

An international patient centred study of Retroperitoneal Fibrosis

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Abstract:

Background:

The impact that rare chronic disorders such as Retroperitoneal Fibrosis (RPF) can have on the physical and psychological aspects of a patient's health is poorly understood. Patient related outcome measures and experiences provide a unique opportunity to understand the impact rare chronic disorders have on a patient's life as well as allowing healthcare providers to compare and improve performance.

Aim:

To understand the physical and psychosocial impact that RPF has upon peoples' lives

Design:

An international online questionnaire was therefore created to gain insights into how patients with RPF, a rare fibro-inflammatory condition, viewed their health and experiences.

Methods:

An international online questionnaire comprising 62 questions/free text options, was designed in collaboration with two patient advocates and the multi-disciplinary Renal Association Rare Disease Registry (RaDaR) RPF Group the questionnaire was anonymous and freely accessible on a GOOGLE Form online platform for 6 months.

Results:

229 patients from 30 countries across 5 continents responded. Four key issues were identified; (1) pain; (2) therapy related side effects; (3) lack of informed doctors / information about their condition and its management; (4) psychological burden. Variations in diagnosis and management are highlighted with 55% undergoing a biopsy to reach a diagnosis of RPF; 75% of patients underwent a further interventional procedure with 60% concurrently treated medically.

Conclusion:

This study will guide further development of clinical and academic multi-disciplinary activity and shows the importance of trying to understand the impact of rare chronic disorders on the physical and psychological aspects of a patient's health.

Introduction

Patient centred care aims to meet the health needs and expectations of the patient whilst valuing their engagement in the design of clinical research and service development. **1** This approach has been shown to improve patient satisfaction and self-management, particularly for chronic conditions.**2,3** Patient reported outcome measures (PROMs) can help to identify how patients feel with regards to their health status, whilst patient reported experience measures (PREMs) allow for an understanding of a patient's experiences whilst receiving health care. **4** PROMs and PREMs provide information that can help to define what is important to the patient (which does not necessarily reflect the views of their care givers) and inform clinical service development **5**. Whilst the concepts of patient centred care, PROMs and PREMs are well established in managing common diseases **6,7** their use in rare conditions is less well described.

Retroperitoneal fibrosis (RPF) is a rare (approx. 1.4 per 100,000 prevalence) **8** chronic fibro-inflammatory condition which frequently develops around the abdominal aorta and encapsulates retroperitoneal structures, including the ureters sometimes resulting in obstructive nephropathy. **9** The majority of cases associate with traditional cardiovascular disease risk factors (eg. smoking and hypertension), or an underlying inflammatory disorder such as Immunoglobulin-4 Related Disease (IgG4RD). **10** Despite these well described associations, the underlying cause and pathogenesis of RPF remains uncertain. RPF is a long-term condition with a relapsing nature causing patients to experience a variety of chronic symptoms associated with acute flares including flank pain, constipation, constitutional symptoms such as night sweats, nausea and reduced appetite. The impact that RPF has upon patients' lives is not clear and because of its rarity, gaining patient perspectives to guide clinical practice in RPF is challenging. **11**

The aim of this study was to gather perspectives from a large cohort of people internationally suffering with RPF to understand the impact of this condition upon their lives and to guide clinicians' approaches to better management.

Methods

An online questionnaire was designed in collaboration with two patient advocates and a multi-disciplinary Renal Associated Rare Disease Registry (RaDaR) RPF Group (<https://rarerenal.org/rare-disease-groups/retroperitoneal-fibrosis-rdg/>). It comprised 82 questions across 8 sections including: demographics, symptoms, medical risk factors, medical sequelae, medical and surgical treatments, psychosocial impact and perceptions of care received (see Supplementary Material). The questionnaire was anonymous and freely accessible on a GOOGLE form online platform for 6 months between September 2016 March 2017. The questionnaire was written only in English and advertised through the RaDaR website (<https://rarerenal.org/rare-disease-groups/retroperitoneal-fibrosis-rdg/>) in addition to a large social media RPF online support group moderated and owned by patients and their advocates.

(https://groups.yahoo.com/neo/groups/retroperitoneal_fibrosisworldsupport/info?guccounter=1).

Formal research ethics approval was not required for this study since it was a service evaluation study. Ethical guidance and confirmation of this status was gained from the

Imperial College London Research Governance and Integrity Team (evidence supplied to journal). A Patient Information Sheet was provided as an introduction to the questionnaire (see Supplementary Material). No written consent was sought, the questionnaire was voluntary, and no patient identifiable data were gathered or stored.

Results:

Demographics:

A total of 229 patients from 30 countries across 5 continents responded. Mean age at diagnosis was 51 years (range 17-76) with a female to male ratio of 3:2 and 83% of patients identifying as of white ethnicity. 52% respondents came from North America, 25% British Isles, 9% Mainland Europe, 5% Australasia, 4% Asia and 2% from South America. 78% of participants identified as a current or previous smoker. Table 1.

Symptoms:

Prior to starting treatment for RPF, the most commonly reported physical symptoms included pain (95%), fatigue (66%), nausea/vomiting (34%) and weight loss (27%). Figure 1 Pain was most commonly reported in the abdomen (69%), lower back (60%), or flanks (55%). Furthermore, pain ranked as the worst aspect of RPF overall (in 57% of respondents). Other symptoms experienced prior to treatment for RPF included lower limb oedema (25%), loss of libido (22%) and significant joint pains (21%). A high proportion (47%) of respondents reported experiencing symptoms for more than 6 months and needing to see multiple specialties prior to receiving a diagnosis of RPF with 92% of respondents needing to see 2 or more specialists.

Associated medical conditions:

Medical problems reported prior to diagnosis included traditional cardiovascular disease risk factors hypertension (33%) and hypercholesterolaemia (23%) with a smaller number of respondents reporting preceding cardiovascular events including myocardial infarction (6%) and cerebrovascular accidents (1%). Prior malignancy was reported in very few cases (6%).

Intervention:

Approximately half of (55%) all respondents underwent a biopsy to reach a diagnosis of RPF. 75% of patients underwent an interventional procedure to treat problems related to RPF with ureteric stents being the most common in 139 respondents (61%), of which 45% required regular stent changes. Less frequently patients underwent a ureterolysis operation (34%) or required a nephrostomy (20%). Figure 2a. 49% of respondents who had surgical intervention, had more than one procedure. 60% received both surgical and medical treatments.

Treatment:

74% of respondents reported having been initiated on corticosteroids following diagnosis, 54% of which subsequently also received at least 1 steroid sparing agent. A variety of immunosuppressive medications were used as alternatives or steroid-sparing agents; mycophenolate (21%), tamoxifen (20%), azathioprine (11%), methotrexate (10%) and rituximab (4%). Figure 2b. A large burden of corticosteroid associated side effects was

reported with weight gain (70%), disturbed sleep (52%) and fragile skin/easy bruising (38%) being most common. Figure 3. Incomplete medication adherence was reported by 26% of respondents with the most commonly cited reason being unintentional forgetfulness (68%).

Following diagnosis and initiation of treatment, 41% of patients reported uncontrolled pain despite being on at least 2 analgesic agents. Other significant medical problems encountered by patients following diagnosis included reduced kidney function (50%) and recurrent hospital admissions (39%) mostly related to uncontrolled pain and infection, with one in four patients reporting recurrent urinary tract infections. No respondents reported requiring renal replacement therapy.

Psychological burden and perceptions of care

A number of psychological symptoms were reported to occur following a diagnosis of RPF including low mood (52%), abnormal sleep pattern (50%) and the need to reduce or stop work (49%)/social activities (47%). Figure 4 The reported “worst aspects of RPF and its management amongst all respondents” were pain (57%), medication related side effects (31%) and lack of informed doctors (24%) alongside a wider lack of information (22%). Figure 5.a. The top 3 worse aspects of RPF were mutual amongst respondents who underwent a surgical intervention to treat their RPF and all respondents as a whole. Figure 5.b. For all respondents a lack of informed doctors posed a significant problem to respondents with 53% having difficulties in finding a doctor whom they felt understood RPF. 48% of all respondents felt their medical team had not provided them with enough information regarding their condition with material available via the internet ranked more informative than that provided by health care professionals. A similar proportion of patients (49%) felt that there was no coordination of their care (92% of respondents saw more than 2 specialty teams). All respondents rated their satisfaction with the medical care received to be five out of ten or lower.

Discussion:

This is a large, international patient-centred study of patients with RPF and provides valuable insights into their experience of the condition and its management. Four key issues relevant to the care and well-being of people with RPF were identified; (1) pain; (2) therapy related side effects; (3) lack of informed doctors / information about their condition and its management; (4) psychological burden. This was true for all respondents regardless of if they underwent a surgical intervention or not.

Almost 60% of all respondents reported pain amongst the worst aspects of RPF, with over 40% reporting their pain was not well controlled despite analgesia. 80% of respondents experiencing continual pain had undergone a surgical intervention with ureteric stent (66%), ureterolysis (35%) and nephrostomy (26%) being the most common surgical procedures performed. Patients diagnosed with RPF frequently undergo a surgical intervention often aimed at preserving kidney function but they are not without risk of long term sequelae including bladder irritation, infections, complications from complex procedures, reduced quality of life and an increased stress burden.

Given that many respondents received parallel medical and a number of surgical treatments (eg. combinations and sequences of nephrostomy, ureteric stent and then ureterolysis), it

was not possible to define whether the reported pain was disease or treatment-related. Interestingly however, when comparing all respondents versus respondents receiving surgical treatments, pain was the foremost worst aspect of RPF in both groups, although in a higher proportion in all respondents (57%) than in the surgically treated (51%). Whilst surgery and ureteric stent-related pain is clearly a problem for many patients with RPF, these data indicate that it is not necessarily the overriding cause of pain in these respondents. Additionally, patients receiving surgical treatments more frequently reported anxiety/depression, lack of treatment options and a lack of coordinated care as significant issues. Figure 5.b. This further illustrates the need to improve the co-ordination of care in rare, chronic disorders such as RPF, with better information sharing, shared decision making and psychological support.

The profound psychological and socioeconomic impact that chronic pain and long-term conditions can have is well recognized across large cohorts **12** and respondents in this study consistently reported reduced psychological and social well-being including fatigue, anxiety and depression, reduced hobbies/activities and financial difficulties. A better understanding of the mechanisms of pain experienced in RPF, in addition to a specialist approach to pain management, is likely to improve patient experience and reported outcomes in RPF.

The mainstay of medical therapy for RPF continues to be corticosteroids, with other agents used to lesser extents. **13** Corticosteroids can improve symptoms, reduce RPF mass volume and have been shown to be superior to tamoxifen in preventing relapse. **14** However, many of the well-recognized side effects of corticosteroids were prevalent within the respondent cohort, reiterating the need to find alternative therapies. Figure 3. The wide variety of steroid sparing agents used to treat RPF in this and other studies **15** illustrates the challenges of gaining reliable information for managing rare conditions and the need for more multi-centre drug trials. Rituximab, a monoclonal antibody to CD20, depletes circulating B cells and shows efficacy in treating IgG4-RD with or without RPF **10**, but also shows promise treating idiopathic RPF cases where IgG4-RD is not identified as an underlying pathology. **16**

Difficulties in reaching a diagnosis were highlighted by the duration respondents waited between experiencing their first symptoms of RPF, and receiving a diagnosis, with 47% waiting more than six months. This is further highlighted by the high number of different specialties needed to be seen in relation to RPF, with 92% of respondents needing to see 2 or more specialists prior to receiving a diagnosis, and 47% of respondents seeking a second opinion. This overall dissatisfaction is of course multi-faceted deriving from non-specific symptoms making immediate diagnosis unlikely. Some clinicians have little or no experience in managing a rare condition such as RPF, and potentially contrasting information is gained from different medical or surgical specialties – each with their own perspectives. It is of little surprise that the majority of respondents placed more value in the information gained from online forums than their healthcare professionals. Difficulties in gaining clear information can diminish trust and confidence that patients have in their clinicians, particularly in the context of rare conditions. **17**. Collaborative and coordinated working between specialties and centers, tertiary referral pathways and emphasis upon patient centered care are all likely to have a positive impact upon the care experienced by people suffering from rare conditions such as RPF.

This study has certain limitations. The questionnaire was completed on a voluntary and anonymous basis, collecting subjective accounts and qualitative data. An inherent reporter bias was likely illustrated by the majority (59%) of female responders despite consistent reports that males appear to be more pre-disposed to RPF (male: female ratio approximately 3:1). **18** Furthermore, the majority of questionnaire responders were Caucasian whereas previous reports do not indicate any ethnic predisposition to RPF. Given our study was an online questionnaire written only in English, we were unable to include patients without access to the Internet or non-English speakers - potentially excluding a significant number of patients. Reported experiences will differ according to gender and socioeconomic / cultural backgrounds and hence the results here may not necessarily represent the breadth of perspectives across all demographics.

The management of rare diseases is challenged when it comes to gaining patient perspectives on a larger scale. **19** Despite their limitations, online international patient centred studies provide the means to better understand the impact of rare medical disorders on the lives of affected individuals. This study highlights the key issues faced by the patient suffering with RPF, which do not necessarily reflect those of the care providers. The traditional paternalistic patient – doctor relationship has been challenged in recent years, with much more emphasis being placed upon patient centred care and shared decision making **20,21** In addition to reports of improvements in patient satisfaction and adherence, patient centred approaches can guide health policy. **22** This work serves as an example of how patient perspectives can be collected and used to help inform health care teams how to improve the design of their services and approaches to managing rare, chronic conditions such as RPF.

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Renal Associated Rare Disease Registry (RaDaR) RPF Group

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Table 1: Patient demographics.

Mean age at diagnosis (years)	51 (range 17-76)	Occupation	
Female (%)	59	Managers	21 (9%)
Smoker/ previous smoker (%)	78	Professionals	21 (9%)
Ethnicity		Technicians/ associate professionals	57 (25%)
White	190 (83%)	Clerical support workers	20 (9%)
Black African/ African American	8 (4%)	Service and Sales Workers	19 (8%)
Hispanic or Latino	8 (4%)	Skill agricultural, forestry and fishery workers	1 (0.4%)
Asian/ Pacific Islander	11 (5%)	Craft and related trade workers	14 (6.1%)
Other	11 (5%)	Plant and machine operators and assemblers	1 (0.5%)
Country of origin		Elementary occupations	3 (1%)
North America	118 (52%)	Armed forces	0
British Isles	57 (25%)	Unemployed/ retired (undefined)	63 (28%)
Mainland Europe	21 (9%)	Medical retirement	0
Australasia	12 (5%)	Housewife	0
Asian/ Pacific Islander	9 (4%)	Unknown.	9 (4%)
South America	4 (2%)		

Figure 1. Most commonly reported physical symptoms in RPF.

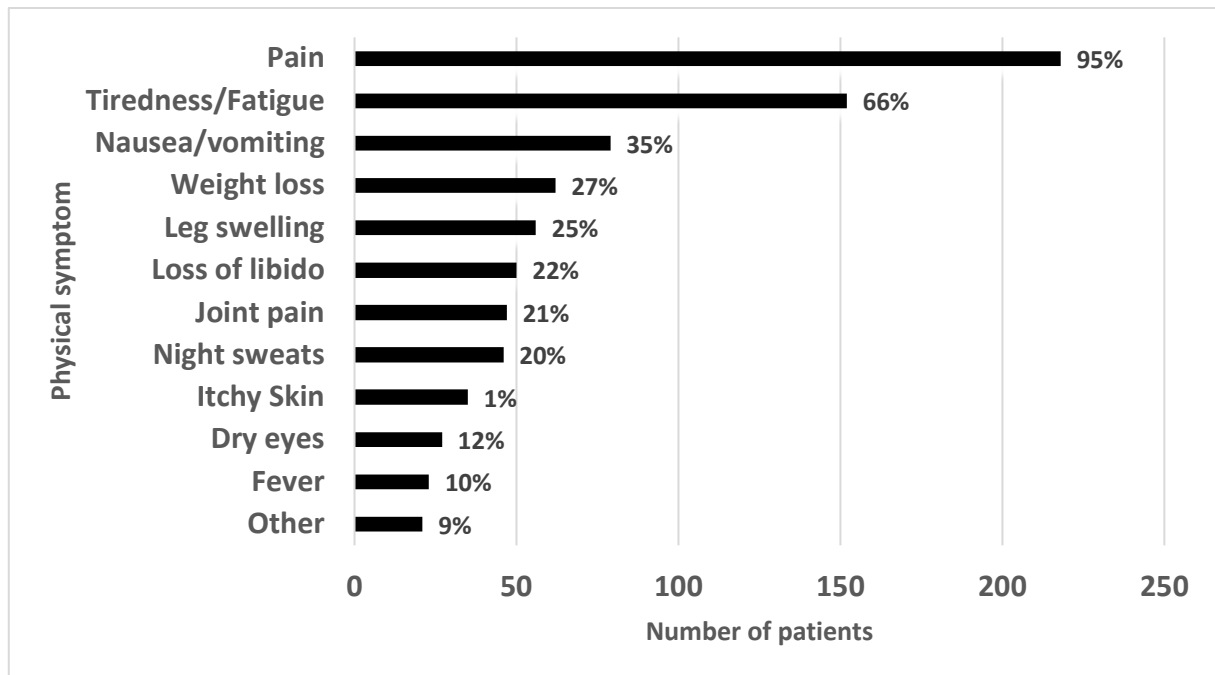


Figure 2.a Surgical treatments received by patients diagnosed with RPF.

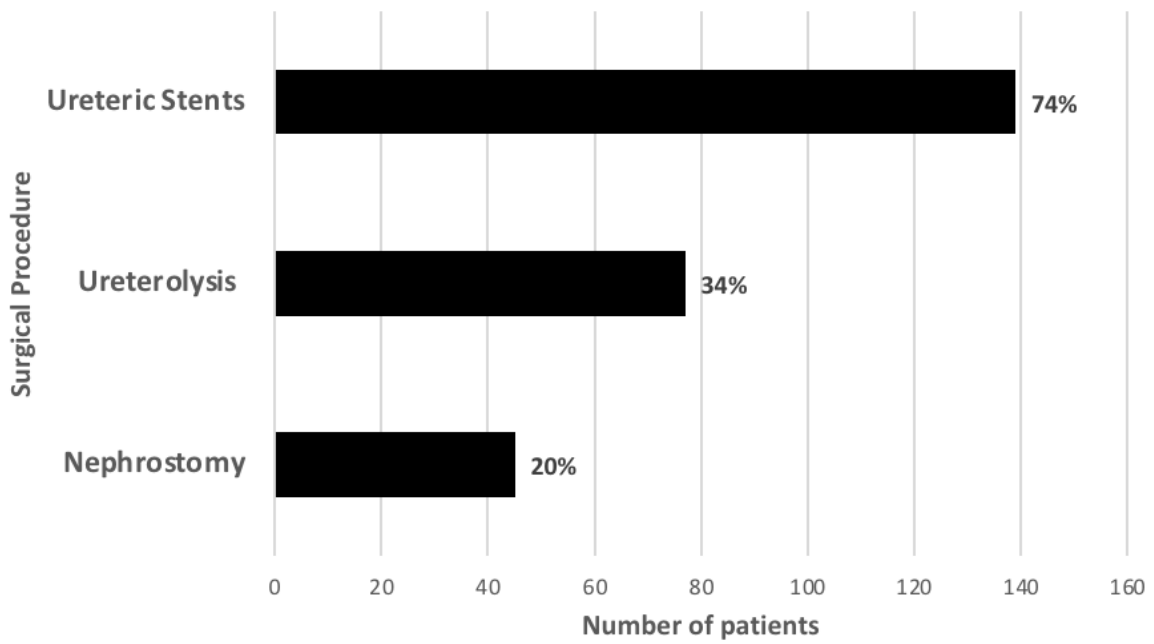


Figure 2.b Medical treatments received by patients diagnosed with RPF.

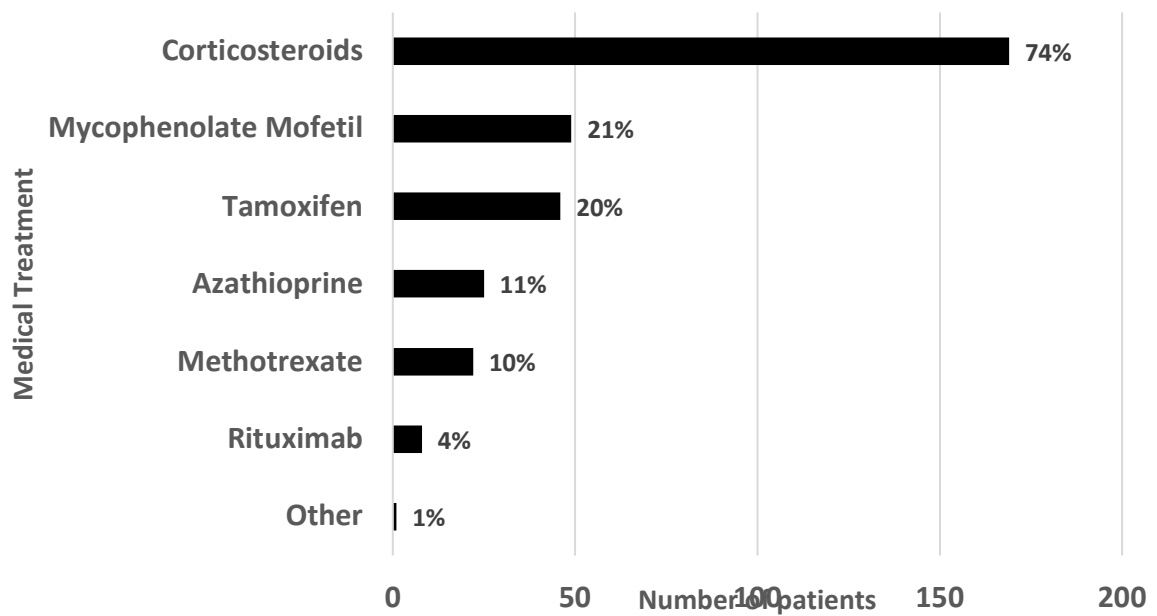


Figure 3. Side effect profile in patients treated with corticosteroids.

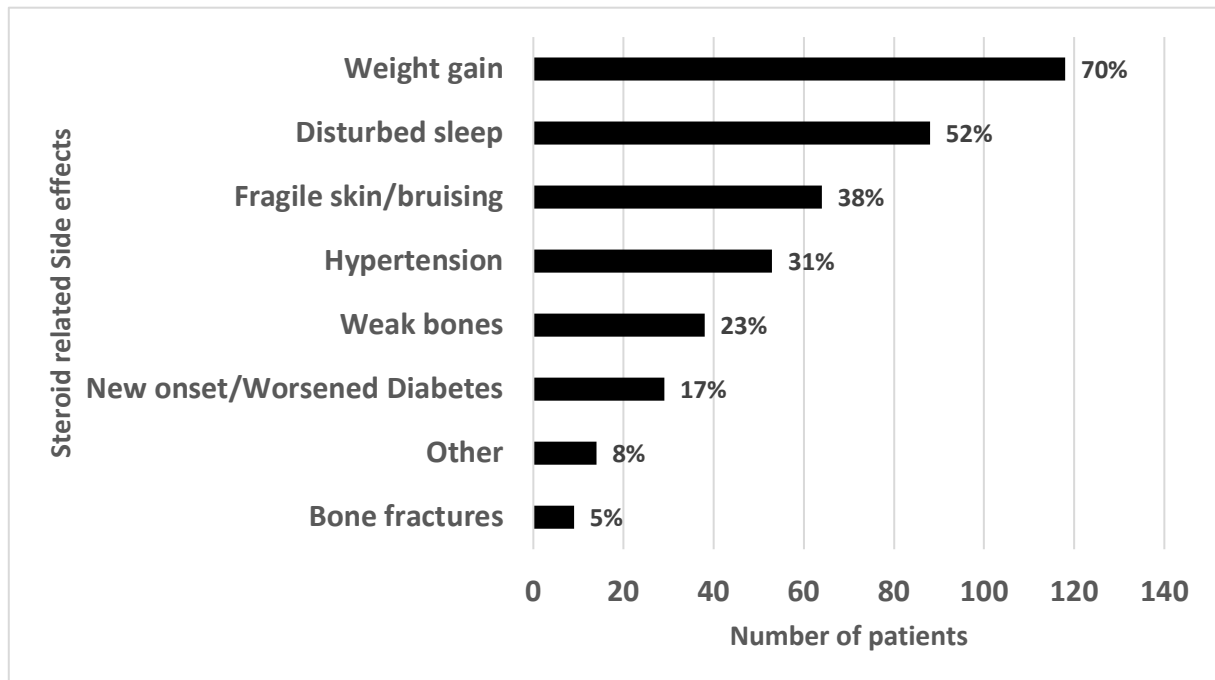


Figure 4. Psychological symptoms reported by patients with RPF.

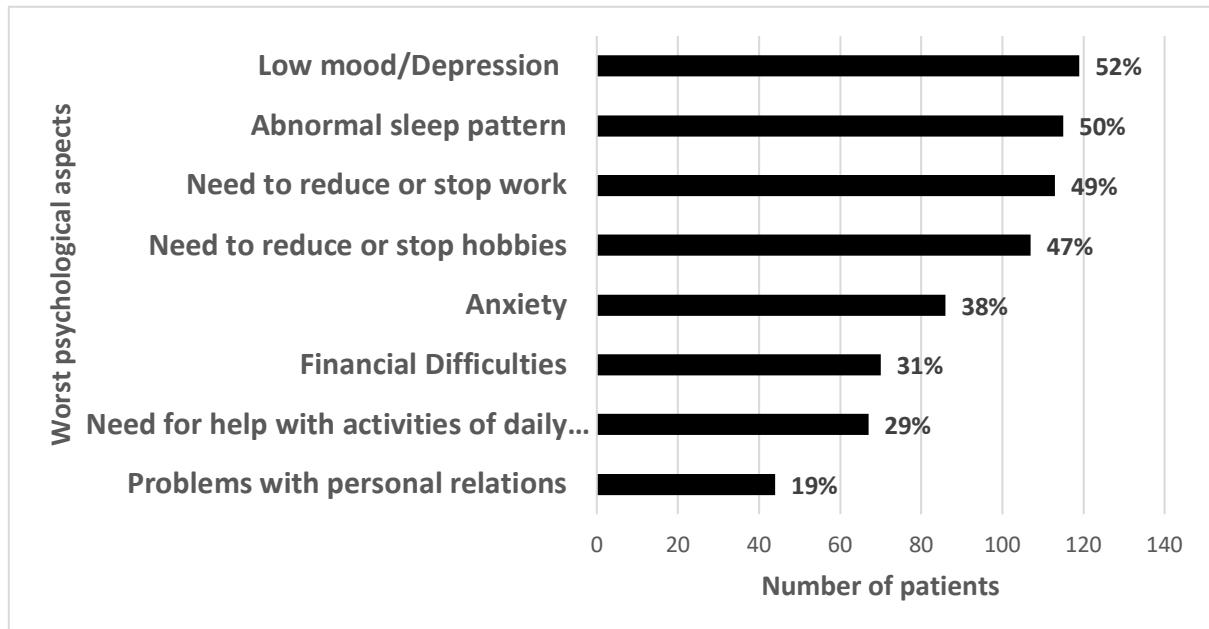


Figure 5.a Worst aspects of living with RPF as reported by all respondents.

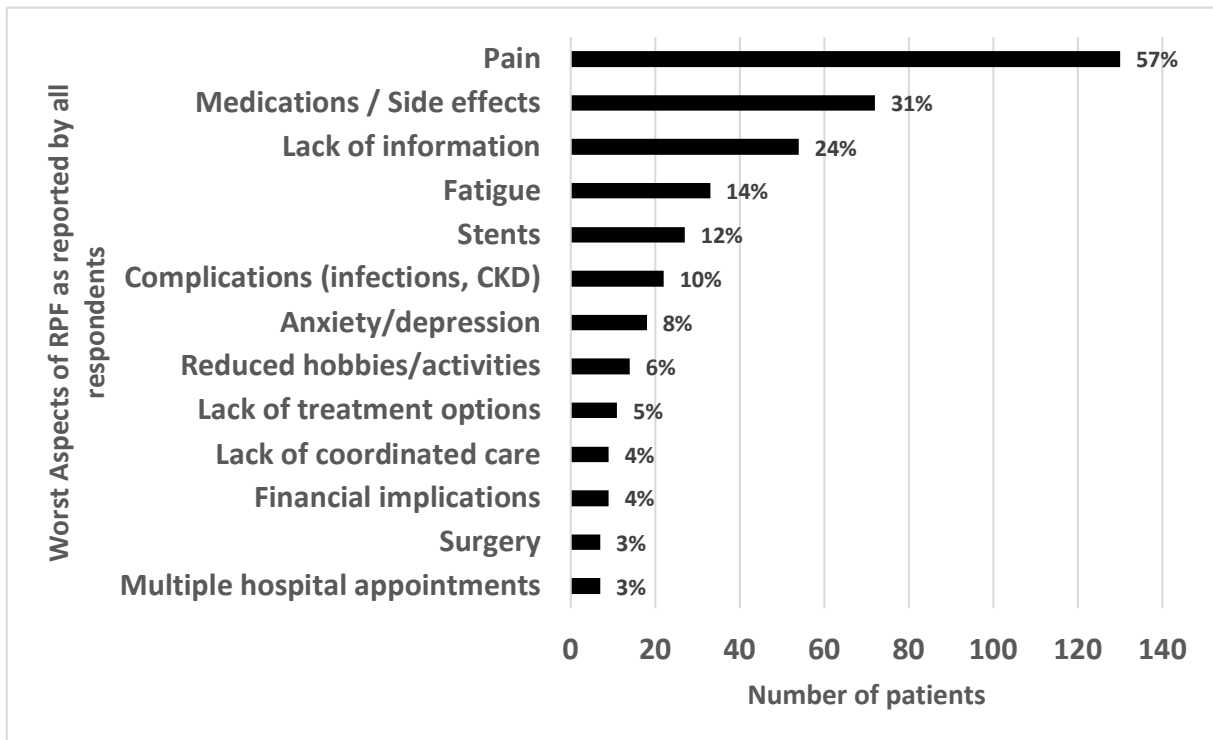


Figure 5.b Worst aspects of living with RPF as reported by respondents who underwent surgical intervention.

