure 6.1 [276, 292], sharply contrasting the observed linear decline of advanced cancer patients, clinicians need to pay focused attention to the clinical trajectory in order to regulate expectations and guide timely decision, as heart failure patients enjoy good days and superficial stability which may give respite to the patients and their care team into deferring vital decisions.

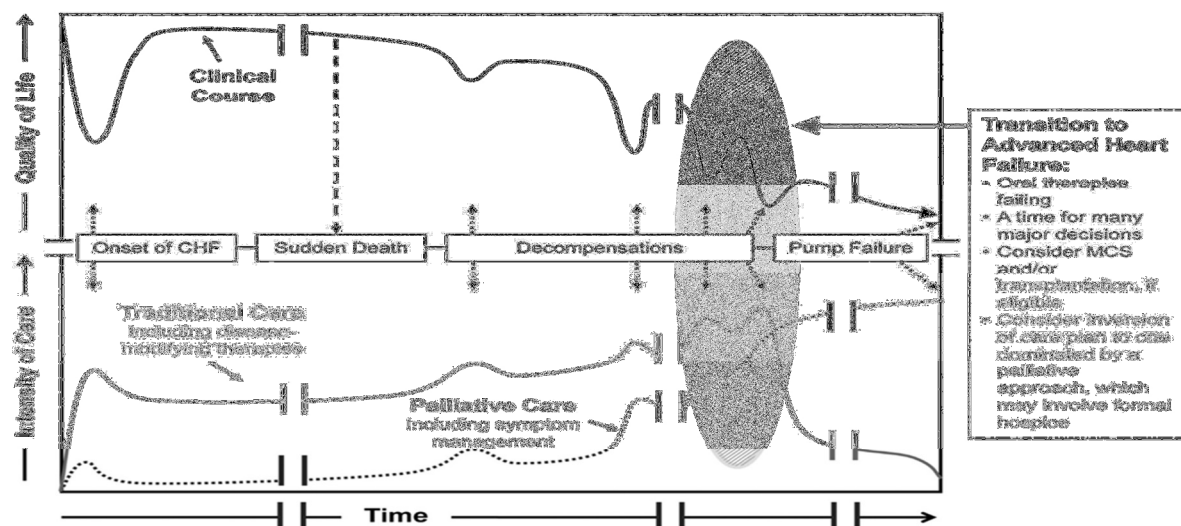


Figure 19 - 8.1 illustrations of clinical progression of heart failure with its related forms and intensities of presented therapies. Figure adopted from Lanken etl.

(https://www.google.co.uk/search?q=lanken+et+al+heart+failure&source=lnms&tbn=isch&sa=x&ved=0ahukewjdpouehijtahnkimakhqlldx_oq_auihygc&biw=1920&bih=963&dpr=1&surl=1#imgsrc=tp6RoUzTy1GhvM:&spf=19)

When taking into consideration all factors, it is obvious that most prognostic models in heart failure emphasise on mortality. However other clinical outcomes are crucial to different patients 8.2. This includes perceived improvement in quality of life, functional capacity, independence regain, participation of social activity and decreased reliance on caregiver commitment [297]. Evidently research on these factors is still in its infancy stages and there are almost no empirical real-world data that quantifies the perceived benefit or the opposite of these perceptions (risks) on outcomes. Allen et al [293] is the only study that reported a model that estimates the risk of poor future quality of life highlighting crucial contrast from risk models for adverse outcome, particularly the comparative significance of current measures of quality of life.

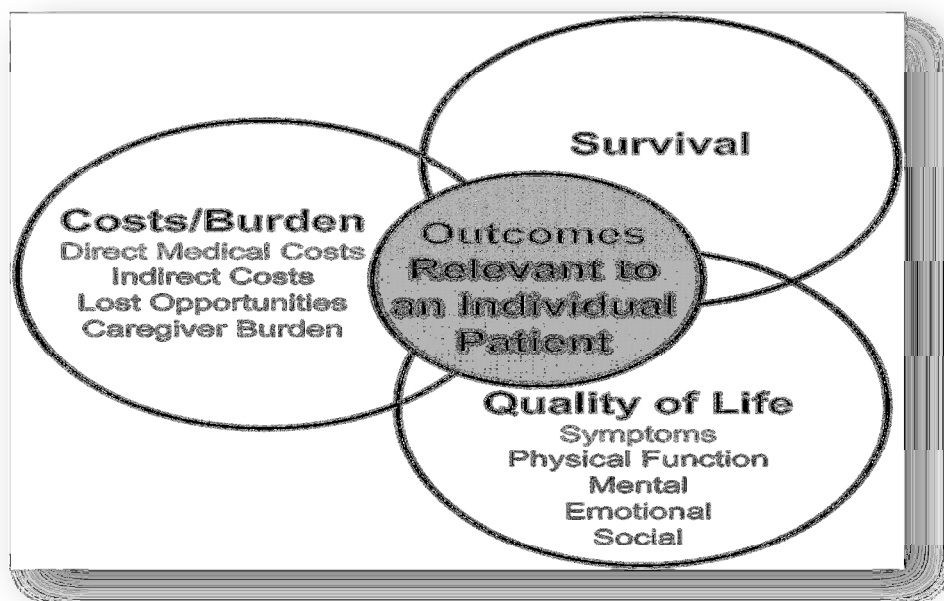


Figure 20 - 8.2 Multiple domains that is crucial for heart failure patients other than the usual adverse outcome. Adapted from Spilker et al.

https://www.google.co.uk/search?q=spilker+prognosis&source=lnms&tbm=isch&sa=x&ved=0ahukewiq4ki81o_tahwfkmaxhaxlbtwq_auibygc&biw=1920&bih=963&surl=1#imgsrc=wDwxQHOfhmEFgM:&spf=283.

In order to investigate further what constitutes effective MDT process and whether frailty factor is considered, a national survey was conducted and sent via the Society of Cardiothoracic Surgery (SCTS) to all cardiac MDT members in UK and N. Ireland in order to provide an insight into the current clinical practice regarding essential component and ways to improve and measure the quality of adult cardiac MDT.

8.4 Aim & objectives

The aim is to complete a comprehensive survey, assessing all UK Heart Team opinions on the performance of working MDT meeting. The specific objectives are:

1. To develop quality criteria for assessment of characteristics observable in Multi-disciplinary Team Meetings.
2. To develop and evaluate a checklist to support decision making in Heart team Multidisciplinary meeting (MDM).
3. To assess opinion on the MDT decision making process, frailty consideration and barriers to reach a decision.
4. The study will provide recommendations to improve patient selection criteria for cardiothoracic surgery within the framework of MDT process.

8.5 Methodology

8.5.1 Survey Design

In order to achieve the above objectives a unique questionnaire has been designed using the following methods:

1. A literature search was performed in order to develop the relevant themes.
2. Focus group semi-structured interviews including consultant surgeons, interventional cardiologists, cardiologists, MDT Nurse & MDT coordinator were performed which uncovered unexplored themes not present within the literature.

Questionnaire validation through techniques such as inter-domain comparison (with the use of Cronbach's alpha etc.) is not feasible in this questionnaire since around 100 respondents would be needed to pilot such a survey.

The questionnaire has been transferred to 'Qualtrics', an advanced piece of online survey software to which Imperial College is subscribed.

https://imperial.eu.qualtrics.com/jfe/form/SV_4IMfpczcEd0DXpj

Anonymity was guaranteed to respondents and in May 2015 the survey was emailed to a database of UK Heart Teams after being endorsed by SCTS president Tim Graham. This was followed by a reminder email 2 weeks later, and the survey was closed after a month. Before dissemination, advanced statistical and qualitative analysis was performed.

8.5.2 Survey Content.

The survey consisted of 16 main questions within which most had a subset of multiple questions. Others required just yes or no answers. Overall four themes were explored: six questions explored the team (attendance, leadership, team work & culture, team sociability, mutual respect and professional development & training); two questions assessed infrastructure (meeting venue and technology & equipment); Four questions emphasised consulting team and logistics (agenda, prioritisation of complex cases, patient notes and case presentation); Two questions covered clinical decision making and frailty consideration (patients centered care and treatment plans). There was also a further two questions exploring demographic representation and sub-speciality professional role within the Heart Team.

8.6 Participants

8.6.1 Inclusion criteria

1. All members of Heart Team participating in MDT meeting and working in Great Britain.
2. No other inclusion criteria

8.6.2 Exclusion criteria

In order to complete the survey, participants must meet the single inclusion criteria listed above. If they do not meet this, they will be excluded from the survey.

8.7 Regulatory issues

8.7.1 Ethics approval

Our overall assessment of this project is that it is a low-risk one, which does not raise any serious ethical issues whatsoever. Specifically, we are performing this survey in a group of professional individuals who will imply consent by completing the survey. No individual will be put at risk given the complete anonymity of the survey.

Despite this, we feel it is important to get ethical review for two reasons:

1. It is accepted good research practice to ensure some form of ethical review is required
2. In order to publish in a reputable peer reviewed journal some form of ethical review will be required.

According to Health Research Authority (HRA) guidance, a review by a 'National' Research Ethics Service is not normally required for research involving healthcare staff by virtue of their professional role. Please see pages 10, 13 & 16 from:

<http://www.hra.nhs.uk/documents/2013/09/does-my-project-require-rec-review.pdf>. [298].

8.7 Consent

In this study participant's consent was assumed when they opted to complete the questionnaire. Given that the group of people being surveyed were professionals we did not anticipate any issues surrounding the consent process.

Contained in Appendix 6 is the email we sent out which describes the purpose of the survey and gave participants enough information to decide whether to participate. If during the survey they wished to withdraw, they were simply able to discontinue the survey/close the browser. Once their responses had been submitted they were not be able to withdraw because the responses were anonymous.

8.7.1 Sponsorship

Imperial College London acted as the main sponsor for this study.

8.7.2 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies that apply to this study.

8.7.3 Audit and project management

Investigator (YS) monitored the conduct of this survey. We did not anticipate any adverse events given the nature of the project (an online survey). Any questions that arose from participants were directed towards Professor Athanasiou (contact details available in email to participants) in the first instant.

The data has been stored in a secure dedicated location at Imperial College London (Hammersmith Hospital campus) for a period of 10 years as per college policy.

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

8.7.4 Funding

Given the nature of the project, we did not apply for funding and no direct costs were incurred.

Imperial College
London

Imperial College Healthcare 
NHS Trust

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Imperial College London and
Imperial College Healthcare NHS Trust
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Ruth Nicholson
Research Governance Manager

21/05/2015

Mr Yusuf Abdullahi
Imperial College London
Hammersmith Hospital
Du Cane Road
W12 0HS

Dear Mr Abdullahi

RE: National Survey of Heart Team: Measuring the quality of MDT Process

Joint Research Compliance Office Reference number: 15IC2708

This is to confirm that the above named research project utilises human participants, their organs, tissue and/or data as defined under the sponsorship requirements of the Research Governance Framework for Health and Social Care 2005, incorporating the Medicines for Human Use (Clinical Trials) Regulations 2004.

On behalf of Imperial College of Science, Technology and Medicine, we undertake to act as the identified Research Sponsor for this project.

This letter confirms:

- The research proposal has been discussed, assessed and registered with the Joint Research Compliance Office, Imperial College Academic Health Science Centre, Imperial College London and provisional sponsor approval granted.
- The Chief Investigator has undergone a process of scientific critique commensurate with the scale of the project.
- Indemnity and insurance arrangements have been put in place to cover the project.
- Resources and support are available to the research team to aid delivery of the research as proposed.
- Management, monitoring and reporting responsibilities for the research have been approved.
- Imperial College will undertake and enforce those sponsor duties set out in the NHS Research Governance Framework for Health and Social Care.

Imperial College Sponsorship is conditional on the project receiving applicable ethical and regulatory approval for all research related aspects of its conduct. It is also conditional on successful contract and agreement negotiations and sign off via the Joint Research Office, where relevant, and before the study commences.

A copy of the ethics approval letter **must** be sent to the Research Governance Manager prior to the study commencing. Sponsorship is dependant on obtaining R&D Office approval for all NHS sites where the research is being conducted.

Yours sincerely

Ruth Nicholson
Research Governance Manager

8.8 Results.

8.8.1 Statistical Analysis

Statistical analysis was performed using Matlab 2015a to quantify any relationship between answers and the constructed characteristics deemed crucial in a Heart Team MDT.

Overall 62 Heart Team members responded and a diverse opinion was noted across the different specialities and the represented regions. The survey questions assessing Four-point likert scales was pooled to binomial coefficient, scores 4 & 3 on the scale (eg, always present and usually present) were recorded into 1 and scores 2 and 0 (eg, sometimes and never) were recorded into 0.

Questions were entered into the model and a colour coded heat map was created to highlight the matching variables with statistically significant outcome values. The breakdown of survey answers evaluating the characteristics deemed invaluable when measuring the quality of Heart Team MDT is reported below.

8.8.2 MDT Team characteristics (Q1-6).

The attendance question was highly noted as crucial for a successful Heart Team and should comprise of a surgeon, interventional cardiologist and cardiologist, nurse and radiologist; however different regions and specialities reported diverse answers to these variables when asked to indicate how often one of the above is present at their local MDT (figure 6.3)

Ideally MDT lead should attend at least 90% of session but due to the design of the survey we did not see the need to separate the lead attendance from the core team. cardiologist (87% present vs. 13% absent), interventional cardiologist and surgeon both had similar result (85% present vs. 15% absent), nurse/ coordinator (50% present vs.50% absent), radiologist had the lowest attendance (38% present vs.62% absent).This can be explained as either many Heart Team centres not being well established or their respective meeting venues lacking the appropriate technology and equipment. Another possibility is that radiologists will be mainly left out during case discussion as surgeons and cardiologists dominate the session, hence they will not be intrigued to take part every session [299].

Leadership competency was assessed with the majority of respondents rating the chair keeps the meeting to agenda (74.51% yes, 25.49 no), encourages meetings participation (75% yes, 25% no), focused discussion encouraged (69.09% yes, 30.91% no), and speaks clearly on the recommendations (73.68% yes, 26.32% no).

Another question assessed was factors contributing to inclusivity of the relevant team members in order to quantify another quality of a successful Heart Team meeting i.e team working dynamics & culture. The majority of the respondents feel that the meeting is open (77.50% yes, 22.50% no), questions and ideas input are encouraged (75.44% yes, 24.56% no), focused attention harnesses decision-making (75.93% yes, 24.07% no), and finally that the experience of the respondents' was strongly predictive of diversity in unanimity of decision making (42.59% yes, 57.41% no).

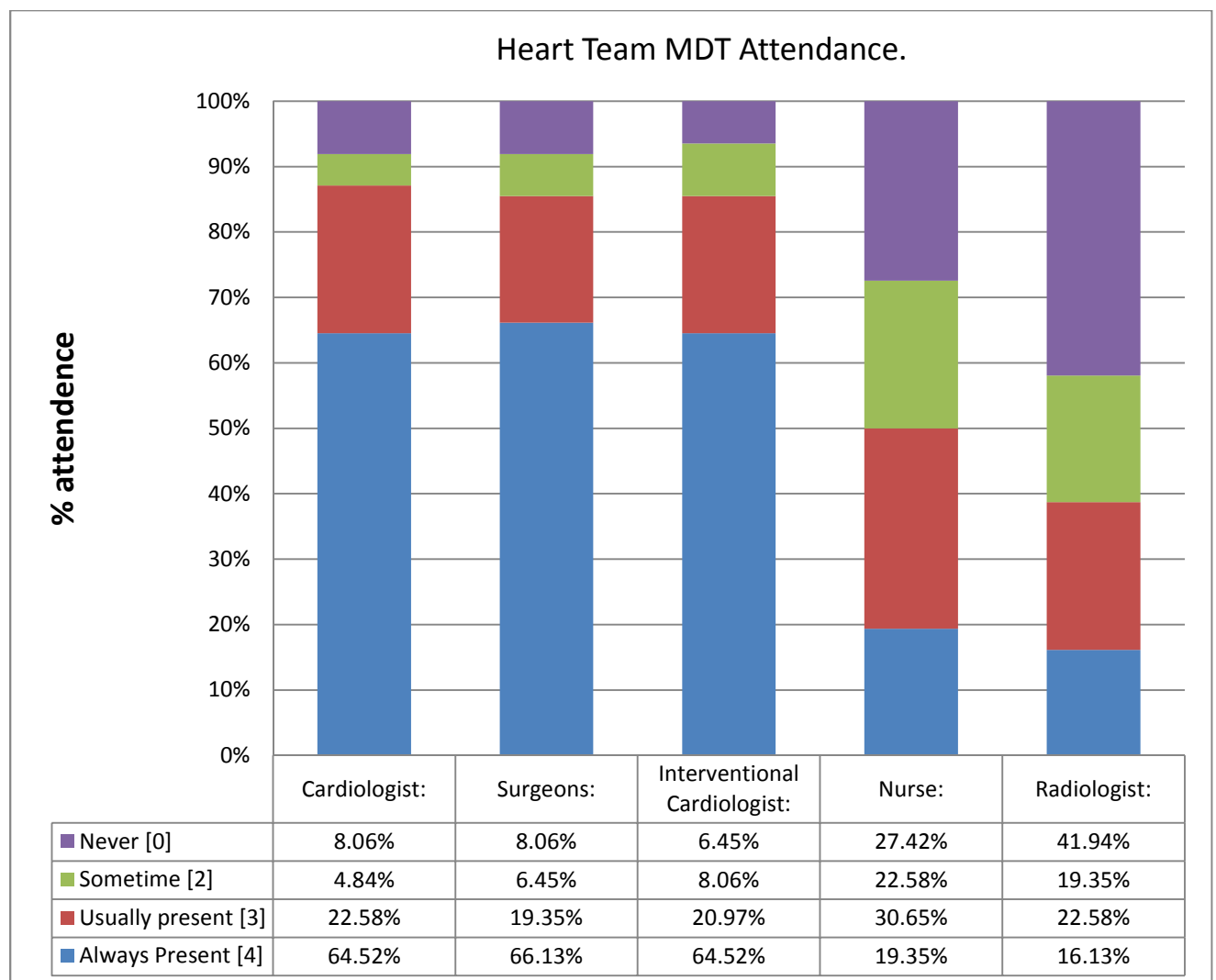


Figure 21 - 8.3 present key Heart Team MDT members attendance.

None the less, opinion was different when participant were asked to indicate the level of team rapport and sociability with regards to: team appear relaxed with one another (67.86% yes, 32.14% no), warm and supportive team environment (72.88% yes, 27.12% no), and friendly and accommodating communicative style (66.67% yes, 33.33% no).

Another interesting question asked was what would help them to improve their MDT meeting participation at individual level. Opinion was split with regards to; focused attention (69.64% yes, 30.36% no), respect for speaker (51.72% yes, 48.28% no), no simultaneous discussion (65.52% yes, 34.48% no), and asking and evaluating relevant contribution (67.24% yes, 32.76% no).

The final question under the theme ‘team’, participants were asked to rate the opportunity for an MDT team member to benefit from case discussions in terms of research evidence communication for professional development or in some instance training opportunities discussed. An overwhelming majority felt that their MDT hardly provides a platform for research or training with mean value less than 4.10.

8.8.3 MDT infrastructure (Q7-8).

The venue for productive Heart Team meetings and associated infrastructures was assessed. The majority of the respondents agree their respective MDT members are all seated comfortably on a chair (80.77% yes vs. 19.23% no), layout of chairs facilitates good viewing of diagnostics (67.92% yes vs. 32.08% no), room design enables viewing of other team members (50.94% yes vs. 49.06% no), and suitable venue with regards to location, ventilation & lighting (58.49% yes vs. 41.51% no).

Evidently when asked if their meetings rooms facilitated the necessary technology and equipment suitable for a state-of-the art Heart Team discussion venue, the respondents answered: projector that enables viewing radiological images including retrospective images (76.09% yes vs. 23.091% no), connection to PACS and/or multiple screens (90.57% yes vs. 9.43% no), access to electronic proforma or database to populate recommendations instantly (31.82% yes vs. 68.18% no), and video conferencing and/or live projection facilities so members can view/share and confirm recommendations being recorded (38.46% yes vs. 61.54 no).

8.8.4 Consulting Team and logistics (Q9-12).

This theme explored Heart Team preparedness and agenda (figure 6.4 & 6.5). Respondents were asked to answer whether patients list and planned agenda was distributed prior to the meeting. The majority were on the view that there was no available agenda prior to meeting

(46.43%), agenda available but lacks detail information (42.86%), all inclusive agenda available (10.71%).

Likewise when asked whether complex cases on the agenda are prioritised, frailty factor considered and sufficient time allowed for the discussion, opinion was significantly not favourable for a world class Heart Team meeting. The scores were; cases not prioritised with regards to complexity & frailty and that unnecessary amount of time is spent on cases (40%), some cases are prioritised with regards to complexity & frailty but unnecessary amount of time is spent on discussing some cases (21.54%), patient cases are discussed in a clear sequence but unnecessary time is spent in some cases (20%), and patient cases are discussed in a clear sequence, frailty considered and necessary time is spent in some cases (18.46%).

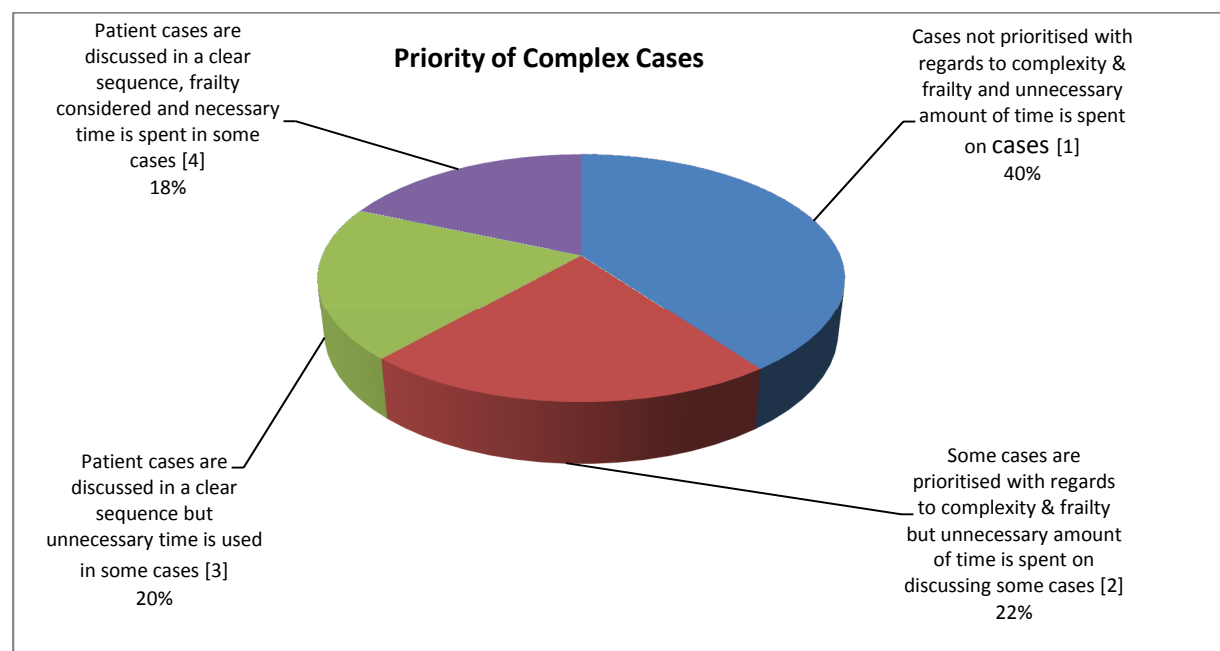


Figure 22 - 8.4 Indicates the result of the sequence of case discussions in Heart Team meeting.

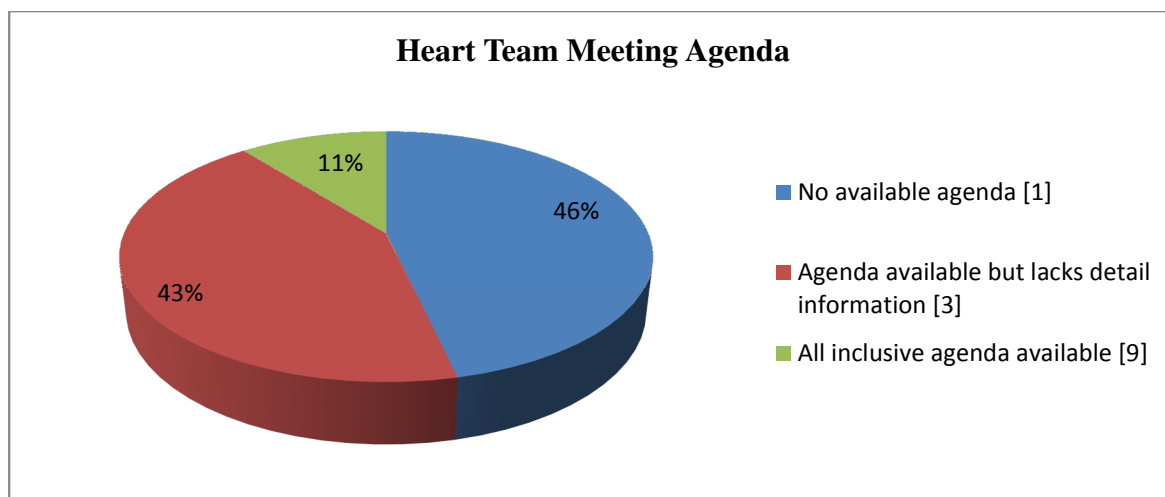


Figure 23 – 8.5 Heart team meeting agenda.

Another integral part of high quality MDT meeting that aids clinical decision making is the availability of patient's notes and relevant diagnostic information in the venue during treatment plan discussion. Most Participants felt that there were no patient's notes available at the meeting (20%), some required past/current reports not available (33.85%), medical notes and all appropriate past/present reports available (25%), and electronic access to patient notes and all appropriate past/present reports available (23.08%). However, when participants were further asked if at their local MDT it is clear who needs to present a particular patients case and why they are being discussed. The participants overwhelmingly reported that the presenter does not seem familiar with patients and reads from the notes, (68.86%) vs. (31.15%) presenter shows some evidence of familiarity with patient and findings.

8.8.5 Clinical Decision Making (Q13-14).

This theme explored patient centeredness, frailty consideration and treatment plan evolution. Participants were asked whether in their local MDT patients demographic, views, and needs are presented by a clinician or staff who has met the patient before or the presence of their surrogate carer. Majority of participants reported inadequate level of patient-cantered aspect acknowledgement (60.34%) vs. (39.66%) reporting patient-centered aspects adequately acknowledge in 50% or more instances.

Additionally, when participants were asked to rate the clarity of the recommended treatment plan resulting from the meeting and frailty factor influence; they felt treatment plan not distinct (5.26 %), treatment plan only communicated verbally (14.04 %), treatment plan communicated verbally and recorded (54.39 %), and treatment plan communicated verbally and recorded with great deal of clarity highlighting next step (26.32 %)

8.8.6 Participant Professional Role & Region (Q15-16).

The majority of the survey participants were surgeons (61.90 %), cardiologist (7.94 %), and interventional cardiologist (30.16 %). The participants region is shown in figure 6.6 below.

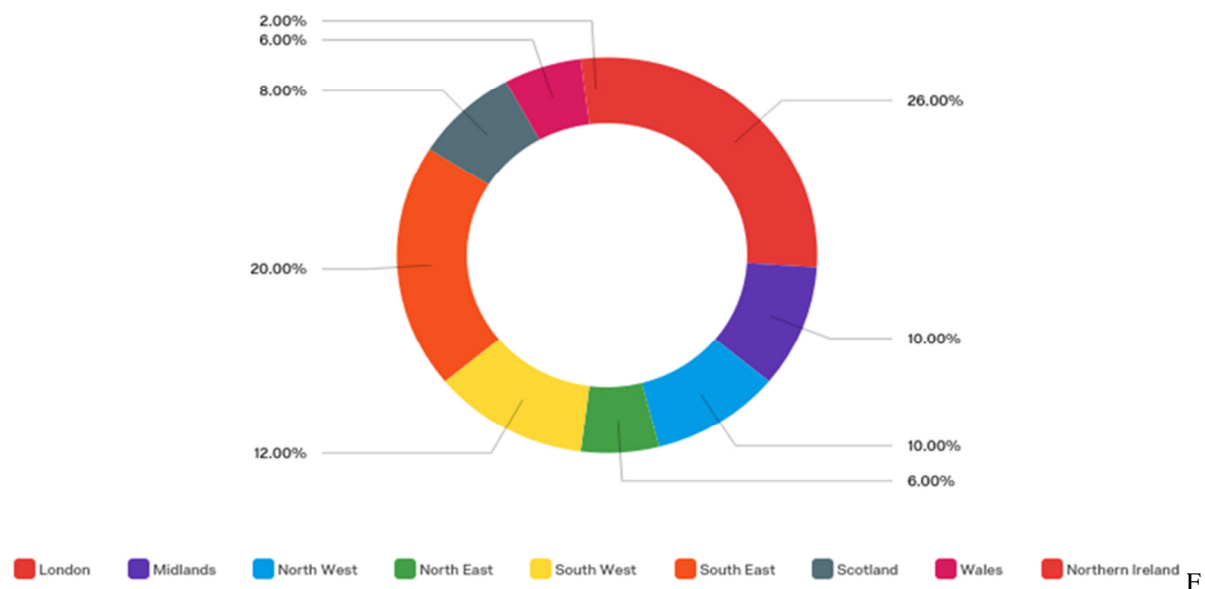


Figure 24 – 8.6 Representations of survey participant regions.

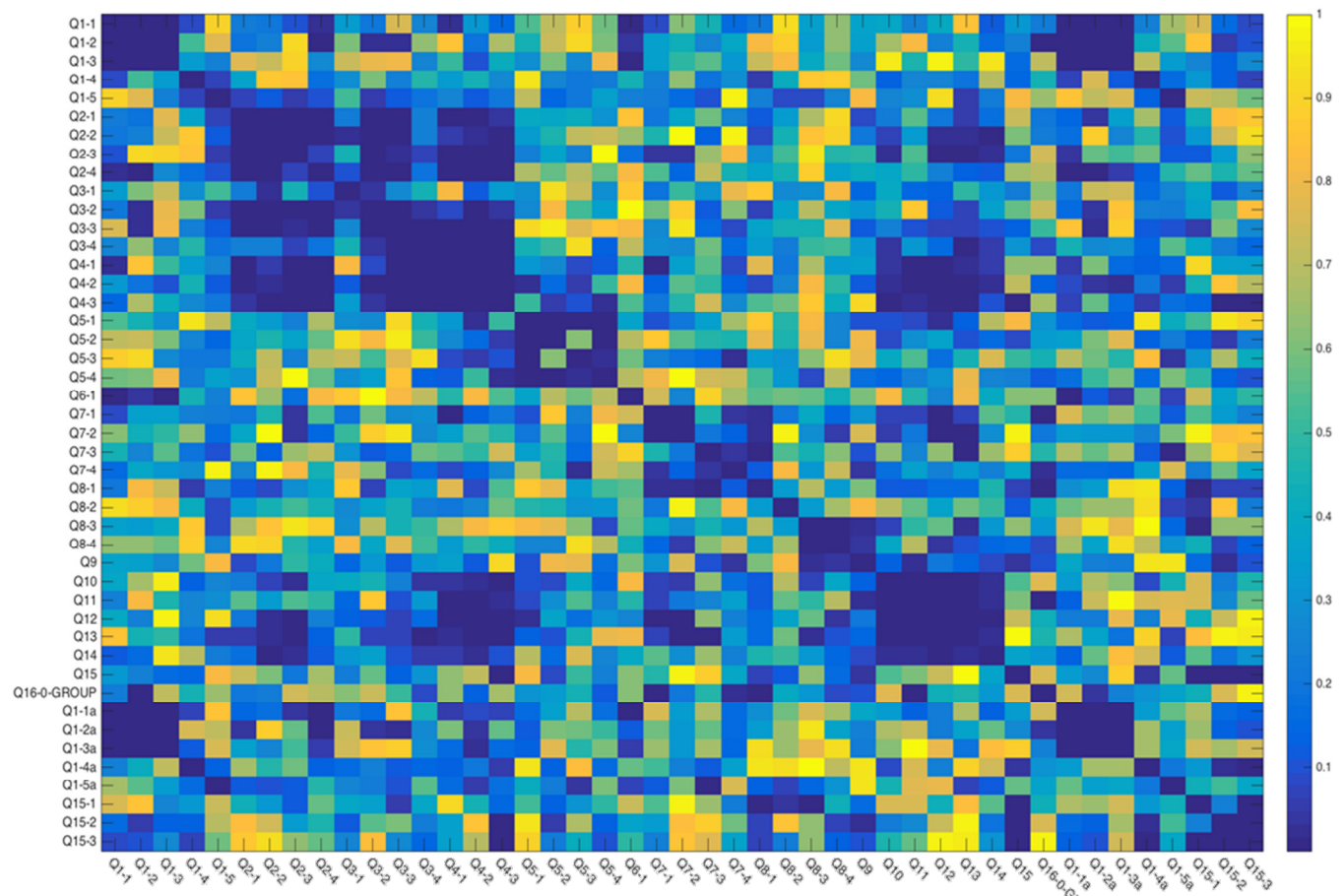


Figure 25 – 8.7a Heat map presentation

Figure illustrates colour coded heat map which highlights variables that were significant and dependent to one another (dark blue colour) – P -value less than 0.05.

Heat Map Analysis.

The above heat map presents the 1369 variables compared to one another, of which 281 variables had a direct relationship and were dependent to one another meaning that their respective P -value was statistically significant and less than 0.05. From the heat map looking into key themes and comparing each other, significant sub-findings can be extracted as shown in figure 6.7b & 6.7c below.

Aim 1:Leadership vs decision making	
P -values = Q2 vs. Q14	
Q2_1	0.18551
Q2_2	0.0037569
Q2_3	0.026905
Q2_4	0.12443

Aim 2:Leadership vs. teamwork				
p -values = Q2 vs. Q3				
	Q3_1	Q3_2	Q3_3	Q3_4
Q2_1	0.2268	0.0001	0.0001	0.2415
Q2_2	0.0195	4.25E-06	1.40E-05	0.2415
Q2_3	0.4389	0.0002	0.0264	0.0680
Q2_4	0.0957	0.0001	0.0004	0.1995

Overall our results indicates viable decision making in MDT is influence by core team attendance, information richness, full participation of attending professionals, meeting preparation, patient centeredness and linking to research questions, focused leadership, IT&C infrastructure and administration process that disseminate recommendations from meeting in time.

The multivariable models results generated the following variables (He/She encourages participation $p=0.003$, and He/She encourages focussed discussion $p=0.02$) as predictors of good leadership when corrected for decision making variables. Likewise for leadership and teamwork only one variable (He/She encourages participation $p=0.019$) was crucial for ideas generation and harnessing enlightened decision making.

8.9 Commentary

This study reports statistical evidence that Heart Team MDT members from different regions across UK are in a sound agreement about what instigates effective MDT working. The result provides a robust validation for the pre-requisite characteristics for an effective Heart Team MDT meeting, which can also act as a benchmark to assess local performance for different types of Heart Teams. Even though there exist different pathways or guidelines for COPD, Arrhythmia, and revascularisation MDTs, the areas of case selection, meeting preparation, clinical decision making and the reproducibility of recommendations should all be adjusted accordingly to ensure the incorporation of the effective MDT characteristics which adopts a strategy to uphold what is beneficial to patients and healthcare professionals.

8.9.1 What constitutes effective Heart Team meetings and predictors of MDT Quality?

The ability of Heart team meetings to develop MDT quality ratings and checklist is of the utmost importance: (i) the quality checklist should reflect the implementation of process measures such as time from first referral to diagnosis, duration to first treatment, and cost effectiveness. (ii) Clinical outcomes should be given due consideration when rating MDT performance, not just the traditional measure of survival data and the perceived account that named intervention being effective or superior to others but MDT discussions resulting in improved survival rates at appropriate intervals [291, 299]. (iii) Another marker of MDT performance is the ability of the team to reach decision on the first-case presentation and the robust implementation of the recommendation [300]. (iv) Additionally, another surrogate for quality improvement that augments the effectiveness of Heart Team meetings is patients reported outcomes measure (PROMS) and patients and healthcare professional satisfaction score [299]. (v) Peer review process to assess effective MDT should use valid, reliable and structured proforma. Data from assessment and risk stratification tools such as Edmonton

frailty score, EuroSCORE and EQ5D-3L as well as health related patient's quality of life improvement measures should be available for all cases discussed.

(vi) Prepopulated patient's proforma should be emailed/circulated to the core MDT team and attendees a day or more before the actual meeting. This should also be linked to specific questions and evidence based learning and outcome. (vii) Adequate information richness on disease burden, images and research evidence as well as a high degree of mutual respect and social presence combined is an invaluable integral part of effective MDT. It is also a determinant factor for a high quality MDT meeting [301]. (viii) Furthermore, to quantify whether overall approach of Heart Team meeting is improving the management of heart failure patients, data on team organisation and performance should be pooled locally and nationally and should be readily available in real time [302]

Table 15 – 8.1. Domains for assessing Heart Team MDT Performance

Process measures
Evidence that referrals are processed and populated onto proforma within 7 days of receiving
Indication that meeting encourages inclusivity and participants contribute to discussion and decision unanimity
Confirmation that appropriate information is retrieved and utilised accordingly
Indication that discussions are pleasant and efficiently moderated
Evidence that the IT&C infrastructure functions well consistently
Outcome measures
Treatment plan delivered to referring clinicians within 2 weeks
Confirmation that treatment plan was executed accordingly
Proof that the process and its treatment plan were up to standard to and beneficial to patient
Proof that costs were kept within budget
Evidence of improved outcome for patients (patients' perceptions of decision-making; patient satisfaction; QoL; survival)
Evidence that team participants found the process adequate, beneficial and stress free.

Table modified from Munro et al.

8.9.2 Predictors of success in Heart Team MDT meetings

Among the determinants of success in Heart Team MDT; is integrating these meetings into the job plan of consultants, personnel and other technical back up staffs as well as the meetings always held in a dedicated room that offers privacy when discussing a named patient. The meeting should also be scheduled in working hours and should take place for a minimum of one session per week [303]. The tenacity of key MDT members (surgeons and cardiologists) to consistently attend the meetings and substantiate treatment plans with evidence based research is another key predictor of successful Heart Team meetings [304].

In addition when measuring the determinants of high quality Heart Team meetings that encourages patient's centeredness. One needs to observe whether factors like patient's health behaviours such as smoking rate, amount of alcohol intake and physical inactivity are discussed in the meeting [302].

Similarly clinical aspects such as family history, frailty, disability and other medical comorbidities should be fully acknowledged. Another key constitute of success in decision making is the degree to which patients or duly appointed surrogate treatment preference were mentioned and incorporated to the final treatment plan. Equally the ability of the team to send out minutes or treatment plan recommendations from MDT meetings on the same day is a proven predictor of a successful team meeting.

None the less, a large study by Raine et al [305] focusing on MDT performance for different specialities reported a good team atmosphere and fewer memberships variety aggregated for important predictors of treatment plan implementation across the investigated teams. However a robust and tested method for quality improvement that also acts as quality measuring backup when making decision is to develop and use a checklist. Checklists standardises process and mitigates risk and human error, it has been successfully and widely

used in complex industries as well as also being a WHO surgical safety recommendation [304, 306, 307]

Evidently our survey highlighted opinion diversity in fundamental domains such as the meeting not inherently structured, lack of frailty data and lack of uniformity in decision making, perhaps due to lack of either strong leadership/chair or comprehensiveness of available information. We therefore deduced the following checklist table 6.2 to support and improve decision-making. Major factors that determine the quality of the decision made are the available patient's information richness including frailty scores and inputs of most of the professionals during case discussion. Studies in cancer have shown the use of decision tools or checklist has markedly improved implementation of clinical practice guidelines [308].

Table 16 – 8.2. Quality Checklist for Heart Team MDT meeting

Table 7. Quality Checklist for Heart Team MDT meeting	
Before the session begins	
1.	Is the session quorate with core MDT members?
2.	Is anyone present who met/knows the patients?
3.	Is the patients or dully appointed surrogate present?
During discussion	
Minimum dataset availability	Minimum case participation & inputs
1. Disease burden (history)	Surgeon
2. Comorbidities	Interventional cardiologist
3. Radiological images	Cardiologist
4. Socioeconomic data	Cardiac physiologist
5. Patients preference information	Cardiac anaesthetist
6. Research evidence/trials findings	Geriatricians
7. Risk score data	Allied healthcare professionals
8. Frailty Score data	MDT coordinator
Outcome	
Frailty factor considered? Treatment plan recommendations documented?	
Is the decision unanimous? Or any objections documentation?	
Does this case need re-presentation? & discussion date documented?	

Shows quality checklists information content for a high performing Heart Team MDT. Modified from Lamb et al 2012.

Additionally some of the benefits/aims of developing Heart Team MDT checklist are that it encourages patient's centeredness during decision making. Previous studies [309] demonstrated smooth implementation of recommendation when an MDT professional who met the patient was present during case discussion and factors such as patient treatment preference, socioeconomic matters and comorbidities were considered. This study adds the use of simple tools such as REFS to generate meaningful frailty scores may influence the decision of the MDT team and the treatment plan considered.

Hence the more fields populated/ticked in the checklist above during case presentation, the higher the quality ratings of the MDT meeting and overall team performance. Such a checklist also enhances self-assessment of a particular Heart Team MDT meeting performance and their desired end point clinical outcome goal.

Checklist also reinforces the want to modernise MDT teams by equipping with them the necessary infrastructure, resources and training opportunities in order to maximise their performance and in order to enrich patient's safety and care [303].

Lastly but not the least, our survey highlights the need to introduce and develop training module for Heart Team MDT coordinators. Evidence suggest viable decision making in MDT is influence by core team attendance, information richness, full participation of attending professionals, meeting preparation and linking to research questions, focused leadership, IT&C infrastructure and administration process that disseminate recommendations from meeting in time.

It is interesting to note most of the above characteristics fall within the remit of MDT coordinator role and can be argued without them it's difficult to reach a conclusive decision, as their role immensely supports the ease with which decision could be made [290]. Some of the ways in which this role can be easily implemented in Heart Team MDT meeting is to

incorporate these responsibilities into the job plan of the cardiac/cardiology pre-assessment nurse or to one of the advanced cardiac nurse practitioners (ACNP). The advantage of this method is that they can act as the patient's representative when case discussion is taking place, with the hope that they met the patients beforehand and can report to the team the patient's treatment preference, socioeconomic circumstances and comorbidities.

Limitation

The study benefits from using more advanced survey instrument and builds on methodologies of the well-established previous cancer MDT surveys, however few limitations are worth highlighting. To begin with it is difficult to preclude conclusion on this type of survey because the majority of respondent belief and stated their MDT structure and functioning is hindered by inadequate resource and support from their department. Secondly gaming of individual respondents answer and discrepancies regarding the performance of their respective MDT meeting couldn't be verified as it is above the scope of this study. Thirdly the survey was only active for a period of one month, and even though a reminder emails were sent only 62 heart team members responded. We believe double that figure would have provided a wider picture and enabled more robust analysis. Future studies should aim to activate their survey for at least six week period but also put in place measures to identify discrepancies (repeat & duplicate) entries.

8.10 Conclusion

Our survey demonstrated a reasonable gap in heart team meeting specially frailty factor and consideration. The study provided platform and crucial strategies and ways to investigate what constitutes quality improvement or acts as a proven backup for quality of care. Managing heart failure patients can take several years, their treatment and interventional procedures vary at individual level. In addition the complexity of the presented clinical conditions largely due to frailty, the presences of significant co-morbidities, and

polypharmacy merits a shared decision making. Furthermore, the continuous technological advancement and therapeutic procedures can augment important benefits and carry complications such as hospital bed retention, re-admissions and diminished quality of life for a cohort of frail patients not identified in the pre-assessment clinics [281].

MDT meetings are believed to encourage better teamwork with the sole purpose of improving patients' safety and care [282]; such prolific meetings should also offer an environment for education and training even though it is currently under-developed. The availability of risk stratification and frailty score data to the team will strengthen and improve the quality of the decision made.

Key Points

- A robust database and a mechanism should be put in place to not only monitor compliance with treatment plan devised by the heart Team but to also track patient frailty effects and outcomes.
- Professional guidance's must be adhered and treatment plan maximised whilst delivering care that translates to improvement in patient centeredness outcome.
- Ambiguity about what constitutes effective MDT meeting structure and process has resulted considerable diversity in the recommended guidelines and there is no randomised trial on survival and quality of life regarding follow-up on MDT decisions or even its reducibility.
- Some of the ways in which this role can be easily implemented in Heart Team MDT meeting is to incorporate these responsibilities into the job plan of the cardiac/cardiology pre-assessment nurse or to one of the advanced cardiac nurse practitioners (ACNP).
- MDT checklist enhances self-assessment of a particular Heart Team MDT meeting performance and their desired end point clinical outcome goal. The more fields populated/ticked in the checklist during case presentation, the higher the quality ratings of the MDT meeting and overall team performance.
- Checklist also reinforces the want to modernise MDT teams by equipping with them the necessary infrastructure, resources and training opportunities in order to maximise their performance and in order to enrich patient's safety and care.

9.0 Chapter 9

The relationship between Health Related Quality of Life (HRQOL), Frailty Scores and Post-operative Outcome in Cardiac Surgery.

9.1 Chapter Overview.

This chapter defines and studies the relationship between patient reported health related quality of life (HRQOL), their frailty status and the impact of cardiac surgeries to their quality of life and functional status. It reports preoperative frailty & QoL status and compares both to postoperative QoL and to outcome.

9.2 Hypothesis.

1. High frailty reduces QoL at least by 1 standard deviation (1Stdv).
2. High frailty affects QoL immediately after cardiac surgery and changes between high frail and low frail can affect at least 1 standard deviation of QoL.

9.3 Introduction.

Its predicted by the year 2050, the number of persons aged 80 years will have increased at a staggering rate of 26% compared to the current 10%, this is in parallel with the general steep rise in the world population. It's also expected over 2 billion people will be over 65 years of age worldwide at the same time period [310]. A crucial factor that facilitated the projected greater life expectancy is the prompt improvements and advances in surgical techniques, myocardial protection, implementation of enhanced recovery protocols and overall improvement in postoperative care [311].

Despite such a profound development, its known cardiovascular disease presents a challenge and greater risk to the elderly population and many are symptomatic. Similarly, cardiovascular diseases inhibit the functional capacity in more than 25% of octogenarians [312]. Satisfactory level of operative morbidity and mortality does not warrant improvement in quality of life (QoL), as it doesn't give sufficient information on patient's physical, functional, emotional wellbeing and general health status [313].

Interest in health related quality of life post-surgery and its evaluation in the clinical setting is growing. It's equally becoming an important factor in many patients during decision making as elderly patient's primary goal in cardiac surgery is their perception to improve their quality of life and functional status [314]. It is ethically and morally upright to investigate parameters that constitute QoL in the elderly population preoperatively, as they may have underlying conditions such as higher prevalence of comorbidities, anxiety and stress precipitated by the thought of undergoing surgery and concerns of complication rates.

The current pre-operative assessments and risk stratification tools that helps the surgeon to anticipate a patients chances of survival and impact of surgery doesn't account for frailty status or their likelihood of improvement in quality of life [143]. The current gold standard risk stratification tool in cardiac surgery; EuroSCORE is not robust in surgical risk evaluation and it assumes the age variable as a predictor of risk as older age leads to a high EuroSCORE value, which is in essence irrelevant as shown by Machler and colleagues [315].

The authors further added a replacement of EuroSCORE to tools that evaluate fragility is more appropriate and robust in octogenarians. Such tools should be able to accurately capture mental health, social functioning, energy/vitality, functional status and general health. Currently, validated QoL tools such as RAND-36 and EQ-5D measure these parameters and even group their checklist into physical and mental component summary as well as index scores for EQ-5D.

It is interesting to highlight many studies have reported QoL in cardiac surgery patients, however to date none of them evaluated frailty scores pre-surgery using validated tools and investigated any relationship between frailty tools and QoL tools in predicting the impact of cardiac surgery in frail patients. Furthermore, previous studies did not account for combined geriatric and QoL outcome at the follow-up stage.

This study is therefore unique in its own as it measures the frailty level at baseline pre-operatively using validated frailty tool - the Reported Edmonton Frailty Scale (REFS) as well as three different sets of validated Quality of life measuring tools. The study aims to answer questions and controversies in the literature on how to balance the diminishing health status of the elderly and the benefits associated with cardiac surgery for frail patients. It will also report on the relationship between pre-cardiac surgery symptoms, comorbidities and QoL at four time points post-operatively.

9.4 METHODS:

9.4. 1 Participant and protocol

The sample consisted of 105 patients undergoing elective cardiac surgery at Hammersmith Hospital with no contraindications who satisfied the following inclusion criteria: (i) age ≥ 65 years, (ii) agreed and signed the content in the consent form. (iii) were able to walk freely (not wheelchair bound). Emergency cases were excluded due to the time factor and convenience required for comprehensive QoL and frailty status evaluation.

Patients were asked to complete a simple questionnaire including a basic standardised frailty score - the Reported Edmonton Frail Scale (Appendix 2) and QoL questionnaire; RAND 36, EQ-5D (Appendix 3), taking about 25 minutes all together. This was conducted at the pre-assessment clinics by the researcher 2 to 4 weeks preoperatively. Further data was obtained from patient's records and during their perioperative and postoperative stay.

Follow-up data was collected during patients hospital visit (routine post cardiac surgery follow-up clinics) and mainly by telephone calls by the researcher at 30 days, 90 days, 6 months and 12 months. This did not interfere or influence the patients planned treatment.

9.4.2. Ethical approvals

NRES Committee London - Harrow Research Ethics Committee (14/LO/0693) approved the study protocol.

9.4.3. Frailty score (REFS)

In this study, the Reported Edmonton Frail Scale (REFS) was applied to measure frailty due to the following reasons. (i) REFS are a reliable tool that has been validated and applied by multiple studies; (ii) It associates moderately well with the Geriatrician's Clinical Impression of Frailty (GCIF) - cognitive impairment, increasing comorbidity and functional impairment; (iii) It has been proven to have excellent inter-rater reliability when administered by researchers without medical training.

The REFS samples nine main domains with a maximum frailty score of 18. One domain – the clock test for cognitive impairment quantifies performance-based items. The other domains are general health status, mood, functional independence, medication use, social support, nutrition, continence, self-reported performance measuring physical activity, burden of medical illness and quality of life, which are all standard historical items in geriatric assessment.

9.4.4. Quality of life assessment tools.

Overall, three Health related quality of life instruments were administered by the researcher in person. Two validated HRQOL tools (RAND-36 and EQ-5D) were used preoperatively at the pre-assessment clinics and one self-rated cardiac specific health at post surgery (appendix 4). QoL and frailty parameters were accounted postoperatively at three time points. EQ-5D was equally applied at pre-operative stage, at 30 days, 3months, 6months and 12 months postoperatively.

9.4.4.1 EQ-5D

The EQ-5D questionnaire is user friendly and can be applied to any study population. It allows to be administered either individually or in an interview to generate a descriptive profile and a single index value that can be useful in both medical and financial studies.

The descriptive system is made up of five questions, which reflect the five different dimensions. This includes ‘Mobility, self-care, usual activity, pain/discomfort and anxiety/depression’. The parties answering the questionnaires are expected to choose one answer out of three likely levels provided. They could tick no problem, some problem or extreme problem based on the one they consider most comparable to their health.

The Visual Analogue Scale (EQ-VAS) self-rating requires participants to rate the state of their health using a vertical graph of analogue scale, which ranges from 0-100, zero representing the worst imaginable health status and hundred representing the best imaginable health status. Chapter 3 contains detailed description of EQ-5D.

9.4.4.2 RAND-36

RAND-36 is a robust tool that gives scale scores and two summary scores (physical and mental); with its eight score dimensions formulated from the RAND 36-item which was originally modified and selected from a larger pool of instruments participated by patients recruited to RAND Medical Outcome Study (MOS) [165, 166]. To group the eight domains namely: Physical functioning, role limitation due physical health problems, role limitation due to emotional problem, bodily pain, vitality/energy, emotional wellbeing, social functioning and general health status; different criteria is applied compared to the straight forward grouping in SF-36. Six of these domains make up the physical component summary (PCS) whilst five domains make up the mental component summary (MCS). PCS accounts for Physical functioning, role limitation due physical health problem, bodily pain, vitality/energy, social functioning and general health status. MCS summarises role limitation due to emotional problem, bodily pain, emotional wellbeing, social functioning and general health status.

The RAND-36 takes about 7-10 minutes and it can be either self-administered or with an interview by a trained researcher via telephone or face to face. Several studies have utilised RAND-36 as a generic profile HRQOL measures, comparing the relative burden of disease for patients with diverse chronic illnesses [165, 166]. Chapter 3 contains detailed description of RAND-36 scoring.

9.4.4.3 Research Data

Data Collection and end-points

Clinical data at baseline, perioperative, intraoperative and postoperative were collected that included patients baseline characteristics, comorbidities and complications. Follow-up data for clinical and quality of life was also collected at each of the four-time points up-to and including 1-year post surgery. Results were populated at specialist research proforma and workbook.

Statistical analysis

Multiple statistical tools were utilised to highlight relationships between the diverse variables in the workbook. IBM SPSS (version 24.0) for windows, Matlab 2015a were all applied to generate meaningful data. A $p < 0.05$ was deemed significant for all statistical tests. In some sections, frail vs. non-frail was thoroughly compared to baseline characteristics, postoperative data and quality of life.

Mean values and standard deviation was reported for dichotomous variables subject to normality distribution. Chi-square test was used to differentiate categorical variables, similarly student *t*-test or Mann-Whitney U test was applied to cater differences in continuous variables. One-sample *t*-test was employed to compare EQ-5D mean index score at four different time points with mean age and population matched norms. Similarly, PCS & MCS scores were normalised to equate the mean score of reference population norms.

Power calculation

As there was a lack of availability of data in the literature concerning our hypotheses, it was hence difficult to calculate the exact sample size required to study our multiple outcomes. Our study is explorative in nature, with an aim of testing new hypotheses and providing pilot data as a proof of principle. We used correlation coefficient between frailty and QoL index score to calculate the sample size for an α -level of 0.01 and β -level of 0.01.

The 135 QoL parameters of the RAND-36 form were used for sample-size calculation. Mean QoL by index score is 0.6 with SD 0.2; thus to see change of 0.2 from 0.6 between high frail and low frail groups with power of 0.8 and alpha 0.05, we needed 40 patients. However, we aimed for a minimum of 50 participants from each of the two cohort group (high frail vs. low frail) in order to recompense for common trial problems such as unexpected withdrawal at any stages of the follow-up and issues that may arise with sample and data processing.

Frailty and HRQOL Influence

To evaluate baseline characteristics and clinical relevance of frailty the patients were grouped depending on their REFS scores into two groups: Frail vs. non-frail. The influence of frailty to baseline characteristics and quality of life at four time points including preoperative index's score was calculated. First by univariable analysis: (PCS, MCS, index score & Frailty score) were entered as the dependent variable and then corrected for other covariables one by one with respect to the investigated factor. The sample was then tested for multivariable model after adjusting for age and sex. Likewise,

to assess the predictors of baseline health related quality of life, univariable and multivariable analysis was adopted.

Longitudinal HRQOL dynamics

Generalised estimation equation (GEE) was applied to measure the influencing factors of quality of life at the four different time points. GEE is utilised when measuring different types of outcome variables. GEE adds repeated measures capability to generalised linear model [316] meaning its most flexible regression model and accounts for any outcome variable such as continuous, ordinal, binary, counts and skewed or non-skewed continuous. It also accommodates time changing covariates unlike the old linear or regression techniques. Furthermore, it does not exclude patients with missing variable but assumes selective missing as it also accommodates differential observations.

GEE is robust for correlation structure and in this study during the analysis stage linear model and ordinal logistics was selected for continuous and categorical variables respectively. To differentiate between the four time points unstructured correlation matrix was enabled.

The longitudinal QoL variable EQ-5D index (4 time points) was set as the dependent variable and baseline characteristics, postoperative data and complication were consecutively entered one-by-one along with pre-op EQ-5D index score as covariate. Interaction with time was investigated by assuming time as a factor and multiplying it with the variable under investigation. A *p*-value < 0.05 was considered significant either independently or along with time interaction.

9.5. RESULTS.

Descriptive results.

From October 2014 to April 2017, 105 patients (40 females) with a mean age of 77.22 ± 10.55 years were successfully enrolled to the study. Common cardiovascular comorbidities such as angina (79%), diabetes (16.19%), AF (19.05%), current smokers (45.71%), extent of coronary vessels disease (38.10%) and NYHA class ≥ 2 (96.19%) were prevalent in the study population necessitating procedures such as CABG (41.90%), Valve (68.57%) and other cardiac procedures (7.91%). Within the valve cohort: 49 (46.67%) patients underwent aortic valve surgery and 25 (23.81%) had mitral valve procedure. The cohort of elderly patients that were clinically frail was (51.43%).

Table 17 -9.5.1: Baseline characteristics and procedure variables

Baseline Characteristics & Procedure	Count/Mean*	Percentage %
Mean Age (year)	77.22 $\pm$ 10.55*	-
Sex (Male)	65	61.90
Frail	54	51.43
Angina status pre-surgery	83	79.05
Previous cardiac surgery	2	1.90
Diabetes management	17	16.19
History of hypertension	89	84.76
Cigarette smoking history	48	45.71
NYHA Class	101	96.19
History of pulmonary disease	11	10.48
History of neurological disease	5	4.76
Pre-operative heart rhythm	20	19.05
Extent of coronary vessel disease	40	38.10
Renal function/Dialysis	5	4.76
LV Function <50 %	22	20.95
EuroSCORE	11.25*	-
CABG	44	41.90
Valve	72	68.57
Major aortic	2	1.90
Other Cardiac Procedures	6	5.71
Aortic valve procedure	49	46.67
Mitral valve procedure	25	23.81

Frailty factor and its influence on Baseline characteristics and Outcome.

Table 18 - Table 9.5.2 – Frail vs. Non-Frail

FRAIL Vs. NON-FRAIL			
Variables	Non - Frail	Frail	<i>p</i> -value
Male	33	32	0.566
Female	18	22	0.566
Angina status pre-surgery	40	43	0.880
Previous cardiac surgery	1	1	0.967
Diabetes management	4	13	0.024
History of hypertension	42	47	0.504
Cigarette smoking history	17	31	0.013
NYHA Class	49	52	0.954
History of pulmonary disease	6	5	0.675
History of neurological disease	3	2	0.600
Pre-operative heart rhythm	12	8	0.256
Extent of coronary vessel disease	14	26	0.029
CABG	16	28	0.034
Valve	40	32	0.034
Major aortic	1	1	0.967
Other Cardiac Procedures	2	4	0.442
Aortic valve procedure	26	23	0.389
Mitral valve procedure	16	9	0.077
Tricuspid valve procedure	1	3	0.336

Tables 9.5.1 and table 9.5.2 represents the demographic statistics and complication rates respectively between the two groups. Frail vs. Non-frail. P-values from Chi-Square are reported.

Table 19 - 9.5.3: Describes complication rates between the two groups at 30 day post-surgery.

FRAIL Vs. NON-FRAIL			
Postoperative Complication	Non - Frail	Frail	<i>P</i>
Re-Admission	4	6	0.569
Renal Problem	1	7	0.034
SSI	0	3	0.088
Stroke	0	2	0.165
Re-Operation	3	7	0.217
New AF	10	11	0.922
Pace-Maker	3	3	0.943
Composite Complication	7	21	0.003
Death	0	1	0.329

Frailty influence on Baseline characteristics, QoL, Procedure & activity.

In order to investigate the influence of frailty on cardiac surgery, the patient's baseline characteristics were evaluated against frailty score, similarly to quantify the predictors of frailty influence postoperatively univariable and multivariable regressions was employed. The relationship between frailty and its influence is reported in table 9.5.4. & 9.5.5 below.

The univariable and multivariable models had good predictive power when corrected for baseline characteristics. The following eight variables were predictors of baseline characteristics reaching statistical significance in both models and had established association with higher frailty scores. In the multivariable model: severity of coronary artery disease ($p=0.030$), current smoker ($p=0.007$), diabetes ($p=0.030$), CABG surgery ($P=0.036$), Valve surgery ($P=0.030$), sedentary life style ($p=0.0001$), light activity ($p=0.016$) and interestingly moderate activity ($p=0.044$) was a predictor of frailty in the univariable model.

Higher frailty score had significant interaction with health related quality of life parameters, in both univariable and multivariable models. The following seven QoL components and index scores were significant. In the multivariable model: EQ-5D pre-op index score ($p=0.003$), physical functioning ($p=0.021$), role limiting due to physical problem ($p=0.024$), social functioning (0.001), pain ($p=0.004$), general health ($p=0.043$) and PCS ($p=0.003$).

The association between baseline activity level and frailty influence revealed strong interaction in three out of the four activity levels. The following two variables were predictive of frailty effect in the multivariable model (adjusted for age and female sex): Sedentary life style ($p=0.0001$), light activity ($p=0.016$). Moderate activity ($p=0.044$) was predictive of frailty in the univariable model as well as (Sedentary life style ($p=0.001$) and light activity ($p=0.018$)).

Table 20 - 9.5.4: Univariable Results of Frailty Influence on Baseline Characteristics, QoL, Procedure & Activity

Demographic	B	Univariable_SE	P
01) Age	-0.005	0.005	0.326
02) Sex	0.058	0.101	0.570
03) Height	-0.004	0.005	0.420
04) Weight	0.000	0.003	0.961
05) BMI	-0.001	0.001	0.334
06) BSA	0.007	0.224	0.976
QoL parameters			
07) Pre-OP INDEX SCORE	-0.710	0.208	0.001
08) Pre-Op VAS SCORE	0.001	0.003	0.812
17) Physical Functioning	-0.004	0.002	0.038
18) R L Physical	-0.003	0.001	0.025
19) R L Emotional	0.000	0.001	0.729
20) Energy/Fatigue	-0.002	0.003	0.415
21) Emotional well-being	0.001	0.002	0.756
22) Social Functioning	-0.006	0.002	0.001
23) Pain	-0.006	0.002	0.002
24) General Health	-0.006	0.003	0.034
25) Health change	-0.005	0.002	0.064
26) PCS	-0.007	0.002	0.003
27) MCS	-0.004	0.003	0.134
Clinical characteristics			
28) Angina status pre-surgery	0.018	0.121	0.882
29) Previous cardiac surgery	-0.015	0.360	0.968
30) Diabetes management	0.299	0.130	0.024
31) History of hypertension	0.091	0.137	0.509
32) Cigarette smoking history	0.242	0.096	0.013
33) NYHA Class	0.015	0.257	0.954
34) History of pulmonary disease	-0.067	0.161	0.679
35) History of neurological disease	-0.120	0.231	0.604
36) Pre-operative heart rhythm	-0.141	0.125	0.260
37) Extent of coronary vessel disease	0.219	0.099	0.029
Procedure			
38) CABG	0.210	0.098	0.034
39) Valve	-0.222	0.104	0.035
40) Major aortic	-0.015	0.360	0.968
41) Other Cardiac Procedures	0.162	0.212	0.447
42) Aortic valve procedure	-0.084	0.098	0.394
43) Mitral valve procedure	-0.202	0.114	0.078
44) Tricuspid valve procedure	0.245	0.256	0.341
Physical activity			
48) Sedentary	-0.001	0.000	0.001
49) Light A	-0.003	0.001	0.018

Table 21 - 9.5.5: Multivariable Results of Frailty influence on Baseline Characteristics, QoL, Procedure & Activity

Demographic	B	Multivariable_SE	P
01) Age	-0.006	0.005	0.246
02) Sex	0.079	0.108	0.468
03) Height	-0.006	0.007	0.353
04) Weight	0.000	0.004	0.906
05) BMI	-0.001	0.001	0.294
06) BSA	0.047	0.279	0.867
QoL parameters			
07) Pre-OP INDEX SCORE	-0.678	0.226	0.003
08) Pre-Op VAS SCORE	0.002	0.003	0.584
17) Physical Functioning	-0.005	0.002	0.021
18) R L Physical	-0.003	0.001	0.024
19) R L Emotional	0.000	0.001	0.765
20) Energy/Fatigue	-0.003	0.003	0.323
21) Emotional well-being	0.001	0.003	0.769
22) Social Functioning	-0.007	0.002	0.001
23) Pain	-0.006	0.002	0.004
24) General Health	-0.006	0.003	0.043
25) Health change	-0.004	0.003	0.107
26) PCS	-0.007	0.002	0.003
27) MCS	-0.004	0.003	0.151
Clinical characteristics			
28) Angina status pre-surgery	0.046	0.124	0.709
29) Previous cardiac surgery	0.012	0.370	0.975
30) Diabetes management	0.310	0.141	0.030
31) History of hypertension	0.095	0.139	0.497
32) Cigarette smoking history	0.302	0.110	0.007
33) NYHA Class	0.008	0.259	0.974
34) History of pulmonary disease	-0.030	0.165	0.858
35) History of neurological disease	-0.096	0.240	0.690
36) Pre-operative heart rhythm	-0.129	0.130	0.324
37) Extent of coronary vessel disease	0.252	0.115	0.030
Procedure			
38) CABG	0.233	0.110	0.036
39) Valve	-0.258	0.117	0.030
40) Major aortic	-0.022	0.368	0.952
41) Other Cardiac Procedures	0.175	0.219	0.426
42) Aortic valve procedure	-0.052	0.106	0.625
43) Mitral valve procedure	-0.231	0.120	0.057
44) Tricuspid valve procedure	0.255	0.260	0.330
Physical activity			
48) Sedentary	-0.001	0.000	0.000
49) Light A	-0.004	0.002	0.016

Predictors of frailty influence postoperatively

Postoperatively higher frailty score was associated with a higher complication rate, diminished QoL and very low physical activity levels: In the multivariable model, the following six variables (composite complication (0.002), QoL index score at 3M & 6M (P=0.000 vs. 0.027) respectively, moderate activity (p=0.018), renal problem (p=0.032) and LoS (p=0.018)) predicted pre-surgery frailty influenced outcome.

Table 22 - 9.5.6 Predictors of Postoperative Frailty Influence

	Univariable			Multivariable		
Frailty Influence	<i>B</i>	SE	<i>P</i>	<i>B</i>	<i>_SE</i>	<i>P</i>
Post-Op 3m INDEX SCORE	-0.763	0.195	0.000	-0.744	0.200	0.000
Post Op 3M VAS SCORE	-0.006	0.004	0.129	-0.006	0.004	0.174
Post-op 6M INDEX SCORE	-0.590	0.252	0.022	-0.579	0.256	0.027
Post-Op 6M VAS SCORE	-0.005	0.004	0.217	-0.005	0.004	0.198
Post-OP 12MINDEX SCORE	-0.310	0.227	0.175	-0.334	0.234	0.158
Post-Op 12m VAS SCORE	-0.002	0.004	0.515	-0.003	0.004	0.469
Post-OP_Sedentry	-0.001	0.000	0.107	-0.001	0.000	0.112
Post-OP_Light Activity	-0.005	0.003	0.080	-0.005	0.003	0.076
Post-OP_Moderate Activity	-0.012	0.005	0.011	-0.012	0.005	0.018
Post-OP_Light Activity	-0.693	0.488	0.160	-0.663	0.493	0.183
Re-Admission	0.095	0.168	0.573	0.069	0.171	0.687
Renal Problem	0.390	0.182	0.034	0.400	0.184	0.032
SSI	0.500	0.291	0.089	0.479	0.293	0.106
Stroke	0.495	0.357	0.168	0.502	0.364	0.171
Re-Operation	0.205	0.167	0.221	0.207	0.171	0.229
New AF	0.012	0.123	0.923	-0.002	0.127	0.988
Pace-Maker	-0.015	0.212	0.943	0.044	0.218	0.840
Composite Complication	0.321	0.107	0.003	0.335	0.108	0.002
Death	0.490	0.505	0.334	0.499	0.508	0.328
LoS	0.008	0.003	0.019	0.008	0.003	0.018

Pre-op: pre-operative. Post-Op: post-operative

Effect of Frailty on the improvement in quality of life (QoL) - EQ-5D index Scores

Table 23 - 9.5.7 demonstrate comparison between the Frail vs. Non-Frail with respect to QoL index score @ (4-time point).

	Non-Frail				Frail			
	Pre-OP INDEX SCORE	Post-OP 3M INDEX SCORE	Post-OP 6M INDEX SCORE	Post-OP 12M INDEX SCORE	Pre-OP INDEX SCORE	Post-Op 3m INDEX SCORE	Post-op 6M INDEX SCORE	Post-OP 12M INDEX SCORE
Mean	0.6573	0.6304	0.7200	0.7370	0.5139	0.4558	0.6111	0.6614
Stdv	0.2292	0.2037	0.1739	0.2492	0.2006	0.2425	0.2343	0.2440
Median	0.7000	0.6700	0.7100	0.7600	0.6000	0.5000	0.6500	0.6800
Prc_25th	0.6300	0.5825	0.6000	0.6000	0.3200	0.2625	0.5525	0.6050
Prc_75th	0.7600	0.7725	0.7875	1.0000	0.6800	0.6600	0.7600	0.7975
CI_LL	0.5943	0.5734	0.6640	0.6567	0.4604	0.3906	0.5426	0.5884
CI_UL	0.7202	0.6875	0.7760	0.8173	0.5674	0.5211	0.6796	0.7343
Non_Frail_ttp	0.0000	0.0000	0.0000	0.0000	0.0009	0.0002	0.0215	0.1750
Frail_ttp	0.0009	0.0002	0.0215	0.1750	0.0000	0.0000	0.0000	0.0000
Non_Frail_mwp	0.0000	0.0000	0.0000	0.0000	0.0002	0.0001	0.0519	0.1253
Frail_mwp	0.0002	0.0001	0.0519	0.1253	0.0000	0.0000	0.0000	0.0000
Annova P	0.0009	0.0002	0.0215	0.1750	0.0009	0.0002	0.0215	0.1750

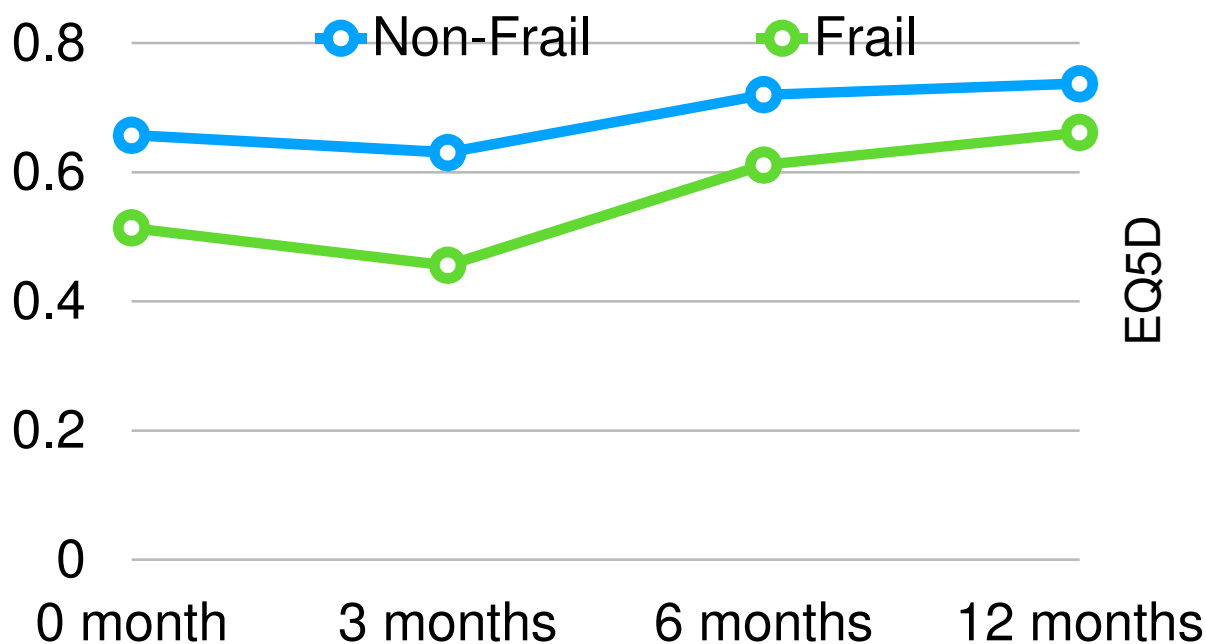


Figure 26 - 9.1. Represent difference in index score between frail and non-frail group along with time interaction.

As shown in figure 9.1 the two groups had significant differences in the preoperative stage and the gap grows wider immediately after surgery, QoL drops in both groups upto 3 months. From 3 months onwards QoL improves in both groups with greater benefit registered by the frail patients. At six

months the gap in QoL improvements narrows between the high frail and low frail but overall QoL is greater at one year than pre-surgery index scores in both groups.

Table 24 - Table 9.5.8 – Effects of frailty on EQ5D

Effect of Frailty on EQ5D			
Index Score	Effect of frailty [#]	95%CI	p-value
Pre-OP	-0.19	-0.29;-0.08	0.001
3 months	-0.23	-0.36;-0.10	0.001
6 months	-0.1	-0.22;0.01	0.08
12 months	-0.1	-0.26;0.06	0.22

[#]adjusted for age, sex, BMI, hypertension, diabetes, smoking, NYHA, AF, neurological history, pulmonary history, IHD

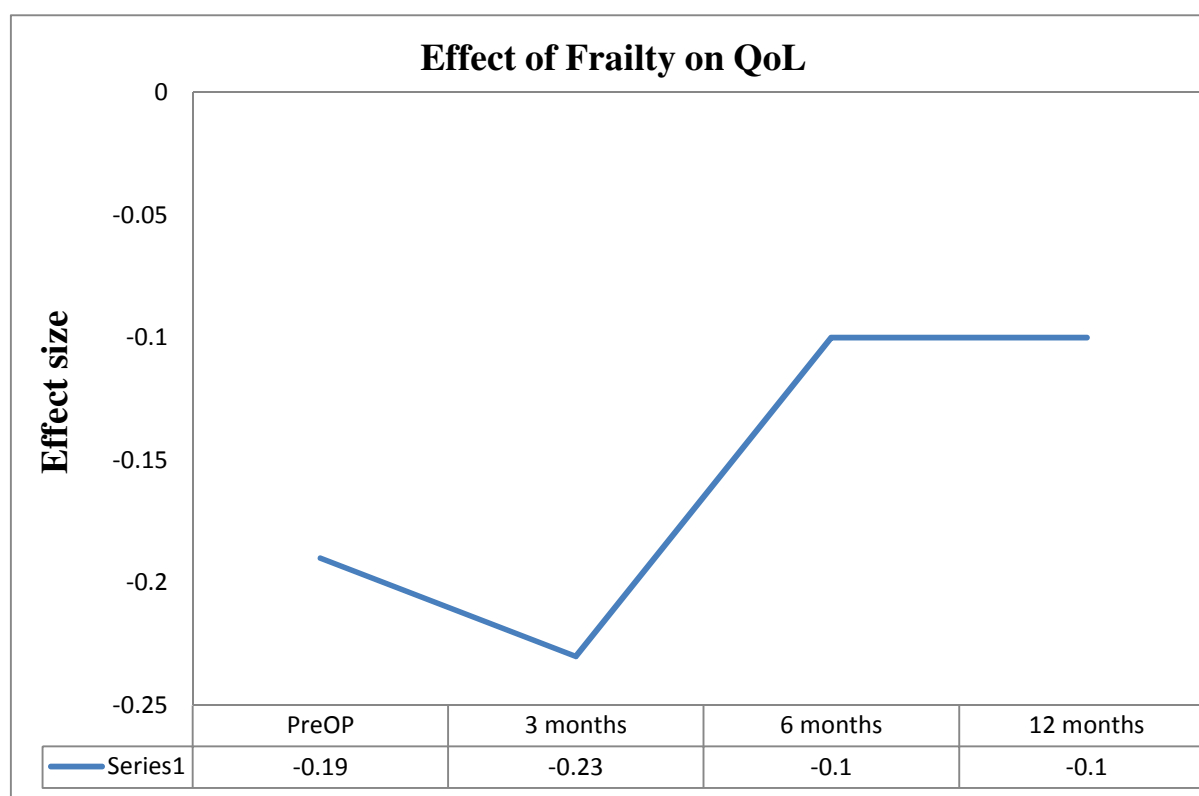


Figure 27 - 9.2. Represent the effect of frailty on quality of life (QoL) index score of EQ-5D

The QoL as assessed by EQ-5D showed that those with greater frailty described a lower quality of life. This difference was significant pre-operatively. Following surgery, this continued to remain significantly lower at the 3months time point. The effect of frailty on the quality of life by 6 months and 12 months had reduced and was now no longer statistically significant. This is summarised in table 9.5.8 and illustrated in figure 9.2 above.

Improvement in quality of life (QoL) Post-surgery and comparison with population matched norms.

Table 25 - 9.5.9 Pre-operative, postoperative and mean population norms QoL values.

HRQOL Tool	Age matched mean population norm	Pre-op Score	Score @ 3M	Score @ 6M	Score @ 12M	One sample t-test population norm Vs. HRQOL tools score			
						Norm Vs. Pre-op	Norm Vs.3M	Norm Vs.6M	Norm Vs.12M
EQ-5D Index	0.773	0.58±0.22	0.53±0.24	0.66±0.21	0.70±0.25	0.0005	0.0001	0.0571	0.2078
EQ-5D VAS	77.3	65.1±18.1	63.4±11.9	91.9±13.8	72.25±15.9	0.0001	0.0001	0.0163	0.033
PCS	45.6	52.8±19.9	NA	NA	NA	0.0174	NA	NA	NA
MCS	53.71	72.25±15.88	NA	NA	NA	0.0001	NA	NA	NA

Pre-op: pre-operative.

EQ-5D index and VAS score for the current study population were both lower than age and population norms at pre-op stage meaning the quality of life of the study population were less than average UK age matched norms. At 3 months the score remained lower than at pre-op or population norms, even though at 6 and 12 months both scores improved, EQ-5D index was still lower than population norms. VAS score at 6 and 12 months were comparable or better than population norm as shown in table 9.5.9.

For PCS and MCS, the study population had a higher pre-operative score than the mean age and population norm (UK). Quality of life generally improved post-surgery. Population norms had association with HRQOL score at the different time point except at 12 months with EQ-5D index score.

A. HRQOL Tool (RAND-36) Score And Baseline Predictors Of Impaired Qol.

Table 26 - Table 9.5.10. Demonstrate baseline predictors of RAND-36 Physical Component Summary (PCS)

PCS vs.	Univariable			Multivariable		
Variable	<i>B</i>	<i>Univariable_S E</i>	<i>P</i>	<i>B</i>	<i>Multivariable_S E</i>	<i>P</i>
Age	-0.090	0.189	0.634	0.064	0.194	0.743
Sex	-9.758	3.932	0.015	-10.443	4.199	0.015
Height	0.327	0.202	0.108	0.027	0.271	0.920
Weight	0.164	0.124	0.189	0.037	0.141	0.795
BMI	-0.027	0.054	0.619	-0.011	0.053	0.841
BSA	12.264	8.909	0.172	0.313	10.928	0.977
Pre-OP INDEX SCORE	65.052	5.957	6.65E-19	66.732	6.280	4.72E-18
Pre-Op VAS SCORE	0.698	0.084	4.04E-13	0.711	0.091	5.87E-12
Post-Op 3m INDEX SCORE	12.047	8.303	0.150	12.848	8.202	0.121
Post Op 3M VAS SCORE	0.464	0.162	0.005	0.466	0.158	0.004
Post-op 6M INDEX SCORE	18.315	10.394	0.082	15.504	10.295	0.136
Post-Op 6M VAS SCORE	0.420	0.157	0.009	0.404	0.157	0.012
Post-OP 12MINDEX SCORE	27.108	9.113	0.004	25.252	9.112	0.007
Post-Op 12m VAS SCORE	0.494	0.138	0.001	0.469	0.141	0.001
Frailty Score (Low)	-1.639	0.707	0.022	-1.546	0.704	0.030
Frailty Score (High)	-11.530	3.765	0.003	-11.216	3.744	0.003
MCS	0.863	0.058	2.83E-27	0.853	0.061	4.51E-25
Angina status pre-surgery	-11.151	4.703	0.020	-11.122	4.684	0.020
Previous cardiac surgery	-19.260	14.254	0.180	-13.707	14.334	0.341
Diabetes management	-8.464	5.270	0.111	-12.319	5.481	0.027
History of hypertension	-4.991	5.447	0.362	-7.813	5.376	0.149
Cigarette smoking history	0.420	3.945	0.915	-3.193	4.434	0.473
NYHA Class	5.888	10.252	0.567	4.350	10.051	0.666
History of pulmonary disease	6.205	6.389	0.334	4.339	6.416	0.500
History of neurological disease	-9.032	9.187	0.328	-5.065	9.348	0.589
Pre-operative heart rhythm	-1.593	5.003	0.751	0.754	5.095	0.883
Extent of coronary vessel disease	-0.622	4.047	0.878	-3.715	4.550	0.416
CABG	0.696	3.983	0.862	-1.512	4.360	0.729
Valve	2.007	4.229	0.636	4.878	4.642	0.296
Major aortic	13.020	14.322	0.365	20.281	14.159	0.155
Other Cardiac Procedures	-26.374	8.059	0.001	-22.786	8.239	0.007
Aortic valve procedure	3.803	3.922	0.335	2.106	4.108	0.609
Mitral valve procedure	1.199	4.613	0.795	5.656	4.727	0.234
Tricuspid valve procedure	-33.830	9.712	0.001	-30.596	9.705	0.002
EuroSCORE	-0.425	0.294	0.151	-0.413	0.379	0.279
sedentary	0.004	0.011	0.726	0.001	0.012	0.925
Light Activity	0.122	0.051	0.020	0.141	0.054	0.011
Moderate Activity	0.088	0.046	0.062	0.082	0.046	0.081

Table 27 - Table 9.5.11. Demonstrate baseline predictors of RAND-36 Mental Component Summary (MCS)

MCS vs.	Univariable			Multivariable		
Variable	B	UniV-SE	P	B	MultiV-SE	P
Age	0.009	0.180	0.961	0.155	0.185	0.405
Sex	-8.176	3.782	0.033	-9.902	4.006	0.015
Height	0.156	0.193	0.420	-0.157	0.258	0.543
Weight	0.181	0.118	0.128	0.102	0.134	0.448
BMI	-0.013	0.051	0.797	0.000	0.051	0.996
BSA	9.854	8.497	0.249	1.990	10.480	0.850
Pre-OP INDEX SCORE	59.340	5.975	1.05E-16	61.631	6.203	1.51E-16
Pre-Op VAS SCORE	0.666	0.080	4.44E-13	0.694	0.085	1.33E-12
Post-Op 3m INDEX SCORE	0.807	8.061	0.920	0.791	8.010	0.922
Post Op 3M VAS SCORE	0.235	0.160	0.144	0.252	0.157	0.111
Post-op 6M INDEX SCORE	11.920	9.570	0.217	9.506	9.490	0.320
Post-Op 6M VAS SCORE	0.160	0.148	0.283	0.146	0.148	0.328
Post-OP 12MINDEX SCORE	23.710	8.595	0.007	22.979	8.536	0.009
Post-Op 12m VAS SCORE	0.347	0.134	0.012	0.336	0.136	0.015
Low Frailty Score	-0.497	0.691	0.473	-0.332	0.687	0.630
High Frailty Score	-5.611	3.716	0.134	-5.340	3.692	0.151
PCS	0.788	0.053	2.83E-27	0.776	0.056	4.51E-25
Angina status pre-surgery	-10.285	4.502	0.024	-9.513	4.494	0.037
Previous cardiac surgery	-24.036	13.533	0.079	-20.302	13.586	0.138
Diabetes management	-1.584	5.096	0.757	-3.097	5.352	0.564
History of hypertension	-2.720	5.218	0.603	-5.111	5.158	0.324
Cigarette smoking history	1.340	3.767	0.723	-0.697	4.241	0.870
NYHA Class	-1.920	9.808	0.845	-3.184	9.594	0.741
History of pulmonary disease	7.209	6.091	0.239	5.188	6.114	0.398
History of neurological disease	-9.593	8.767	0.276	-7.013	8.904	0.433
Pre-operative heart rhythm	-1.859	4.779	0.698	-0.292	4.862	0.952
Extent of coronary vessel disease	3.888	3.848	0.315	3.720	4.340	0.393
CABG	3.909	3.787	0.304	3.706	4.146	0.374
Valve	0.720	4.045	0.859	1.421	4.451	0.750
Major aortic	16.842	13.638	0.220	23.209	13.448	0.087
Other Cardiac Procedures	-26.639	7.653	0.001	-24.005	7.793	0.003
Aortic valve procedure	5.601	3.724	0.136	3.565	3.908	0.364
Mitral valve procedure	-5.092	4.380	0.248	-1.915	4.539	0.674
Tricuspid valve procedure	-28.515	9.399	0.003	-25.859	9.359	0.007
EuroSCORE	-0.339	0.283	0.233	-0.444	0.361	0.222
Sedentary	-0.009	0.010	0.327	-0.017	0.011	0.120
Light Activity	0.080	0.047	0.093	0.083	0.050	0.100
Moderate Activity	0.075	0.041	0.076	0.072	0.042	0.087
Vigorous Activity	0.545	0.716	0.449	0.441	0.723	0.544

The univariable and multivariable results of the two summary components (PCS & MCS) of RAND-36 QoL measurement tools used to quantify baseline predictors of impaired quality of life for patients undergoing cardiac surgery are shown in detail in table 9.5.10 (PCS) and 9.5.11 (MCS) respectively.

Analysis for RAND-36 PCS; 14 variables were significant in the univariable model meanwhile for the multivariable, when the model was adjusted for age and female gender on top of the variable under investigation. 15 variables were significant predictors of impaired QoL. These were female gender (0.015), pre-op index & VAS score (4.72^{-18} , 5.87^{-12}) respectively, 3 & 6 month VAS score (0.004, 0.012 respectively), 12 months index & VAS score (0.007, 0.001 respectively), MCS (4.51^{-25}), angina (0.020), diabetes (0.027), concomitant cardiac procedure (0.007), tricuspid valve procedure (0.002) and light activity (0.011).

PCS had significant interaction with frailty score even though high frail indicated greater association (0.003) compared to low frail (0.030) in the multivariable model.

Furthermore, analysis for RAND-36 MCS; 8 variables had significant association with MCS in both univariable and when adjusted for the multivariable model. These were female gender (0.015), pre-op index & VAS score (1.51^{-16} , 1.33^{-12}) respectively, 12 months index & VAS score (0.009, 0.015) respectively, PCS (4.51^{-25}), angina (0.037), concomitant cardiac procedure (0.003), tricuspid valve procedure (0.007) and light activity (0.011).

Table 28 - Table 9.5.12. Cross-sectional relationship between disease-specific, general variables and the QoL domains scores of RAND-36

	RAND 36									
	Physical Functioning	Social Functioning	Role Impairment (physical)	Role Impairment (emotional)	Pain	Mental Health	Vitality	General Health	Physical Component	Mental Component
Gender (Female)	-15.90**	-6.25	0.12	7.19	-13.40**	-6.98	-7.09	-9.19**	-8.62*	-4.47
Age	-0.77**	0.24	-0.24	0.66	0.13	-0.23	-0.3	0.38*	-0.09	0.15
BMI	-0.04	-0.04	-0.08	-0.6	-0.02	-0.007	0.003	0.02	-0.03	-0.02
Angina (2/3/4)	-8.44	-19.31**	-16.89	0.85	-15.29*	2.21	-9.53	-6.98	-12.74*	-6.55
AF	-2.86	3.1	1.09	-6.57	1	4.99	-3.7	1.11	-0.04	-0.22
Diabetes	-4.11	-5.67	-21.53	4.49	-10.49	0.1	-3.88	-3.14	-8.14	-1.62
Hypertension	-2.62	-1.83	-8.99	-1.11	-4.89	0.02	1.15	0.73	-2.75	-0.21
Smoking	-8.71	-10.24	0.85	-11.24	3.27	-4.83	-0.41	-4.88	-3.35	-6.32
NYHA (3/4)	-9.67	-11.78*	-1.39	-5.83	-6.64	-3.08	-1.36	-5.76	-6.1	-5.56
Cardiovascular disease	-0.88	6.61	12.85	-1.74	8.34	6.64	7.55	8.79	7.21	5.57
Neurological disease	4.11	-3.56	-16.9	-25.14	-18.98	11.39	-10.24	-6.22	-8.63	-6.75
Pulmonary disease	2.18	-1.41	-0.39	4.14	-2.37	4.93	1.74	4.38	0.69	2.76
R ²	0.26	0.31	0.1	0.06	0.24	0.17	0.17	0.22	0.2	0.11
(*p<0.05, **p<0.01)										

In order to investigate further the baseline variable associated with poor quality of life (QoL) other than the results presented by the RAND-36 component summary (PCS & MCS); the relationship between cardiovascular disease-specific and general demographic variables were evaluated against the domains of RAND-36 as shown in table 9.5.12 above. Female gender had significant negative association with the domain 'physical functioning', 'pain', 'general health' as well as physical component summary (PCS). Similarly, age had negative association with 'physical functioning', and 'general health' domain. Angina ≥ 2 had negative interaction with the domains 'social functioning', 'pain', 'general health' as well as physical component summary (PCS). NYHA class ≥ 3 had negative association with the 'social functioning' domain.

B. HRQOL Tool (EQ-5D) Score And Baseline Predictors Of Impaired QoL.

Seven variables were predictors of diminished QoL in both models when tested against EQ-5D index score. The following were significant in the multivariable analysis: female gender (0.004), PCS (4.72E^{-18}), MCS (1.51E^{-16}), high frailty score (0.003), diabetes (0.038), other cardiac procedure (2.73E^{-05}) and tricuspid valve procedure (0.011).

Table 29 - 9.5.13. Describes baseline predictors of EQ-5D pre-op index score.

EQ-5D Index Score vs.	Univariable			Multivariable		
Variable	B	Univariable_S E	P	B	Multivariable_S E	P
Age	0.001	0.002	0.507	0.004	0.002	0.099
Sex	-0.130	0.044	0.004	-0.145	0.046	0.002
Height	0.002	0.002	0.327	-0.002	0.003	0.504
Weight	0.000	0.001	0.735	-0.001	0.002	0.432
BMI	0.000	0.001	0.848	0.000	0.001	0.596
BSA	0.053	0.099	0.593	-0.083	0.119	0.485
Frailty Score (Low)	-0.016	0.008	0.045	-0.013	0.008	0.101
Frailty Score (High)	-0.143	0.042	0.001	-0.123	0.041	0.003
PCS	0.008	0.001	6.65E^{-19}	0.008	0.001	4.72E^{-18}
MCS	0.008	0.001	1.05E^{-16}	0.008	0.001	1.51E^{-16}
Angina status pre-surgery	-0.051	0.054	0.351	-0.068	0.052	0.195
Previous cardiac surgery	-0.151	0.161	0.350	-0.109	0.157	0.489
Diabetes management	-0.100	0.059	0.096	-0.126	0.060	0.038
History of hypertension	-0.081	0.061	0.190	-0.108	0.058	0.068
Cigarette smoking history	-0.008	0.044	0.850	-0.045	0.048	0.352
NYHA Class	-0.116	0.115	0.316	-0.126	0.109	0.250
History of pulmonary disease	0.110	0.071	0.127	0.070	0.070	0.318
History of neurological disease	-0.075	0.104	0.470	-0.053	0.102	0.606
Pre-operative heart rhythm	0.030	0.056	0.592	0.043	0.056	0.444
Extent of coronary vessel disease	-0.007	0.046	0.873	-0.025	0.050	0.621
CABG	0.013	0.045	0.777	0.002	0.048	0.971
Valve	0.036	0.048	0.455	0.056	0.051	0.276
Major aortic	0.149	0.161	0.357	0.224	0.155	0.150
Other Cardiac Procedures	-0.400	0.087	1.19E^{-05}	-0.376	0.086	2.73E^{-05}
Aortic valve procedure	0.089	0.043	0.044	0.063	0.045	0.162
Mitral valve procedure	-0.043	0.052	0.409	-0.005	0.052	0.926
Tricuspid valve procedure	-0.308	0.112	0.007	-0.278	0.108	0.011
Cumulative bypass time	0.001	0.001	0.312	0.001	0.001	0.413
Cumulative cross clamp time	0.001	0.001	0.151	0.001	0.001	0.201
EuroSCORE	-0.003	0.003	0.448	-0.004	0.004	0.289
Sedentary	0.000	0.000	0.098	0.000	0.000	0.292
Light Activity	0.001	0.001	0.148	0.001	0.001	0.197
Moderate Activity	0.001	0.001	0.088	0.001	0.001	0.180
Vigorous Activity	0.013	0.010	0.193	0.008	0.009	0.399

C. Longitudinal HRQOL (GEE) Outcome

Table 30 - 9.5.14. Describes predictors of diminished longitudinal health related quality of life.

EQ-5D vs.	Generalised Estimation Equation (GEE)			Weight of Interactions of variable with time			
Variable	B	SE	p	Time Point	B	SE	P
Age	0.001	0.0021	0.516				-
Female	-0.131	0.045	0.004	2	-3.8E-06	1.67E-06	0.024
Male	0		-		0	0	-
Height	0.002	0.002	0.249				-
Weight	0.001	0.0013	0.687				-
BMI	0.0001	-8.89E-05	0.22				-
BSA	0.057	0.0864	0.509				-
Comorbidities							
Angina	0.298	0.1083	0.006	2	-241	0.0794	0.002
Previous cardiac surgery	-0.109	0.484	0.025				-
Diabetes management	-0.099	0.0571	0.084	1	-0.196	0.071	0.006
Hypertension	-0.079	0.0462	0.086				-
Cigarette smoking	-0.199	0.078	0.011	1	0.211	0.0843	0.012
NYHA Class (2-4)	-0.116	0.0359	0.001	4	-5.9E-06	2.55E-06	0.021
Pulmonary disease	0.111	0.0417	0.019	2	0.141	0.0596	0.018
Neurological disease	-0.074	0.0917	0.417		0	0	-
Atrial fibrillation	0.029	0.046	0.532		0		-
Extent of coronary vessel disease	-0.007	0.0424	0.874	2	-3.4E-06	1.68E-06	0.039
HRQOL							
PCS	0.008	0.0007	0.00001	2	-1.5E-05	7.51E-06	0.041
MCS	0.008	0.0008	0.00001	2	-2.8E-05	-8.3E-06	0.001
Operative data and risk score							
EuroSCORE			-				-
CABG	0.013	0.0423	0.755				-
Valve	0.035	0.0465	0.045	4	-4.1E-06	-2.1E-06	0.031
Concomitant procedure							
Cumulative bypass time	0.001	0.0007	0.311				-
Cumulative cross clamp time	0.001	0.001	0.181				-
Complication							
Re-Admission	0.085	0.0797	0.286	2	-4.4E-06	-2.2E-06	0.048
Renal Problem	0.033	0.0844	0.695	3	-7.3E-07	-3.2E-06	0.022
Surgical site infection (SSI)	-0.061	0.1096	0.577	2&3*	-9.2E-06	-6.6E-06	0.005
Stroke	-0.134	0.1045	0.199				-
Re-Operation	-0.06	0.0731	0.412				-
New AF	0.048	0.0541	0.375				-
Pace-Maker	0.124	0.0853	0.147	4	4.92E-06	1.78E-06	0.006
Composite Complication	-0.02	0.044	0.651				-
Mortality	0.108	0.0221	0.0001	2&4*	1.98E-05	3.99E-06	0.0001

When EQ-5D index scores was evaluated over the 4-time period using the GEE model, eleven variables were independent predictors of quality of life, additionally when interaction with time was investigated fifteen variables were predictive of either negative or improved quality of life post-surgery.

The following eleven variables: female gender (0.024), diabetes (0.006), current smoker (0.012), pulmonary disease (0.018), PCS (0.041), MCS (0.001), re-admission (0.048), renal problem (0.022), surgical site infection (0.005), pacemaker (0.006) and mortality (0.0001) had a negative impact on patients post-surgery and were predictive of worse longitudinal quality of life

Improvements in longitudinal quality of life were described at different time points by the following variables: angina relief (0.002), extent of coronary vessel disease (0.039), post valve procedure (0.042) and NYHA (0.021) at time point four.

D. Cardiac Specific Self-Rated Quality Of Life Post-Surgery Outcome.

Table 31 - 9.5.15. Presents the evolution of QoL and interaction with frailty.

Effect of frailty on cardiac-specific disease and health status			
	Effect of frailty [#]	95%CI	p-value
CS_3 months	0.39	-0.06;0.84	0.09
CS_6 months	0.63	-0.05;1.32	0.07
CS_12 months	0.44	-0.25;1.14	0.21

[#]adjusted for age, sex, BMI, hypertension, diabetes, smoking, NYHA, AF, neurological history, pulmonary history, IHD

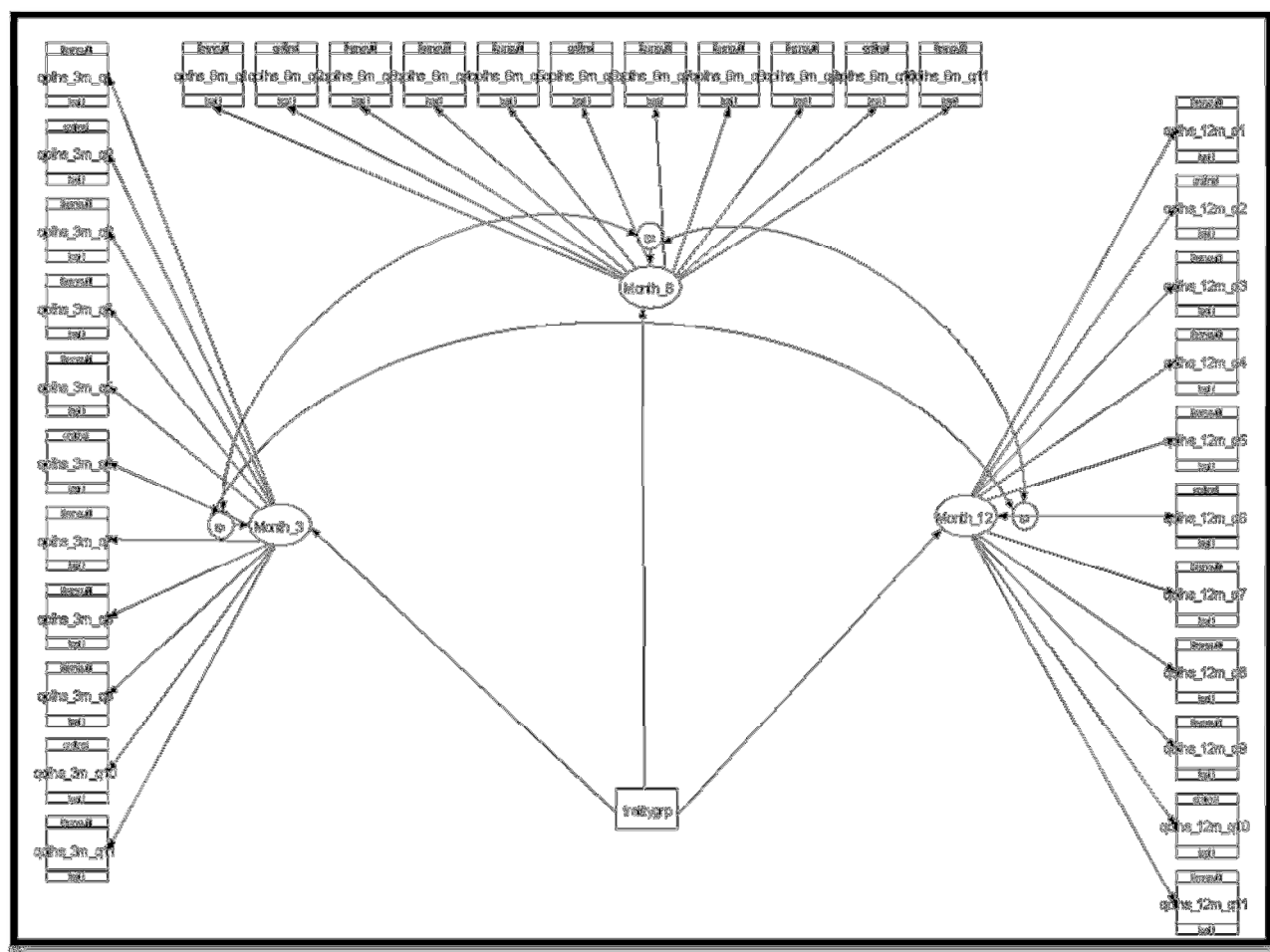


Figure 28 - 9.3. Describes SEM modelling and interface association between QoL and frailty impact.

Patient's self-rated cardiac specific disease and health status QoL was assessed by questionnaire at 3, 6 and 12 months. The effect of frailty at these three time points was assessed by structural equation modelling (SEM). The model is shown diagrammatically above (figure 9.3) and the effects summarised in the table (9.5.15) above. A trend was seen where those with greater frailty described a lower QoL at 3 and 6 months. However, by 12 months any effect of frailty on the self-rated QoL was not seen.

E. Isolated Valve Surgery Cohort Predictors Of Quality Of Life (QoL)

Table 32 - 9.5.16. Predictors of PCS & MCS (Valve cohort).

VALVE	PCS						MCS					
	Univariable			Multivariable			Univariable			Multivariable		
Variable	B	SE	P	B	SE	P	B	SE	P	B	SE	P
Age	-0.398	0.265	0.138	-0.214	0.268	0.427	-0.257	0.263	0.332	-0.090	0.268	0.737
Sex	-12.388	4.799	0.012	-11.958	5.059	0.021	-10.244	4.830	0.037	-10.841	5.055	0.036
BMI	-0.028	0.057	0.630	-0.008	0.055	0.888	-0.015	0.056	0.789	0.001	0.055	0.989
BSA	24.444	11.830	0.043	2.860	15.397	0.853	19.572	11.725	0.100	3.841	15.503	0.805
Pre-OP INDEX SCORE	67.292	7.565	4.12E-13	67.516	7.809	1.65E-12	67.665	7.390	1.97E-13	70.241	7.427	5.85E-14
Pre-Op VAS SCORE	0.668	0.095	1.02E-09	0.665	0.106	3.22E-08	0.676	0.093	3.66E-10	0.712	0.102	1.47E-09
Post-Op 3m INDEX SCORE	5.114	10.871	0.640	7.669	10.408	0.464	-5.166	10.873	0.6363	-3.556	10.634	0.739
Post-Op 3m VAS SCORE	0.300	0.213	0.163	0.295	0.204	0.152	0.130	0.215	0.5481	0.149	0.210	0.481
Post-op 6M INDEX SCORE	10.650	12.875	0.412	8.622	12.206	0.483	4.725	12.194	0.7000	2.913	11.716	0.805
Post-Op 6M VAS SCORE	0.354	0.186	0.063	0.296	0.179	0.106	0.073	0.181	0.6897	0.015	0.176	0.933
Post-OP 12M INDEX SCORE	29.961	11.447	0.012	22.819	11.289	0.049	26.006	11.280	0.0234	19.469	11.242	0.090
Post-Op 12m VAS SCORE	0.503	0.165	0.004	0.404	0.164	0.018	0.333	0.168	0.0537	0.244	0.168	0.153
Frailty Score	-0.703	0.867	0.420	-0.679	0.839	0.421	0.242	0.864	0.7803	0.273	0.842	0.746
Frailty Score	-8.051	4.929	0.107	-8.548	4.771	0.078	-2.993	4.970	0.5490	-3.730	4.859	0.445
MCS/PCS*	0.860	0.063	1.85E-21	0.842	0.066	1.60E-19	0.846	0.062	1.85E-21	0.840	0.066	1.60E-19
Angina status pre-surgery	-7.423	5.592	0.189	-4.489	5.652	0.430	-7.927	5.537	0.157	-5.024	5.640	0.376
Previous cardiac surgery	-20.082	14.994	0.185	-11.393	14.964	0.449	-24.485	14.779	0.102	-17.850	14.857	0.234
Diabetes management	-6.244	12.465	0.618	-12.404	12.144	0.311	-3.869	12.381	0.756	-8.923	12.179	0.466
History of hypertension	-3.028	6.295	0.632	-5.615	6.099	0.360	-1.815	6.252	0.772	-4.291	6.109	0.485
Cigarette smoking history	3.907	5.133	0.449	-2.878	5.719	0.616	2.184	5.107	0.670	-2.966	5.713	0.605
NYHA Class (3/4)	6.664	10.865	0.542	5.704	10.477	0.588	-1.716	10.807	0.874	-2.839	10.486	0.787
History of pulmonary disease	11.568	8.309	0.168	7.595	8.601	0.380	14.613	8.172	0.078	11.469	8.530	0.183
History of neurological disease	-9.921	9.744	0.312	-3.489	9.804	0.723	-10.061	9.665	0.301	-5.017	9.786	0.610
Pre-operative heart rhythm	-1.425	5.659	0.802	0.983	5.531	0.859	-1.333	5.615	0.813	0.810	5.526	0.884
Extent of coronary vessel disease	6.425	6.442	0.322	3.299	6.376	0.607	11.602	6.286	0.069	9.554	6.276	0.133
CABG	6.352	6.259	0.314	3.170	6.225	0.612	11.444	6.104	0.065	9.294	6.127	0.134
Valve	26.742	1.239	1.16E-32	37.848	10.571	0.001	28.927	1.229	5.67E-35	34.729	10.562	0.002
Major aortic	15.481	21.242	0.469	34.021	20.521	0.246	17.184	21.056	0.417	24.681	20.491	0.233
Other Cardiac Procedures	-28.908	9.188	0.002	-24.363	9.189	0.010	-29.246	9.091	0.002	-25.383	9.139	0.007
Aortic valve procedure	2.716	5.283	0.607	-1.053	5.336	0.844	7.476	5.176	0.153	4.203	5.309	0.431
Mitral valve procedure	0.434	5.241	0.934	4.991	5.313	0.351	-6.289	5.146	0.226	-2.618	5.334	0.625
Tricuspid valve procedure	-35.123	10.053	0.001	-31.141	9.918	0.003	-39.281	10.226	0.006	-25.674	10.140	0.014
Cumulative bypass time	0.010	0.083	0.903	0.005	0.081	0.955	-0.012	0.083	0.883	-0.016	0.082	0.849
Cumulative cross clamp time	0.079	0.105	0.458	0.069	0.104	0.508	0.027	0.105	0.798	0.030	0.104	0.773
EuroSCORE	-0.573	0.358	0.114	-0.305	0.431	0.482	-0.433	0.358	0.231	-0.262	0.431	0.546
Sedentary	-0.009	0.016	0.551	-0.009	0.018	0.622	-0.025	0.015	0.090	-0.027	0.017	0.116
Light Activity	0.110	0.064	0.091	0.148	0.065	0.028	0.102	0.061	0.103	0.125	0.063	0.054
Moderate Activity	0.095	0.053	0.078	0.099	0.053	0.068	0.098	0.050	0.058	0.108	0.050	0.038
Vigorous Activity	1.103	0.834	0.193	0.931	0.860	0.285	0.679	0.806	0.404	0.747	0.828	0.373
PostOP_Sedentary	-0.034	0.019	0.079	-0.034	0.019	0.084	-0.044	0.018	0.018	-0.041	0.018	0.028

Our decent study sample enabled us to conduct sub analysis of the study population. Table 9.5.16 describes predictors of impaired quality of life for the valve surgery cohort. Univariable analysis for PCS highlighted nine variables that had significant interaction with the tool and were considered predictors of poor QoL. In multivariable models, the following eight variables were predictors of poor QoL: female gender (0.021), pre-op index and VAS score (1.65E^{-12} , 3.22E^{-08}) respectively, Post-operative index and VAS score at 12 month (0.049, 0.018) respectively, MCS (1.60E^{-19}) other cardiac procedure (0.010) and light activity (0.028).

For MCS univariable and multivariable analysis presented nine variables, even though they shared some of the PCS predictors of impaired quality of life, moderate activity (0.038) and post-operative sedentary (0.028) and PCS (1.60E^{-19}) were predictive of poor quality of life as presented by MCS multivariable model.

Furthermore, when baseline predictors of poor quality of life for patients undergoing valve surgery was investigated using EQ-5D index score (table 9.5.17) below. The univariable and multivariable models indicated significant association of the following five variables with the tool: female gender (0.007), PCS (1.65E^{-12}), MCS (5.85E^{-14}), other cardiac procedure (9.94E^{-05}) and tricuspid valve procedure (0.010).

Table 33 - 9.5.17. Predictors of EQ-5D. (Valve cohort).

<i>EQ-5D Index Score</i>	<i>Univariable</i>			<i>Multivariable</i>		
<i>Demographic</i>	<i>B</i>	<i>SE</i>	<i>P</i>	<i>B</i>	<i>SE</i>	<i>P</i>
Age	-0.002	0.003	0.508	0	0.003	0.887
Sex	-0.155	0.051	0.003	-0.152	0.054	0.007
BMI	0	0.001	0.853	0	0.001	0.549
BSA	0.185	0.13	0.159	-0.062	0.167	0.713
Frailty Score	-0.097	0.053	0.071	-0.087	0.051	0.095
PCS	0.008	0.001	4.12E-13	0.008	0.001	1.65E-12
MCS	0.008	0.001	1.37E-13	0.008	0.001	5.85E-14
Clinical Characteristics						
Angina status pre-surgery	-0.022	0.061	0.718	-0.018	0.061	0.769
Previous cardiac surgery	-0.164	0.163	0.318	-0.088	0.161	0.586
Diabetes management	-0.043	0.135	0.75	-0.119	0.131	0.365
History of hypertension	-0.074	0.068	0.278	-0.097	0.065	0.14
Cigarette smoking history	0.033	0.056	0.551	-0.041	0.061	0.512
NYHA Class	-0.106	0.117	0.368	-0.113	0.112	0.316
History of pulmonary disease	0.136	0.09	0.135	0.065	0.093	0.488
History of neurological disease	-0.089	0.106	0.403	-0.039	0.105	0.71
Pre-operative heart rhythm	0.045	0.061	0.463	0.059	0.059	0.317
Extent of coronary vessel disease	0.098	0.069	0.16	0.06	0.068	0.386
Procedure						
CABG	0.102	0.067	0.132	0.06	0.067	0.374
Valve	0.297	0.013	0	0.316	0.114	0.007
Major aortic	0.168	0.23	0.468	0.254	0.221	0.254
Other Cardiac Procedures	-0.422	0.094	2.52E-05	-0.384	0.093	9.94E-05
Aortic valve procedure	0.085	0.056	0.135	0.052	0.057	0.367
Mitral valve procedure	-0.067	0.056	0.235	-0.028	0.057	0.627
Tricuspid valve procedure	-0.325	0.111	0.005	-0.287	0.109	0.01
Cumulative bypass time	0	0.001	0.821	-5.64E-05	0.001	0.95
Cumulative cross clamp time	0	0.001	0.708	-5.22E-05	0.001	0.964
EuroSCORE	-0.005	0.004	0.162	-0.005	0.005	0.267
Activity Level						
Sedentary	0	0	0.546	5.41E-05	0	0.8
Light Activity	0.001	0.001	0.368	0.001	0.001	0.298
Moderate Activity	0.001	0.001	0.144	0.001	0.001	0.2
Vigorous Activity	0.013	0.01	0.195	0.01	0.01	0.335

F. Isolated CABG Surgery Cohort Predictors Of Quality Of Life (QoL)

Table 34 - 9.5.18. Predictors of PCS & MCS. (CABG cohort).

	PCS						MCS					
	Univariable			Multivariable			Univariable			Multivariable		
Variable	B	SE	P	B	SE	P	B	SE	P	B	SE	P
Age	0.234	0.278	0.406	0.253	0.279	0.370	0.593	0.218	0.009	0.611	0.218	0.008
Sex	-6.193	7.130	0.390	-6.686	7.166	0.356	-4.920	6.005	0.417	-6.108	5.583	0.280
BMI	-0.067	0.599	0.912	-0.073	0.603	0.904	0.452	0.499	0.370	0.467	0.464	0.320
BSA	-0.436	13.032	0.973	-2.066	14.395	0.887	-1.428	10.963	0.897	2.194	11.212	0.846
Pre-OP INDEX SCORE	65.998	11.992	2.05E-06	71.391	13.488	4.64E-06	49.994	10.758	3.32E-05	42.758	11.918	0.001
Pre-Op VAS SCORE	0.761	0.186	0.000	0.780	0.208	0.001	0.629	0.157	0.000	0.520	0.169	0.004
3m INDEX SCORE	30.575	11.781	0.013	29.202	11.952	0.019	19.496	10.398	0.068	17.634	9.741	0.078
3M VAS SCORE	0.868	0.228	0.000	0.872	0.226	0.000	0.413	0.217	0.064	0.417	0.199	0.043
6M INDEX SCORE	34.549	14.226	0.020	32.878	14.901	0.034	19.277	12.201	0.122	21.517	11.488	0.069
6M VAS SCORE	0.467	0.192	0.019	0.509	0.191	0.011	0.167	0.168	0.326	0.252	0.153	0.108
12MINDEX SCORE	25.298	13.382	0.066	30.584	13.637	0.031	10.471	11.421	0.365	17.861	10.443	0.096
12m VAS SCORE	0.437	0.188	0.025	0.469	0.189	0.018	0.188	0.163	0.255	0.244	0.147	0.104
Frailty Score	-22.096	4.976	6.41E-05	-22.067	5.052	8.64E-05	-14.658	4.544	0.002	-14.927	4.160	0.001
MCS*/PCS*	0.896	0.120	3.44E-09	0.982	0.131	3.70E-09	0.634	0.085	3.44E-09	0.596	0.079	3.70E-09
Angina status pre-surgery	-32.170	8.789	0.001	-31.958	8.859	0.001	-18.775	7.984	0.023	-17.196	7.466	0.027
Diabetes management	-10.398	5.815	0.081	-10.722	6.103	0.087	-4.178	5.035	0.411	-1.705	4.928	0.731
History of hypertension	-11.655	9.933	0.247	-11.474	10.012	0.259	-3.061	8.480	0.720	-2.001	7.921	0.802
Cigarette smoking history	-6.380	5.952	0.290	-7.982	6.533	0.229	-3.788	5.042	0.457	-2.067	5.173	0.692
NYHA Class	26.629	1.434	7.27E-22	18.131	10.198	0.083	29.950	1.207	1.01E-26	8.431	7.945	0.295
History of pulmonary disease	-4.582	7.902	0.565	-7.016	8.377	0.407	-2.128	6.668	0.751	-7.995	6.460	0.223
Pre-operative heart rhythm	33.330	18.780	0.083	40.220	19.841	0.049	28.754	15.771	0.075	29.305	15.557	0.067
Extent of coronary vessel disease	-8.679	10.005	0.391	-9.217	10.957	0.405	1.493	8.490	0.861	8.223	8.513	0.340
CABG	26.629	1.434	7.27E-22	18.131	10.198	0.08303	29.950	1.207	1.01E-26	8.431	7.945	0.295
Valve	7.837	6.112	0.207	6.767	6.884	0.332	10.522	4.984	0.041	5.784	5.350	0.286
Aortic valve procedure	3.873	6.899	0.578	1.190	7.866	0.881	6.682	5.734	0.250	-0.448	6.129	0.942
Mitral valve procedure	23.480	10.928	0.037	24.271	10.972	0.033	19.507	9.207	0.040	19.716	8.502	0.026
Tricuspid valve procedure	-21.240	19.194	0.275	-22.923	19.303	0.242	-5.863	16.359	0.722	-7.529	15.255	0.624
Cumulative bypass time	0.018	0.101	0.862	0.035	0.115	0.762	-0.021	0.086	0.812	-0.084	0.093	0.375
Cumulative cross clamp time	0.212	0.122	0.091	0.280	0.140	0.054	0.131	0.107	0.231	0.068	0.121	0.575
EuroSCORE	-0.313	0.524	0.553	-0.993	0.717	0.173	0.210	0.442	0.637	-0.867	0.555	0.126
Sedentry	0.011	0.016	0.515	0.007	0.017	0.700	0.005	0.013	0.696	-0.003	0.011	0.796
Light Activity	0.144	0.090	0.121	0.154	0.089	0.097	0.020	0.073	0.783	0.008	0.064	0.900
Moderate Activity	0.055	0.099	0.582	0.052	0.096	0.592	-0.025	0.078	0.751	-0.028	0.066	0.670
Vigorous Activity	0.736	4.537	0.872	0.607	4.431	0.892	-1.724	3.513	0.627	-1.619	3.011	0.596

CABG patient's baseline characteristics had far greater interaction with PCS (12) than MCS (7) variables. Age as a predictor of poor QoL was unique in the MCS analysis. In the multivariable analysis for PCS: EQ-5D index and VAS score at all-time points was predictive of diminished QoL. Frailty ($8.64E^{-05}$), MCS ($3.70E^{-09}$), pre-surgery angina (0.001), and mitral valve procedure (0.033) were equally predictive of impaired QoL.

The MCS for CABG patients, the variables: Age (0.008), pre-op index and VAS score (0.001, 0.004) respectively, frailty (0.001), pre-surgery angina (0.027), PCS (3.70E^{-09}) and mitral valve procedure (0.026) were predictors of poor QoL.

Table 35 - 9.5.19. Predictors of EQ-5D. (CABG cohort).

EQ-5D Index Score vs.	Univariable			Multivariable		
<i>Demographic</i>	<i>B</i>	<i>UniV_SE</i>	<i>P</i>	<i>B</i>	<i>MultiV_SE</i>	<i>P</i>
Age	0.007	0.003	0.013	0.007	0.003	0.009
Sex	-0.093	0.069	0.184	-0.107	0.064	0.105
BMI	-0.003	0.006	0.579	-0.003	0.005	0.553
BSA	-0.072	0.127	0.575	-0.071	0.129	0.584
Frailty Score	-0.175	0.053	0.002	-0.174	0.048	0.001
PCS	0.006	0.001	2.05E-06	0.006	0.001	4.64E-06
MCS	0.007	0.001	3.32E-05	0.006	0.002	0.001
EuroSCORE	0.008	0.005	0.136	0.002	0.007	0.813
Clinical Characteristics						
Angina status pre-surgery	-0.139	0.097	0.157	-0.123	0.09	0.179
Previous cardiac surgery	0	0	-	0	0	-
Diabetes management	-0.126	0.056	0.029	-0.11	0.054	0.048
History of hypertension	-0.073	0.098	0.461	-0.063	0.091	0.49
Cigarette smoking history	-0.064	0.058	0.276	-0.061	0.059	0.304
NYHA Class	0.295	0.014	6.70E-24	0.056	0.092	0.545
History of pulmonary disease	0.063	0.077	0.416	0.012	0.076	0.876
History of neurological disease	0	0	-	0	0	-
Pre-operative heart rhythm	0.04	0.191	0.835	0.043	0.187	0.818
Extent of coronary vessel disease	-0.131	0.097	0.184	-0.097	0.098	0.329
Procedure						
CABG	0.295	0.014	6.70E-24	0.056	0.092	0.545
Valve	0.126	0.058	0.035	0.075	0.061	0.228
Major aortic	0	0	-	0	0	-
Other Cardiac Procedures	0	0	-	0	0	-
Aortic valve procedure	0.115	0.066	0.086	0.045	0.07	0.522
Mitral valve procedure	0.078	0.112	0.493	0.084	0.104	0.422
Tricuspid valve procedure	0.101	0.19	0.597	0.076	0.176	0.67
Cumulative bypass time	0.002	0.001	0.038	0.002	0.001	0.043
Cumulative cross clamp time	0.004	0.001	0.001	0.004	0.001	0.001
Activity Level						
Sedentary	0	0	0.038	0	0	0.085

CABG patients interacted better with the quality of life tool EQ-5D index scores compared with the valve surgery cohort. Eleven predictor variables in the univariable analysis for CABG patients however when the same variables were entered into the multivariable models, the following seven variables: age (0.009), frailty (0.001), PCS (4.64E^{-06}), MCS (0.001), diabetes (0.048), cumulative bypass time (0.043) and cross clamp time (0.001) were predictors of decreased QoL.

G. Euroscore Vs. Baseline Characteristics And Outcome.

To investigate the relationship between EuroSCORE, post-op complication and baseline risk predictors univariable and multivariable analysis were performed. Six variables were predictors in the univariable model and three in the multivariable model. The multivariable predictors were age (6.71E^{-11}) negatively associating with EuroSCORE, major aortic surgery (0.001) and pace maker implantation post-surgery (0.045) as shown in table (9.5.200 below.

Table 36 - 9.5.20.Describes predictors of risk - EuroSCORE II

<i>EuroSCORE II</i>	<i>Univariable</i>			<i>Multivariable</i>		
Demographic	<i>B</i>	<i>UniV_SE</i>	<i>P</i>	<i>B</i>	<i>MultiV_SE</i>	<i>P</i>
Age	0.402	0.049	7.33E-13	0.374	0.051	6.71E-11
Sex	4.435	1.276	0.001	1.922	1.106	0.085
BMI	0.006	0.018	0.747	0	0.014	0.973
BSA	-9.996	2.84	0.001	-1.865	2.885	0.52
Low Frailty Score	0.047	0.241	0.844	0.245	0.188	0.195
High Frailty Score	0.362	1.314	0.784	1.075	1.024	0.296
PCS	-0.047	0.033	0.151	-0.029	0.026	0.279
MCS	-0.041	0.034	0.233	-0.034	0.028	0.222
Procedure						
CABG	-3.526	1.282	0.007	0.179	1.149	0.876
Valve	4.395	1.354	0.002	0.424	1.228	0.731
Major aortic	15.698	4.521	0.001	12.129	3.564	0.001
Other Cardiac Procedures	2.972	2.8	0.291	-0.611	2.251	0.787
Aortic valve procedure	2.339	1.296	0.074	0.381	1.082	0.726
Mitral valve procedure	2.434	1.517	0.112	0.39	1.253	0.756
Tricuspid valve procedure	4.205	3.388	0.217	1.356	2.677	0.614
Cumulative bypass time	0.056	0.021	0.009	0.03	0.017	0.086
Cumulative cross clamp time	0.068	0.026	0.012	0.032	0.022	0.147
Activity Level						
Sedentary	0.013	0.004	0.002	0.003	0.004	0.508
Light Activity	0.034	0.022	0.124	-0.008	0.018	0.68
Moderate Activity	0.001	0.02	0.967	-0.014	0.015	0.355
Vigorous Activity	0.108	0.331	0.744	0.063	0.261	0.808
Post-Op Complication						
Re-Admission	-0.051	2.227	0.982	0.028	1.753	0.987
Renal Problem	-1.077	2.462	0.663	0.934	1.931	0.63
SSI	-3.941	3.903	0.315	-2.11	3.039	0.489
Stroke	0.842	4.78	0.86	-3.058	3.753	0.417
Re-Operation	0.564	2.226	0.8	-1.46	1.762	0.409
New AF	3.526	1.598	0.03	2.471	1.277	0.056
Pace-Maker	6.337	2.745	0.023	4.445	2.193	0.045
Composite Complication	-0.935	1.477	0.528	-0.528	1.155	0.648
Death	2.005	6.725	0.766	4.362	5.207	0.404
LoS	0.016	0.045	0.722	-0.007	0.034	0.828
Pain/Discomfort	-3.502	1.063	0.001	-1.231	0.908	0.178

H. Postoperative Complication

Period	Mortality	Re-Admission	Renal Problem	SSI	Stroke	Re-Operation	New AF	Pace Maker	Composite Complication
1 Month	0.95	9.52	7.62	2.86	1.90	9.52	20.00	5.71	26.67
3 Month	0.00	5.71	2.86	4.76	0.95	7.62	9.52	2.86	15.24
6 Month	0.95	7.50	12.50	5.00	0.00	5.00	6.25	3.75	15.00
12 Month	1.92	6.17	3.70	2.50	0.00	2.47	4.94	3.70	12.35

Table 37 - 9.5.21. Overall postoperative complications

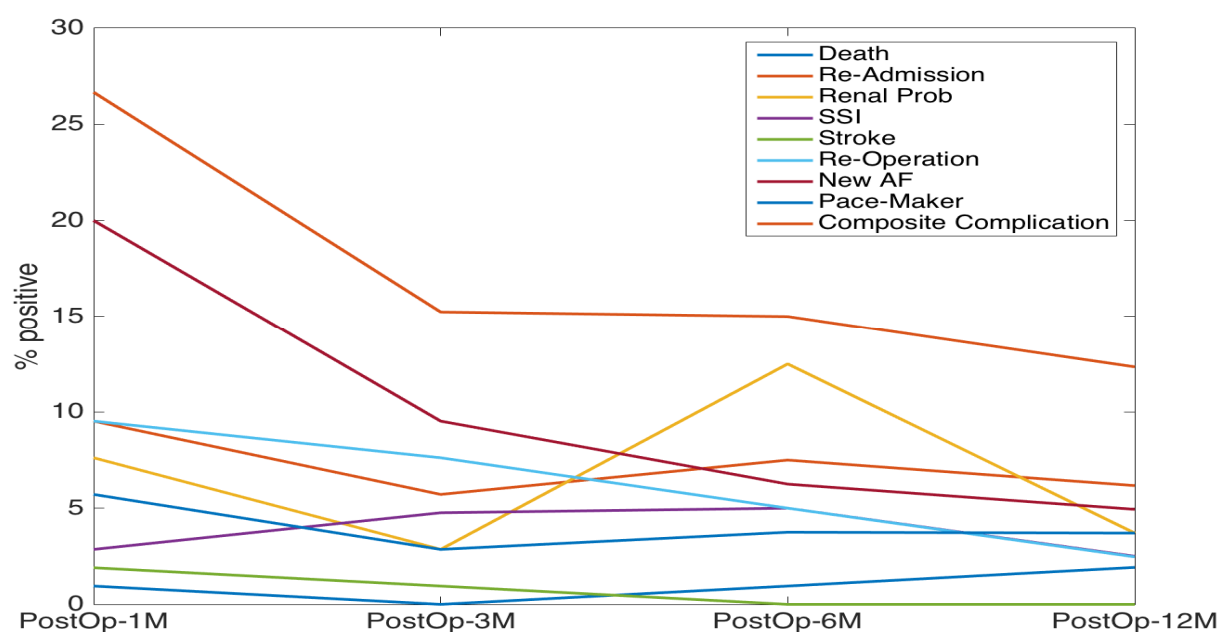


Figure 29 - 9.4 Describes complication type and rate

Complication List	30th Day			3 Month			6 Month			12 Month		
	Non-Frail	Frail	P	Non-Frail	Frail	P	Non-Frail	Frail	P	Non-Frail	Frail	P
Re-Admission	4	6	0.57	2	4	0.44	3	3	0.80	3	2	0.51
Renal Problem	1	7	0.03	0	3	0.09	1	3	0.41	0	3	0.11
SSI	0	3	0.09	0	5	0.03	1	3	0.41	0	2	0.20
Stroke	0	2	0.17	0	1	0.33	0	0	0	0	0	0
Re-Operation	3	7	0.22	2	6	0.17	2	2	0.84	0	2	0.19
New AF	10	11	0.92	5	5	0.92	2	3	0.82	0	4	0.06
Pace-Maker	3	3	0.94	0	3	0.09	1	2	0.68	2	1	0.46
Composite Complication	7	21	0.00	5	11	0.13	6	6	0.71	4	6	0.70
Mortality	0	1	0.33	0	0	0	0	1	0.37	0	2	0.11

Table 38 - 9.5.22. Postoperative complications categorised into the two groups (Frail vs.Non-Frail)..

Study Quality and Completion.

Questionnaires Completeness	Number and (%)
Preoperative stage	105 (100%)
Postoperative (3 Months)	104 (99.04%)
Postoperative (6 Months)	96 (91.43%)
Postoperative (12 Months)	93 (88.57%)
Number of patients requiring reminders messages	38 (36.54%)
Consistent responses	98.67%
Internal consistency	93.51%
Discriminatory validity	98.15%
Scale reliability	100%

Table 39 - 9.5.23. Describes study completeness and quality.

The table above summaries study quality score and follow-up completeness in each of the four stages. Other than the loss of patient to mortality, few other patients were un-contactable at 6 months and 12 months despite the fact that several attempts were made to get in touch with patients that didn't return their follow-up questionnaires including direct phone calls. None the less, three patients that did not return their questionnaires at 6 months' time points were later able to participate the followup interviews at 12 months' time points. Almost a third of the patients population required one or more phone call reminders and where possible follow-up interviews was conducted over the phone subject to patients consent. To conclude follow-up response for this study was excellent as recommendations from QoL studies states a minimum of 80% completion rate must be achieved [317].

7.5. DISCUSSION.

This study benefits from its prospective design, relatively large sample size with an accurate control over conceivable confounding. The study utilised validated and recommended HRQOL and frailty tools. Additionally, this study is the first to evaluate frailty impact on QoL and its interaction with HRQOL tools over a long-term period of 12 months for frail patients undergoing cardiac surgery. It is also unique in its use of GEE to discover longitudinal QoL data and frailty influence on baseline data, recovery and QoL improvement in cardiac surgery patients.

Furthermore, the impact of cardiac surgery on QoL improvement was investigated by comparing QoL scores at four different time points with age-matched mean population norms, which provide another estimation of surgical insult.

It's crucial to highlight, many risk factors, are not considered and quantified in a cardiac preoperative setting, variables such as age is mostly taken as proxy for frailty risk factor and consequently singled out for poor recovery and quality of life. This is further amplified by the current cardiac surgery gold standard risk scoring tool-EuroSCORE. The tool assumes the age variable as a predictor of risk as older age leads to a high EuroSCORE value. This study proves age alone is not a predictor of either worse outcome or impaired QoL even though we only found its negative association with MCS in the CABG cohort. This finding is in line with studies by Sedrakyan and Klomp who presented older age was not a limiting factor for improvement in QoL post cardiac surgery [208, 318].

Two quality of life studies [314, 315] investigated the inefficiencies of EuroSCORE, the study by Machler presented the over predictive aspect of mortality by EuroSCORE. Our findings for mortality were 3.8% compared to 11.2% predictions of EuroSCORE for our population, almost 3-fold higher than actual mortality. This high predictive value by EuroSCORE can be explained as the average age for our study population was 77.22 ± 10.55 years, hence older age increases risk in the EuroSCORE algorithm. The second study by chaturvedi and colleagues highlighted EuroSCORE inability to measure long term functional dexterity and fragility post-surgery. This can be explained as

EuroSCORE is validated for the first 30 days mortality and morbidity rather than long term survival and QoL improvement prediction.

Our study recommends frailty score variable and QoL parameters (PCS & MCS) be incorporated to current euroSCORE II. Our findings along with previous studies present the need to develop prediction models for recovery and expected improvement in QoL in order to educate patients the insult of cardiac surgery thereby maximizing their understanding of what they are consenting. Such prediction models will also help clinicians to optimise treatment options by identifying patients who will not benefit from surgery and improvement in their functional autonomy and quality of life is unlikely to be modified.

In our multivariable analysis EuroSCORE was not associated with MCS, PCS and EQ-5D index scores which are all HRQOL measuring tools. Furthermore, it had not registered any interaction with high frailty score, however, it was predictive of risk factors such as age, major aortic surgery and post-operative pace maker implantation. The predictive ability of EuroSCORE for pace maker implantation risks post cardiac surgery needs further investigation.

Impact of frailty on the improvement in quality of life

Frailty is an independent risk predictor for adverse outcome in cardiac surgical patients and has been documented for many years [111]. It is recognised that frailty and the onset of dependency in activity of daily living are strongly related [146]. Lee et al. demonstrated that frail patients were older, had an increased burden of disease and were more likely to undergo more complex operations than non-frail patients [111]. The weak or diminished reserve for mobilisation and ambulation was found to predispose these patients to lung related complications postoperatively necessitating prolonged hospital stay. It is inevitable then to assess frailty using validated tools in the pre-assessment setting in

order to better stratify frail patients, predict the impact of surgery to their QoL and to give honest opinion on patients functional regain expectations.

One of the aims of this study was to evaluate the effect of frailty on QoL and identify baseline predictors of high frailty. It is known frail patients value more improvement in their functional capacity, regaining leisure activity and achieving better QoL for longer term projection than just survival post-surgery. Frail and non-frail patients were thoroughly compared at four successive time points to highlight differences in QoL and recovery. The study findings present the predictive value of greater frailty presence and its negative influence on QoL was more pronounced at the preoperative stage. This continued to remain significant and mar QoL at 3 months after surgery however the impact of frailty on QoL at 6 and 12 months had been greatly reduced and were not statistically significant between the two groups. Whilst QoL improved for both groups, high frail patients benefited most. This suggests frailty can be modified and frail patients do benefit from cardiac surgery at a reasonable risk.

As discussed earlier this is the first study to investigate frailty and its association with QoL in both pre- and post-cardiac surgery, hence we could not find a study to compare our findings. However few studies do exist that investigated the QoL of octogenarians after valve or CABG surgery. A study by Sjogren [319] and colleagues reported whilst using SF-36, QoL and morbidity of octogenarians undergoing valve surgery was similar to age-matched Swedish population after a mean follow-up of 8.3 ± 1.9 years. This was seconded by Maillet and colleagues using the same QoL tool [312]. Similarly two long term studies with a mean follow-up period of 10 to 12 years evaluating the QoL of CABG patients reported long-term health benefit for the elderly, overall improvement in health, functional status and QoL dimensions compared to pre-operative values or age-matched population norms.

In this study both cardiac and non-cardiac factors associated with frailty influenced QoL. In multivariable model baseline predictors of frailty for impaired QoL included impaired physical functioning, role limitation due to physical problem, social functioning, pain and general health. Further analysis was conducted using technology (accelerometers) to objectively track intensity,

duration and frequency of an activity without relying on patient recall or patients self-reported health status which may be biased/unintentional perception of better QoL.

The association between baseline activity level and high frailty influence revealed strong interaction in three out of the four activity levels. Sedentary life style ($p=0.0001$), light ($p=0.016$) and moderate ($p=0.044$) activity variables were predictive of frailty effect in the multivariable model compared to non-frail patients.

Cardiac symptoms such as extent of coronary vessel disease, the indication for CABG or valve surgery were baseline predictors of greater frailty presence. Likewise comorbidities such as diabetes and current smoking profile were also baseline predictors of frailty impact. Postoperatively, high frail group were more prone to higher complication rates. In the multivariable model composite complication ($p=0.002$), renal problem ($p=0.032$) and longer length of hospital stay ($p=0.018$) were characteristics of frail patients compared to non-frail patients.

Health related quality of life tools outcome and comparison with population norms

EQ-5D index and VAS score for this study population were both lower than age-matched population norms at pre-op stage meaning the quality of life of the study population were less than average UK age matched norms. At 3 months, their QoL score remained lower than both at pre-op or age-matched population norms. None the less, at 6 and 12 months both scores (VAS & Index) improved, EQ-5D index was still lower than population norms. Interestingly VAS score at 6 and 12 months were comparable to or better than population norms.

For PCS and MCS score of RAND-36, our study population had a higher preoperative score than the mean age-matched population norms (UK). Quality of life generally improved post-surgery.

Population norms had association with HRQOL score at the different time point except at 12 months with EQ-5D index score.

A number of hypotheses explain the immediate low QoL score following surgery for the two groups. To begin with cardiac surgery is a major surgery that induces surgical stress and systemic inflammation that impacts micro-circulation; factors such as sternotomy, tissue injury, hypothermia, pain, anxiety, occlusion of blood vessels, blood plasma loss and interaction with foreign bypass circuit can all lead to localised ischemia and tissue hypoxia [320]. To overcome these adverse effects enhanced recovery after surgery (ERAS) for cardiac surgery needs to be implemented and optimised. It's worth mentioning ERAS studies in cardiac surgery are under researched and at its infancy stage as opposed to gastrointestinal and cancer surgery procedures. Fleming and colleague reported a widely-accepted ERAS protocol for cardiac surgery is achievable and may have favourable outcome for the elderly cohort and overall improve morbidity and mortality [321]

Secondly, studies in cancer have shown QoL drops following surgery due to surgical stress, patients going through uninterrupted process of adjustment over surgery, recalibration or shift in individual responses [322]. Adding, a greater benefit is associated with patient's positive perception about their surgery, in-hospital stay, discharge and rehabilitation. The degree to which the above psychological factors coupled with patients experience & satisfaction affects their QoL post immediate cardiac surgery has never been investigated to our knowledge.

Progression registered in QoL from six months onwards following surgery for this study population can be explained as patient's acknowledging freedom from the anxiety and thoughts of undergoing heart surgery and experiencing symptoms respite. An appreciation of life since they have survived from a major surgery will on the other hand positively aid their mental strength and play a vital role at an individual level prompting confidence to get on with social functions which will further build their motivation to do more activity as opposed to pre-surgery level. The validity of these study findings is supported by several QoL studies highlighting the effect of aortic stenosis, mitral regurgitation, vessel

disease and angina on QoL and the benefits associated with surgical intervention relieving this burden and ultimately aiding improvement in QoL and life expectancy [214, 223, 323].

Predictors of baseline health related quality of life.

A total of 29 variables were predictors of poor quality of life for the whole study population as described in detail in the result section. However our decent study sample enables us to conduct sub-analysis of the study population in order to quantify common or specific baseline diseases unique for a specific intervention i.e CABG or valve or concomitant procedures. Similarly we were able to quantify which of the HRQOL tool or component interacted most with diseases linked to certain procedures or an alternative HRQOL tools.

The RAND-36 quality of life tool PCS component interacted most with baseline characteristics for CABG patients than MCS component did. On the other hand, CABG cohort interacted better with quality of life tool EQ-5D index score compared to valve surgery cohort. From this it can be said when assessing the QoL of valve surgery patients a different QoL tool other than EQ-5D or with a combination to tools such as RAND-36 or SF-36 will yield greater interactions with baseline characteristics of valve patients. It is known to be very difficult to compare directly the QoL of valve to CABG patents post-surgery due to their disease pathophysiology and other underlying conditions. EQ-5D and RAND-36 MCS component tend to associate more and predict the same baseline variables responsible for impaired QoL. The ability of two different HRQOL tools to independently identify one or more predictor variables simultaneously is promising and will definitely act as a surrogate for quality benchmarking and for validation process.

Several cardiac and non-cardiac specific diseases were identified as significant predictors of impaired QoL namely; pre-surgery angina, NYHA class 3/4, diabetes, indication for mitral and tricuspid valve surgery, other cardiac surgery, bypass and cross-clamp time as well as female gender, higher frailty

score and age in the CABG group MCS & EQ-5D regression analysis were singled out either to independently or collectively as predictors by the different HRQOL tools.

Evidently this study is the first to use two validated HRQOL tool to independently prove the impact of tricuspid valve surgery on the QoL of patients. In both MCS, PCS and EQ-5D score; indication for tricuspid valve was a baseline predictor of impaired QoL and poor morbidity post cardiac surgery. This was expected as an indication for tricuspid valve surgery is secondary to already existing diseases such as left ventricular impairment or mitral valve surgery. Tricuspid valve patients are normally much worse as right ventricular dysfunction is induced by tricuspid regurgitation and vice versa is also true. Studies have shown that this regurgitation negatively impacts cardiac output and as a result tricuspid patients exhibit greater exercise intolerance and worse functional outcome post-surgery [324, 325]. Our findings further support these studies suggesting the event in the right side of the heart are crucial predictors of exercise capacity and QoL [326, 327].

GEE output and HRQOL interaction with time.

To our knowledge this is the first study to employ GEE on frailty and QoL association in cardiac surgery on longitudinal data modelling. After identifying baseline predictors of QoL using different HRQOL tools in univariable and multivariable analysis with some original and interesting outcomes; we were compelled to investigate further baseline characteristics, intraoperative and postoperative outcomes interaction with time.

A number of variables had a negative impact on HRQOL at different stages over the 12 month follow-up period. Among this were female gender, angina, diabetes, current smoker, pulmonary and coronary artery vessels disease and indication for valve surgery. In terms of postoperative complication; re-admission, renal problem, chest wound infection (SSI) and pace maker implantation influenced longitudinal HRQOL.

In our study female gender QoL dropped significantly at time point 2, 1 month post-surgery compared to male. Several studies concur with our findings, adding the insult of surgery negatively impacts female gender which will render them to experience diminished QoL at the immediate period following surgery, affirming female gender is a predictor of poor QoL at 3 months but not significantly different to male counterpart at a longer time follow-up [195, 328]

It is known the presence of angina is associated with diminished physical capabilities and low energy which are also dimensions of HRQOL measuring tools and indicators of worse or improvement in QoL. In this study angina symptoms were present at 79% of our population even though its interaction at time point 2 is original findings not anticipated; conversely from 3 months onwards patients reported relief in angina symptoms especially in the CABG group. Our finding is supported by Huber and Fruitman QoL studies [328, 329]. The later adding elderly patients are prone to lack of functional reserve and harbouring complex comorbidities not easily identified in the pre-assessment clinics.

The presence of diabetes negatively influenced QoL at time point 1 & 2 but was not significant at any other time point. This can be explained by the fact that patients with diabetes had also other cardiovascular diseases preoperatively as we are dealing with high frail patients planned to undergo cardiac surgery to relieve a number of CVD symptoms. This symptoms influence functional capacity and motivation for social functioning and mental health strength as described by de Visser and colleagues [330] reporting diabetes patients with cardiovascular diseases score on average 11 points lower on all the dimensions of RAND-36 QoL tool.

Four studies highlighted the macro-vascular impediments in diabetes predicted impaired QoL. The first study from De Grauw and colleagues [331] whilst using sickness impact profile (SIP) reported cardiovascular morbidity impacts functional health status of diabetes subjects. Studies by Klein and Naess [332, 333] emphasized the lower QoL of diabetes patients is triggered by the frequent manifestation of cardiovascular disease while Mitchell and colleagues [334] summarised vascular problems is responsible for the weak physical and psychological status of diabetes patients. Another

study by Davis and colleagues [335] reported the predictive value of psychosocial influence of diabetes subjects as a factor for mortality.

Diabetes interaction with time point 2 (1month) following surgery was expected, due to sternotomy and wound healing factors. It is known diabetes patients wound healing process takes time compared to non-diabetes patients and the risks of developing surgical site infection increases. It therefore requires a special wound care protocol or the involvement of tissue viability nurse on top of PHE and NICE guidelines.

Another variable identified to negatively impact QoL was habitual behaviour of smoking. Known current smokers in this study were identified to present weak physical health status and overall morbidity issues; one explanation is that habitual smoking deliberates the heart to beat faster even at rest and predisposes weak reserve for strenuous activity. Hence, this non-cardiac variable interaction at time points 1 and 2 was expected. Rumsfeld and colleagues [336] were the first to investigate association between active smoking pre-surgery with poor HRQOL particularly in the physical and mental component post cardiac surgery. Previous studies [337, 338] showed smoking is an independent predictor of QoL impairment in cardiac and non-cardiac subjects. Our study adds weight to those studies recommending modifiable non-cardiac predictors of poor QoL post-surgery such as smoking to be addressed prior to intervention. Our study has so far shown patient benefiting from surgery with regards to cardiac specific symptoms but non cardiac variables continue to influence QoL diluting the overall expected performance of surgery and recovery.

Evidently COPD and vessels diseases were equally predictors of lower QoL following surgery independently or with interaction with time point 2. Our findings are in line with a large Swedish study (n=2000) with a mean follow-up period of 10 years post CABG surgery reporting COPD and diabetes as the main predictors of poor QoL regardless of the HRQOL tool used [339].

Few variables were associated with improvement in QoL post cardiac surgery, substantiating the benefit of surgery to frail patients and its influence on functional regain and overall QoL improvement.

Outcome and survival

Frail patients had a higher prevalence of postoperative complications when compared to non-frail. Lee and colleagues were the first to demonstrate frail patients were older, had an increased burden of disease and were more likely to undergo more complex operations than non-frail patients. Similarly, Sundermann and team identified a slight increase in 30-day and in 1-year mortality with increasing degree of frailty ORs 1.1 (95% CI: 1.06 - 1.2) and 1.3 (95% CI: 1.2, 1.5) [149]. Mortality in this study 3.8% is comparable and fewer to previous studies with similar patient groups and mean age reporting mortality in the octogenarians to range between 4.0 – 16% [340-343]. Renal failure was a risk factor for death at 30th day whilst stroke was attributed for the death of one patient at 6 months. Two more patients died from sudden cardiac arrest at 12 months.

Frailty has been identified as a significant predictor of neurological outcome, all 3 incidence of stroke in this study was from the frail group and all underwent valve procedures. This was expected as aging brain vulnerability pre-disposes this cohort of patients to cerebral vascular diseases, higher rate in ischemic cerebral damage, hypotension and progressive aortic arteriosclerosis further complicates their fragility. A number of studies reported neurological related complications ranging between 2% to 14% post cardiac surgeries in the elderly [344-346].

New atrial fibrillation (AF) onset was noticed to be the most frequented complication affecting both frail and non-frail cohort post-surgery. Evidently the onset of new AF is a predictor of poor QoL predisposing patients into longer length of stay (LoS) and re-admission. Overall frail patients had a longer LoS than none-frail and AF could have been one of the reasons secondary to the prolonged ventilation identified. It's worth noting at 12 months following surgery, the onset of a new AF was only affecting frail patients. This finding is in line with a previous study reporting AF is a major cause for elongated hospitalisation [347].

Renal failure and the need for dialysis frequency increased among the frail patients immediately following surgery ($p=0.03$) and continued to impair their QoL even at 12 months follow-up. Renal failure risk post cardiac surgery has been known and well documented in the literature suggesting preoperative elevated creatinine levels impacts postoperative renal function [315]

The incidence of complete atrio-ventricular block post-surgery was rather higher in our study and 15 patients (14%) required pace maker implantations particularly in the frail group. The implantation of pace maker in a chronic left ventricular warrants negative hemodynamic effect precipitated by the left ventricular remodelling, with a subsequent overall result of weakness on left ventricular function, diminished exercise capacity and poor QoL that might lead to heart failure [348].

Finally our study agrees very well with previous studies on survival and morbidity even though they investigated elderly patients as opposed to high frail patients. We found renal insufficiency, stroke and cardiac arrest post-surgery as independent predictors in early and late adverse outcomes whilst composite complications, SSI, frailty score ≥ 11 and the onset of new AF variables were independent predictors of impaired QoL and functional regain.

Limitation

We didn't evaluate the history of psychiatric disease in our study population which other QoL studies have shown to be an independent predictor of inferior mental health status following cardiac surgery [336]. Even though variables quantifying depression were in our HRQOL tools, we did not develop a test for psychiatric or depression treatment effects in the pre-assessment clinic.

7.6. CONCLUSION.

The quality of life of the vast majority of frail patients improved post cardiac surgery. None the less, few may appear to experience poor projection in QoL and may regret going under the knife. As the number of frail population increases with ever expanding life expectancy, it is inevitable to develop prediction models for recovery and expected improvement in QoL and in order to educate patients the insult of cardiac surgery thereby maximizing their understanding of what they are consenting to. Such prediction models will also help clinician to optimise treatment options by identifying patients who will not benefit from surgery and improvement in their functional autonomy and quality of life is unlikely to be modified.

Main Points & Recommendation.

- The study proved baseline HRQOL has a direct relationship to post-op HRQOL and survival. Our findings supersede existing risk stratification predictions and expand it beyond mortality and morbidity.
- The study contributes original findings and it's the first to utilise GEE modelling to predict outcome and evolution of HRQOL via different time point interactions.
- Our study adds weight to the clinical utility of evaluating baseline HRQOL preoperatively in order to better risk stratify patients and better inform patients realistic improvements in their functional status and recovery.
- Development of a focused treatment plan for depression before cardiac surgery and its likelihood of improving mortality, morbidity and overall QoL needs to be investigated in a multi-centre randomised trial.
- The association between baseline activity level and the influence of frailty revealed strong interaction in three out of the four activity levels evaluated.

10.0 Chapters 10

10.1 DISCUSSION AND FUTURE DIRECTION

The quest to identify a clinically meaningful risk scoring instrument that predicts and assess patient level of frailty and QoL is a matter of continuing debate. Quantifying the requirements of frail individual to withstand the insult of major surgery is dependent upon a comprehensive understanding of their baseline physical capacity, social and psychological aptitude.

Frailty is defined as “a biologic syndrome of reduced reserve and resistance to stressors, resulting from cumulative declines across several physiologic systems, causing eventually increased potential for adverse outcomes” [80]. Given the ageing population, the proportion of frail patients undergoing cardiac surgery is increasing at a significant rate. These patients are difficult and costly to manage at present available strategies in the perioperative stages, and present numerous challenges for all members of the MDT. Highlighting frail patients at the heart team MDT is critical, to help members decide whether intervention (in patients with often limited life expectancy) is in their best interest. The findings of our own national survey on heart team proved the lack of risk stratification data; frailty factor and its influence were rarely discussed in the meeting.

It is crucial to ascertain whether in an individual, their frailty can be made better or worse. Early screening and frailty detection is likely to result in favourable outcomes. Where patient outcome post-surgery is poor, failure to thrive may lead to a non-reversible stage and death [113]. Frailty is a long-term condition just like diabetes mellitus or renal disease and it should not be viewed as an inevitable consequence of ageing.

Additionally our systematic review on the topic presented frailty assessments are performed extremely poorly with inappropriate tools. The current gold standard method of assessing frailty is the Reported Edmonton Frailty Score (REFS, where a score over 7 indicates frailty). Unfortunately, such questionnaires are unpopular in cardiac pre-assessment clinics, and have poor re-test completion rate in

the elderly. Easily measured, cheap and more objective measures of frailty are required to support MDT decisions on top of REFS.

Physical activity is an objective assessment of an individual's physiological reserve. It is used extensively in thoracic surgery to aid risk stratification prior to lung resection. We hypothesise that physical activity is also an objective measure of frailty, and presented it can be used to predict outcomes in this group after surgery.

In this study, one of our primary aim was to assess advanced measures of physical activity (with wrist worn devices-Triaxial accelerometer) at multiple time points, in a large cohort of frail patients undergoing cardiac surgery, with view to developing a risk stratification system. Our study concluded the combined use of (REFS and Tri-axial accelerometer) tools to measure frailty proved to strongly and independently associate with combined outcome of unevaluated and unplanned hospitalisation and death. Furthermore the distinct differences in complication rates between high frail versus low frail patients signified excellent prognostic utility of the frailty tools used which hold a potential promise as a user friendly tools to identify high risk patients.

The study has also shown low frail patients are less likely to have two or more complication with less relative risk when compared to high frail patients. In addition, high frail patients were twice more likely to have longer in-hospital stay than non-frail (Mean 21.2 vs. 9.6 days) respectively with significance ($p=0.016$) value.

To our knowledge we are the only research team with accurate data to proof and support the impact of cardiac surgery on frail patients whilst making use of technology, furthermore highlighting the unmet need for resource utilisation.

This study has shown the most accurate method of evaluating QoL is to use a combination of already existing, validated and reliable HRQOL tools. These instruments can easily be reproduced. None the less and going forward, any QoL study must be prospective in design with a distinct follow-up period.

Furthermore it's crucial that the same HRQOL tools are used at baseline and at all the follow-up stages up-to and including the final follow-up date. Another important dynamic that needs consideration is researcher's capacity to minimise data loss and discrepancies, repeated phone call interviews should be utilised at each stage of the trial. Our study meaningful and reliable findings presented the advantage of accounting frail patient's baseline data, when compared to post-operative data at each of the follow-up stages and, as well as, age-matched population norms. Future trials should aim to conduct pre-operative baseline evaluation and risk stratification before embarking interpretation of post-operative QoL and outcome.

10.2 GOING FORWARD

Experience and knowledge from this study gratify the need to conduct similar study utilising the solid findings of this thesis and incorporating the concept of enhanced recovery after cardiac surgery and pre-habilitation interventional trial. A quick search for a feasibility study on cardiac pre-habilitation studies found only two registered trials in www.clinicaltrials.gov on the topic. Discoveries from this thesis enable me to propose randomised trial on the clinical utility of pre-habilitation in frail patients undergoing cardiac surgery and influence of concept of enhanced recovery after surgery.

Pre-habilitation Interventional Randomised Trial before Cardiac Surgery.

Hypothesis: Frailty factor can be modified and frail patients who undergo 5 weeks of pre-operative exercise training will improve their functional capacity pre-operatively and achieve greater morbidity and functional regain post cardiac surgery.

Null Hypothesis: Frailty factor cannot be modified and frail patients who undergo 5 weeks of pre-operative exercise training will have the same functional and morbidity outcome as patients with standard care post cardiac surgery.

PROJECT OBJECTIVES

1. Recruitment of 250 consecutive patients undergoing elective cardiac surgery at each of the four participating Hospitals, of which at least 500 are frail (as defined by the REFS).
2. Wrist-worn activity data to be collected for 30 day periods at each of the following time point pre-operatively and at 6 weeks, six months and 12 months post-operatively.
3. Frailty (EFS) and Quality of Life assessment (SF-36 & RAND-36) at the same time-periods as above and at time point 1, 2, 3, 4 and 5 years.
4. Functional status preoperatively and at 6 weeks, six months and 12 months using krofts performance test.
5. Depression and psychiatric test at the preoperative stage and 6 weeks post-surgery. HADS and psychiatric tools can be utilised.
6. Plasma Biomarker (blood, stool and urine) to be collected pre-operatively, day of surgery and 7th day following surgery in order to perform metabonomic analysis.

7. Assessment of relationship between patient activity, frailty, QoL and clinical outcomes to be monitored and with follow-up period of 5 years.

10.2.1 METHODS

Design: Prospective longitudinal cohort study

Patient recruitment: 1000 consecutive patients undergoing elective cardiac surgery and age ≥ 75 years will be recruited from the pre-assessment clinic at four cardiac centres. Detailed clinical and peri-operative outcome data will be collected.

Exclusion: non-elective surgery.

Wrist-worn device: A light weight, waterproof tri-axial accelerometer (GeneActive) with a seismic acceleration sensor will be worn by patients for 30 days (continuously) pre-operatively, 6 weeks, six months and 12 months. This data will be downloaded and the following variables will be extracted using an open source algorithm: 1) proportion of sedentary, light, moderate and vigorous activity, 2) sleep duration, 3) sleep efficiency, 4) assessment of posture.

Frailty and QoL questionnaires: EFS, SF-36 and functional status will be collected at the same time points as the wrist-worn device and at time point 1, 2, 3, 4 and 5 years post-surgery.

Biomarker: Specific plasma biomarker (blood, stool and urine) to be collected pre-operatively, day of surgery and 7th day following surgery in order to perform metabonomic analysis.

Pre-habilitation Cohort: Daily exercise duration and intensity prescribed according to individual level depending on their frailty score, cardiac symptoms and comorbidities by physiotherapist and clinicians. Patients are encouraged to populate their diary daily as home based rehabilitation exercise.

They are also required to attend 3 physiotherapy lead supervised strength training session per week for a period of 5 weeks pre-operatively.

Optimising patient before surgery: The concept of enhanced recovery for cardiac surgery patients (ERAS) is fully implemented and adherence to each of its domains recorded for every patient including nutritional optimisation and haemoglobin level. Psychological and social factors are also addressed appropriately and recorded promptly.

Data: Demographic, cardiac and non-cardiac variables are collected preoperatively. Similarly intraoperative and postoperative data are all collected and populated into specialised proforma.

INTENDED IMPACT

Transnationally, it is hoped to prove that collection of advanced and objective physical activity data is more effective than current methods of risk stratification in frail cardiac surgery patients (EFS, EuroSCORE, and visual assessment by clinicians). This would justify a larger multi-centre study and potentially increase the quality of frailty assessments performed nationally. This could save significant amounts of money by assisting the Heart Team in deciding which patients are likely to benefit from cardiac surgery.

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APPENDICES:

Appendix 1:

CONSENT FORM (FOR PARTICIPANTS ABLE TO GIVE CONSENT)
Using Quality of Life and Frailty as Predictors of Recovery in Cardiac Surgery Patients.
(Version 2)

Principle Investigator: Prof Thanos Athanasiou

CI: Yusuf Abdullahi, PhD Student

Please
initial

I confirm that I have read and understand the information sheet dated 27.05.14 Version 2 for the above study. I have had the opportunity to ask any questions which have been answered fully.

☐

I understand that my participation is voluntary, and I am free to withdraw at any time without my medical care or legal rights being affected.

☐

I understand that relevant sections of my notes and data collected during the study may be looked at by individuals from Imperial College London, Imperial College NHS Healthcare Trust or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records

☐

I agree that the research team can access my medical notes to obtain information about my health and clinical care for the purposes of this study. I understand that this information will not be identifiable once obtained and linked to the questionnaires.

☐

I agree to undertake a health and wellbeing questionnaire. If any issues are raised, I agree to allow my researcher to discuss this with my doctor.

☐

I have been shown and agree to wear a sensor to record my levels of physical activity before and after my surgery.

☐

I agree to undergo up to four further short questionnaires over the next 12 months after my operation so researchers can understand how I am recovering.

☐

I agree to take part in this study

☐

Patient Name _____ **Signature** _____

Name of Person Taking Consent ____Yusuf Abdullahi_____
Date _____

1 copy for patient, 1 copy for Chief Investigator, 1 copy for hospital notes

Appendix 2:

Domain	Item	Score 0	Score 1	Score 2
Cognition	Please imagine that this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions then place the hands to indicate a time of 'ten after eleven'	No errors	Minor spacing errors	Other errors
General health	In the past year, how many times have you been admitted to a hospital?	0	1-2	2 or more
	In general, how would you describe your health?	Excellent/ very good/ good	Fair	Poor
Functional independence	With how many of the following activities do you require help? (meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications)	0 -1	2 - 4	5-8
Social Support	When you need help, can you count on someone who is willing and able to meet your needs?	Always	Sometimes	Never
Medication	Do you use five or more different prescription medications on a regular basis	No	Yes	
	At times, do you forget to take your prescription medications?	No	Yes	
Nutrition	Have you recently lost weight such that your clothing has become looser?	No	Yes	
Mood	Do you often feel sad or depressed?	No	Yes	
Continence	Do you have a problem with losing control of urine when you don't want to?	No	Yes	
Self-reported Performance	Two weeks ago were you able to:			
	(1) Do heavy work around the house like washing windows, walls or floors without help?	Yes	No	
	(2) Walk up and down stairs to the second floor without help?	Yes	No	
	(3) Walk 1 km without help?	Yes	No	

Scoring for the REFS (/18)

Not Frail: 0 - 5 Apparently Vulnerable: 6 - 7 Mild Frail: 8 – 9 Moderate Frail: 10 -11 Severe Frail: 12 - 1

Appendix 3:



By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

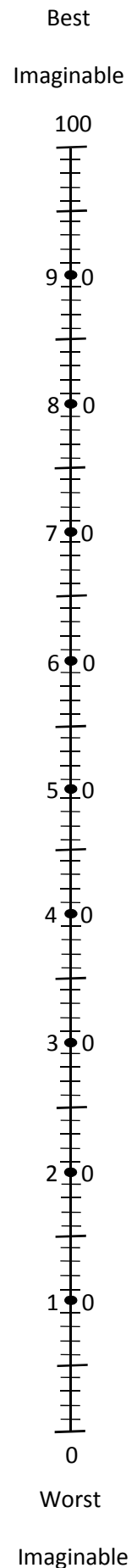
Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state**



RAND Medical

RAND 36-Item Health Survey 1.0 Questionnaire Items

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5
2. Compared to one year ago, How would you rate your health in general now ?	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

(Circle One Number on Each Line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
3. Vigorous activities , such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
4. Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]

5. Lifting or carrying groceries	[1]	[2]	[3]
6. Climbing several flights of stairs	[1]	[2]	[3]
7. Climbing one flight of stairs	[1]	[2]	[3]
8. Bending, kneeling, or stooping	[1]	[2]	[3]
9. Walking more than a mile	[1]	[2]	[3]
10. Walking several blocks	[1]	[2]	[3]
11. Walking one block	[1]	[2]	[3]
12. Bathing or dressing yourself	[1]	[2]	[3]

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle One Number on Each Line)

	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. Accomplished less than you would like	1	2
15. Were limited in the kind of work or other activities	1	2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

(Circle One Number on Each Line)

	Yes	No
17. Cut down the amount of time you spent on work or other activities	1	2
18. Accomplished less than you would like	1	2
19. Didn't do work or other activities as carefully as usual	1	2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(Circle One Number)

Not at all 1	Slightly 2	Moderately 3	Quite a bit 4	Extremely 5
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21. How much **bodily** pain have you had during the **past 4 weeks**?

(Circle One Number)

None 1	Very mild 2	Mild 3	Moderate 4	Severe 5	Very severe 6
--------	-------------	--------	------------	----------	---------------

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

(Circle One Number)

Not at all 1	A little bit 2	Moderately 3	Quite a bit 4	Extremely 5
--------------	----------------	--------------	---------------	-------------

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks** . . .

(Circle One Number on Each Line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6

27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

(Circle One Number)

All of the time 1	Most of the time 2	some of the time 3
A little of the time 4	None of the time 5	

How TRUE or FALSE is each of the following statements for you.

(Circle One Number on Each Line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

Appendix 4.

Cardiac Specific Self-Rated Quality of Life Post-Surgery Outcome

A. Quality of Life and Health Status

Has your health improved since the operation?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ About the same

Do you feel dyspnea?

- ☐ Never
- ☐ After some important and unusual efforts
- ☐ For daily efforts
- ☐ Every time

Do you feel some chest pain?

- ☐ Yes
- ☐ No
- ☐ Don't know

Do you have some gait problem?

- ☐ Yes
- ☐ No
- ☐ Don't know

Do you need more help now than prior the operation concerning self-care

e.g Bathing, dressing, toileting, transferring and eating

- ☐ Yes
- ☐ No
- ☐ Don't know

Do you walk outside?

- ☐ Alone
- ☐ With somebody
- ☐ No

Do you live in your own home? in this case, someone helps you for your housework

- ☐ No
- ☐ Yes more than prior the operation
- ☐ Yes as usual

Have you been hospitalized since the operation?

- ☐ Yes
- ☐ No

Have you lost the interest or the pleasure to perform something's?

- ☐ Yes
- ☐ No
- ☐ Don't know

What do you think about your quality of life, now?

- ☐ Excellent
- ☐ Very good
- ☐ Good
- ☐ Very poor

In the same circumstances will you repeat the operation today?

- ☐ Yes
- ☐ No
- ☐ Don't Know

Please indicate below the follow-up stage: @

- ☐ 3 Month
- ☐ 6 Month
- ☐ 12 Month

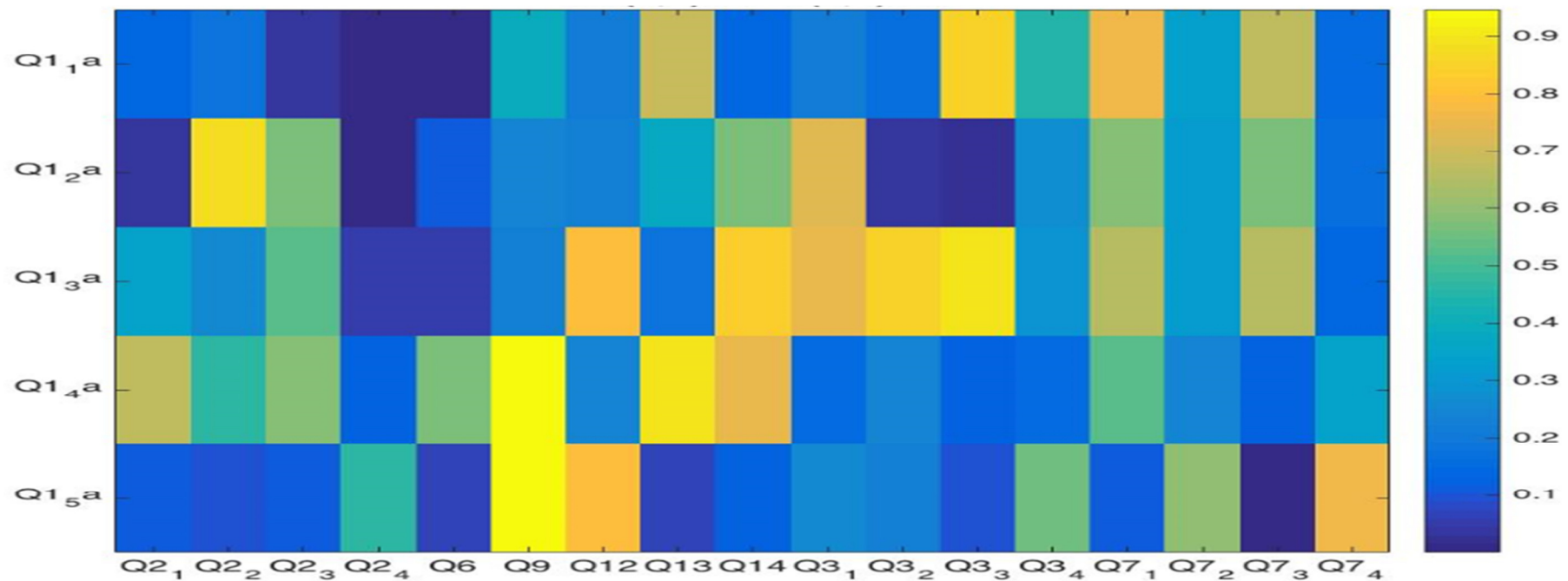
Please ask the patient and list all complications up to this stage

e.g Re-operation, Stroke, Surgical site infection, Renal failure etc...

Patient Study ID

Appendix 5

Aim 3:Q1 Attendance vs. leadership, team work, professional development & training, meeting venue, agenda, case prioritisation, patient centered care and treatment plan.																	
	Q2 1	Q2 2	Q2 3	Q2 4	Q6	Q9	Q12	Q13	Q14	Q3 1	Q3 2	Q3 3	Q3 4	Q7 1	Q7 2	Q7 3	Q7 4
Q1 1a	0.14224	0.17828	0.035169	0.012775	0.0001927	0.38754	0.22108	0.6825	0.13568	0.2157	0.1682	0.84913	0.4514	0.75643	0.33885	0.67437	0.15784
Q1 2a	0.040903	0.87997	0.57338	0.001998	0.10985	0.24474	0.22886	0.37386	0.56296	0.72705	0.0429	0.0227	0.27576	0.59118	0.31672	0.56864	0.17
Q1 3a	0.35384	0.2615	0.52873	0.057289	0.054787	0.22855	0.79565	0.19018	0.83337	0.74714	0.8447	0.88985	0.29343	0.65561	0.31672	0.6571	0.14664
Q1 4a	0.67066	0.47279	0.58767	0.12728	0.57368	0.94607	0.24325	0.89814	0.7463	0.1584	0.2434	0.11851	0.15195	0.52188	0.2463	0.11971	0.35345
Q1 5a	0.11684	0.09829	0.11498	0.46991	0.072432	0.94607	0.78748	0.064618	0.12368	0.25971	0.2237	0.09829	0.54709	0.1142	0.59491	0.014178	0.76237



Presents Kaplan Meyer morbidity risk evaluation between the two groups (High frail vs. Low frail).

