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# Development and implementation of a COVID-19 near real time traffic light system in an acute hospital setting



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# Development and implementation of a COVID-19 near real time traffic light system in an acute hospital setting

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**Key Messages**

***What is already known:***

- COVID-19 causes severe mortality, particularly in patients requiring invasive ventilatory support, developing a cytokine storm, or experiencing thromboembolic disease.
- There is conflicting advice on whether to institute preventative measures, or wait for patients to develop end-stage disease, for example, acting or not acting on elevated D-dimers to modify normal venous thromboembolic prophylaxis.

***What this study adds***

- Implementation of a real time clinical decision tool in the emergency department defines patients' clinical status enabling rapid implementation of clinical care pathways.
- Early detection and enhanced care of patients at risk of developing disease progression is feasible using a COVID-19 battery of tests to identify preventable complications in hospital.
- Separate to emergency respiratory assessments, 342/923 (37.1%) of patients received a thromboembolism or cytokine storm flag in the emergency department – 318 (34.5%) for thromboembolism and 89 (9.6%) for cytokine storm, leading to implementation of accelerated enhanced treatments.

**Key words:**

Emergency care systems; infectious diseases, SARS; resuscitation, clinical care; thromboembolic disease-management, ventilation,

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***ABSTRACT***

*Background:* Common causes of death in COVID-19 due to SARS-CoV-2 include thromboembolic disease, cytokine storm and adult respiratory distress syndrome (ARDS). Our aim was to develop a system for early detection of disease pattern in the emergency department, that would enhance opportunities for personalised accelerated care to prevent disease progression,

*Methods*: A single Trust's COVID-19 response control command was established and a reporting team with bioinformaticians was deployed to develop a real-time traffic light system to support clinical and operational teams. An attempt was made to identify predictive elements for thromboembolism; cytokine storm, and ARDS based on physiological measurements and blood tests, and to communicate to clinicians managing the patient, initially via single consultants, to enhance opportunities for personalised accelerated care to prevent disease progression. The input variables were age; sex and first recorded blood pressure; respiratory rate; temperature; heart rate; indices of oxygenation, and C-reactive protein. Early admissions were used to refine the predictors used in the traffic lights.

*Results:* Of 923 patients who tested COVID-19 positive, 592 (64%) flagged at risk for thromboembolic disease, 241/923 (26%) for cytokine storm, and 361/923 (39%) for respiratory deteriorations. Thromboembolism and cytokine strom flags were met in the emergency department for 342 (37.1%) patients. Of 318 (34.5%) patients receiving thromboembolism flags, 49 [5.3%] were for suspected thromboembolism, 103 [11.1%] high-risk, and 166 [18.0%] medium risk. Of the 89 (9.6%) who received a cytokine storm flag from the emergency room, 18 [2.0%] were for suspected cytokine storm, 13 [1.4%] high-risk and 58 [6.3%] medium risk. Males were more likely to receive a specific traffic-light flag.

*Conclusions:* Emergency department predictors were used to identify high proportions of COVID-19 admissions at risk of clinical deterioration due to severity of disease, enabling accelerated care targeted to those more likely to benefit. Larger prospective studies are encouraged.

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**INTRODUCTION:**

Human infection due to the novel coronavirus SARS-CoV-2 (commonly referred to as COVID-19) was first reported at the end of 2019.[1] The broad spectrum of disease severity ranges from asymptomatic and mild cases, to severe multiorgan failure and death. As in the earliest reports[2], survival for patients developing critical disease remains poor, with adult intensive care units (AICUs) reporting mortality exceeding 50% for patients with completed encounters requiring invasive mechanical ventilation.[3,4] It is imperative to try to understand progression of disease, and whether any critical disease outcomes could be prevented.

Initial attention was focussed towards multilobar viral pneumonia, frequent requirement for supplementary oxygen/ventilatory support, and the development of adult respiratory distress syndrome (ARDS) in more than half of critically ill patients.[2] Early risk factors for in-hospital death included older age, higher Sequential Organ Failure Assessment (SOFA) score, and D-dimer greater than 750ng/mL on admission.[2] By February/March 2020, cytokine patterns were recognised as compatible with a "cytokine storm" of dysregulated inflammation and hyperpyrexia.[5]

At the same time, post mortem results were being shared from Italy (personal communication Dr Puya Dehgani-Mobaraki), the US[6] and reaching peer-reviewed publication.[7,8] These demonstrated that morbid pathology is dominated by thrombosed small vessels, unsuspected venous thromboses, pulmonary emboli, and features of catastrophic microvascular injury, with evidence of a procoagulant state. Thromboembolic events have become one of the most common causes of death following SARS-CoV-2 infection, and multiple advisory bodies are now issuing recommendations for thromboprophylaxis in COVID-19 patients.[9-18] Guidelines are conflicting, but observational studies now suggest that benefit can be obtained from therapeutic anticoagulation,[19,20] including in ventilated patients.[20] Recognising potential hazards of full anticoagulation, the questions on how to risk stratify patients appropriately are taking on further importance.[21]

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In our Trust, we created a near real time traffic light system and accompanying clinical pathways that would allow us to accelerate the administration of personalised care as early as the point of admission into the emergency department. The objective of a dynamic stratification tool was two-fold; 1) early identification of patients at risk of preventable complications, and 2) modification of clinical management based on local clinical policies and emerging evidence. The overall intention was for this to result in an institution-wide approach that facilitated early expert input to the emergency department (ED) to have clear guidelines on disposition and what interventions might be needed while still in the ED.

**METHODS:**

***Institution Details***

The Chelsea and Westminster NHS Foundation Trust comprises two hospitals and 12 community-based clinics in North-West London, delivering acute care to a diverse[22] population of over 1.5 million people. The Emergency Departments at Chelsea and Westminster Hospital and West Middlesex University Hospital treat over 300,000 patients a year. As part of the Trust's COVID-19 response, a reporting and bioinformatics team was deployed to support Clinical and Operational teams. ~~T~~

***Full Traffic light system integrating with electronic patient records***

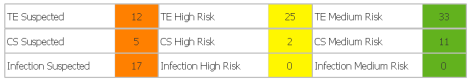
A new cloud database was created in Microsoft Azure with a near real-time pipeline from electronic patient records (EPR) which was dedicated to COVID-19 reporting from an operational, nationally mandated and clinical perspective. The database was kept in a permanent development cycle to facilitate rapid additions and changes. The dashboard was created for use with COVID-19 patients in March 2020, went live on 20/03/2020, and is under continual development, capturing symptoms, observations, blood tests and elements of therapeutics.

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***COVID-19 Patient Classification System***

Our goal was to identify predictive elements in the initial emergency department assessments for thromboembolism, cytokine storm, and ARDS. More than 40 patient-specific variables were identified and examined initially in the first 697 patients admitted with either a positive covid result\diagnosis or contained a pathology order which subsequently came back with a positive result (*Table 1*), and early patterns led to the selection of 11 input variables for the models. These were age; sex and first recorded systolic blood pressure (BP); diastolic BP; respiratory rate; temperature; oxygen saturation ($SpO_2$); fraction of inspired oxygen ($FiO_2$), heart rate and C-reactive protein (CRP). This dataset was passed through a Neural Network algorithm contained in SQL Server Analysis Services (SSAS) Data Mining Package. Highlighted predictive markers in the data were then examined.

**Traffic Light System:**




Thromboembolic events, cytokine storm and ARDS/secondary infection wer flags were triggered by a change in clinical severity. The pathology results used as surrogate of disease progression were C-reactive protein (CRP), D-dimer, ferritin and Pro-calcitonin levels. Progression of disease was defined by no flag, mild risk flag, medium risk fla igh risk flag and suspected event flag (*Table 2)*. During this period, "no flag" and "mild-risk" re considered as "green" traffic lights and managed by standard protocols. The near real-time electronic clinical dashboard was promoted acrossed the organisation, and a link to the traffic lights was shared via internal institutional communication pathways.

The traffic light system adjusts patients' flags every 10 minutes, facilitating recommended dynamic reassessments,[13] and accelerated clinical management of potential thromboembolic events and cytokine storm throughout the hospital stay.

Importantly, due to the nature of COVID-19 disease, and the priority to enhance patient care at all times, the flag system was always interpreted with caution, with anticoagulant changes reviewed at an individual level, particularly in pregnant patients, patients with severe liver disease and patients admitted with primary neurological events.

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***COVID-19 Pathways of Care Pre and Post Traffic Lights***

*Thromboembolic events:*

At the outset of the study, the usual institutional prophylactic dose was enoxaparin (Clexane) 40mg once daily for prophylaxis of venous thromboemboli (VTE), and the usual standard of care for patients with proven or suspected VTE was full anticoagulation, with adjustments to implementation and conventional 6 month duration according to results from imaging and broader patient evaluations. The thromboembolism traffic light flags were developed to allow a broader group of patients earlier in their admission to benefit from enhanced anticoagulation. Thromboembolic events confirmed radiologically and or D-dimer >10,000 ng/mL were accepted as best clinical markers for management of the disease and therefore used to create a predicting model to identify patients at risk of developing such complications. These dashboard markers resulted in urgent feedback to the clinical team.

COVID-19 positive with "suspected thromboembolism were directed towards the usual computerised tomographic pulmonary angiogram (CTPA) to screen for an overt pulmonary embolus (PE), and a non-contrast computerised tomogram of the brain (CTB) using established institutional protocols, to exclude intracranial haemorrhage or an acute cerebral infarct, prior to initiating systemic anticoagulation. If CTB identified an acute cerebral infarct which could be at risk of haemorrhagic transformation, anticoagulation was maintained at prophylactic dose. In the absence of visible thrombus on CTPA, a microvascular thrombosis was assumed as previously reported,[2,6] and therapeutic anticoagulation commenced with an intended shorter duration.

Thromboemboli traffic light flags were used to identify a further group of "Suspected Thromboembolic Risk" patients (red traffic light) received therapeutic anticoagulation unless contraindication present); "High Risk" patients (amber traffic ligtht) to be managed as for the suspected TE cases (therapeutic anticoagulation unless contraindication present); and a "medium risk" group (green traffic light) who would be managed by increasing thromboprophylaxis to 40mg enoxaparin twice daily, recognising the data in reference[2].

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*Hyperinflammatory/'cytokine storm':*

In the earliest stage of the pandemic, this pattern was observed with sudden haemodynamic collapse after relative stability. Initial management consisted of aggressive fluid resuscitation, vasopressors and inotropic support on AICU.

The cytokine storm traffic light flags were developed to allow a broader group of patients, even at the point of admission through the Emergency department, to benefit from early enhanced circulatory support. These dashboard markers resulted in urgent feedback to the clinical team.Patients meeting the criteria were monitored continuously and fluid management adjusted to replace insensible losses ($1ml.kg^{-1}.h^{-1}$ for every degree above 38˚C). If there was no response to initial fluid management and diastolic blood pressure remained <35mmHg, or oxygen requirement increased, then the patients were referred to the AICU for further management.

*Acute Respiratory Failure Syndrome (ARDS)/AICU*

In the earliest stage of the pandemic, only clinically unwell patients were referred to the adult intensive care unit (AICU) by the emergency department team as per standard trust guidelines. Patients admitted to medical wards were then referred to the AICU team when patients presented further clinical deterioration and or failed medical management. They were managed in ward base settings until they deteriorated to reach critical disease endpoints, or were discharged. Patients flagged at risk of ARDS and required AICU review were referred to the AICU Consult

| | | |
|---|---|---|
| Secondary Infection | Suspected | PCT > 1.0 |
| Secondary Infection | High Risk | PCT 0.5 - 1.0 |
| Secondary Infection | Medium Risk | PCT 0.25 - 0.5 |
| Secondary Infectio | No Risk | PCT < 0.25 |

SpO2 <90% on arrival to the emergency department was used t

by the addition of PCT as a surrogate of superimposed second

Patients flagged for ARDS received a 30 minute trial of CPAP in the ED. Failure to respond to CPAP led to call the AICU intubating team and proceed with endotracheal intubation. The initial invasive ventilatory support settings aimed for a target $SpO_2$ 92 % and generally- PEEP of 8 cm of water ($H_2O$), as lung compliance was observed to be normal/high during the early phase of the disease process (pre traffic light). Patients were proned within the first 4 hours of admission to the AICU. Cardiovascular

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support was managed at individual level by continuous assessment of intravascular volume by different methods e.g. passive leg raising, non invasive cardiac output monitoring (Cheetah, Lidco) and an initial transthoracic and lung ultrasound were performed in the ED. There was not a standarised fluid balance, but a daily even balance was targeted and adjusted at individual level when indicated. Patients' fluid balance was part of the overall clinical management in medical wards and in the AICU. Patients admitted to AICU and acute respiratory wards received ascorbic acid 1g bd, given enterally or intravenously by protocol to reduce oxidant stress in the setting of shock/microvascular shutdown.

***Patient and Public Involvement Statement***

As part of clinical care, patients with COVID-19 infections and next of kin were not only informed of the severity of the disease but also background work in the institution to identify preventable complications.

***Data Analyses***

Selected dashboard data were downloaded on 22nd April 2020 for analysis of admission indices, and on 22nd May 2020 to evaluate progression against the Traffic Light flags for thromboembolic disease, cytokine storm, and ARDS. Analyses of perceived and actual benefits will be the subject of future communications..

Statistical analyses were performed in Stata IC version 15 (Statacorp, Texas) and GraphPad Prism 8.1.1 (GraphPad Software, San Diego, California USA). Comparisons were performed using the Kruskal-Wallis equality-of-populations rank test, with Dunn's multiple comparison test used to derive the multiple comparison-adjusted p values.

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**RESULTS:**

***Traffic Lights Real Time Monitoring***

From initial admission in the Emergency units, patient data were autopopulated into the hospital dashboard, and updated every 10 minutes. The flags were univariate, and are illustrated in *Table 2*. In the first phase, reports were sent to an experienced critical care clinician (MPV) for review, interpretation, and feed back to the clinical teams. From April 12th, the flags operated directly in real-time, with the traffic light system available to all clinical practitioners and managers in the organisation (*Figure 1*).

***Traffic Light system flagging categories***

The number of cases in the flagged categories for thromboembolic disease, cytokine storm and/or ARDS are illustrated in *Figure 2*. Patients receiving a cytokine storm flag usually also met a thromboembolic flag. "Medium risk" thromboembolic flags overlapped in >85% of cases with a cytokine storm-flag, "High risk" thromboembolic flags overlapped in 61-67% of cases with a cytokine storm flag and "Suspected thromboembolism" flags overlapped in 30-43% of cases with a cytokine storm flag.

***Value of Traffic Light Flags in the Emergency Department***

Of the 923 patients admitted through the emergency units, 134 (14.5%) received a thromboembolism flag in the emergency department that led to immediate consideration of full anticoagulation. This subgroup comprised 59 [40%] of the 149 patients who at any stage during their admission flagged for "Suspected Thromboembolism" and 75 [35.6%] of all 211 patients ultimately flagged at "High Risk" of thromboembolism. Therapeutic anticoagulation was initiated in all except two patients who also presented small acute cerebrovascular events.

Similar accelerations to care were observed for patients who flagged at risk of moderate risk of thromboembolism, cytokine storm, or ARDS, both in the emergency department, and during later ward-based care as patients moved through categories during their admission (*Figure 3*).

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***Evaluation of accuracy of the Traffic Light System – Preliminary mortality analysis***

The "suspected thromboembolism" flag was associated with an interim mortality of 42% (62/149) compared to 11% (35/331) for patients with no thromboembolic flag. The "high risk" flag derived solely from blood test results was associated with similar interim mortality at 47% (98/211). Interim mortality was lower in the 62 patients who reached "suspected thromboembolism" status after a previous "high risk" flag where full anticoagulation was recommended (17/62, 27.4%), than in the 70 with no prior flag (34/70, 48.6%, Dunn's post test p=0.028, *Figure 4*).

***Value of Traffic Lights by sex of patient:***

Details of the 923 patients admitted to the two hospitals who had tested positive for COVID-19 by 22nd April 2020 are presented in the Data Supplement. Notably, males were over-represented in the higher categories for thromboembolic disease ($\chi^2$ p<0.0001, 3 degrees of freedom), cytokine storm ($\chi^2$ p<0.0001, 3 degrees of freedom), and ARDS ($\chi^2$ p=0.075, 1 degree of freedom). For males, once the "suspected" or "high risk" thromboembolism categories were reached, interim mortality rates were no higher than in females (data not shown).

**DISCUSSION**

We developed a traffic light system dashboard that enabled rapid adjustment of management protocols based on patients' own risk at the point of admission to the emergency department. This enabled an institution-wide approach that facilitated early expert input with clear disposition and management guidelines.

The main study limitation is that it was a single centre study performed at two hospital sites. It is a report of protocols put in place recognising the severe status of patients on admission to our institution, published mortality rates, and the urgent aim to secure better survival rates for those infected by

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COVID-19 and requiring hospital admission. The report is limited to descriptive elements precluding detailed analysis at whether outcomes are improved or whether protocols should be adopted. Similar non-randomised, observational studies are available,[19,20] and prospective clinical studies looking at early enhanced thromboembolic prophylaxis with full anticoagulation based on risk stratification are clearly needed, as indicated by others.

The major strength of this system is that is offers stratifications to assist care delivery particularly in the ER, and prospective clinical trial design. The system represents a real time Clinical Decision Support tool that enables early escalation of treatments. A further strength is the reporting of bundles of care that can be implemented rapidly, synthesising elements in keeping with management practice elsewhere, as it evolves. For instance, elevated D-dimers and other biomarkers are used elsewhere for risk stratification,[9,11,13,15,16] and enhanced prophylactic anticoagulation is considered for selected patient groups.[11,12,15-17] A recent survey of thrombosis/haemostasis experts reported that 30% would use higher dose thromboprophylaxis for COVID-19 positive inpatients, increasing to 50% for patients on intensive care.[16] Additionally, there has been a trend towards including therapeutic dosages in certain thromboprophylaxis settings,[13,16,17] supported by data emerging from clinical practice reports.[19,20]

While the study cannot address at present whether implementation initiated post traffic lights prevented patients deteriorating to more severe disease endpoints, there was evidence of benefit if suspected thromboembolism developed. Thromboembolism was the most common and survival-threatening critical scenario identified. It was recognised early that theoretically, the thrombotic process was most amenable to preventative and early treatments. Results from the current study and elsewhere[19,20] now suggest benefits from full anticoagulation, and more patients may therefore be exposed to potential risks of therapeutic anticoagulation. Our data demonstrate that D-dimer and/or CRP values identify a large (~40%) at-risk subgroup who may benefit from early anticoagulation which was initiated in the emergency department. This makes it difficult for us to concur with the endorsed recent guidelines[14,18] that effectively increase the threshold for anticoagulation in COVID-19 patients by discounting D-dimers and other biomarkers. Additional questions are whether the 25% of patients denoted at “medium risk” of thromboembolic disease would benefitfrom full anticoagulation, and whether the “low-risk”

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group would have benefited from additional intervention: These would be useful prospective studies for the future.

A striking feature was that males were overrepresented in the higher risk categories. Others have reported male susceptibility to severe COVID-19,[1-4,8] and we have recently reported genomic evidence[23] that adds to the compelling clinical data that emphasise males are biologically more at risk of severe complications if infected by COVID-19. The traffic light system appears to be able to capture males with excess risk at the time of admission through the Emergency Department.

In conclusion we developed and implemented a traffic light systems that enabled the detection, in near real time, of the three major patterns of COVID-19 from the point of admission to the ED, where implementation enabled early ascertainment of disease progression in hospital. We report specific clinical bundles of care that could be extended as the place for new elements of COVID-19 care become identified through randomised controlled trials.

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***The Data Supplement details***

Supplementary Table 1

Supplementary Figure 1

Supplementary Figure 2

Supplementary Figure 3

**Authors' Contributions:** The study was conceived and overseen by MPV. Literature searches were performed by MPV, CLS, MH and RD. The traffic light bioinformatics system was designed and implemented by AH, AB and AM. The clinical study design was by MPV. Data analysis for real-time feedback was performed by MPV and AM. Real time analytic data application was performed by MPV, MH, SS, LC, AS, RD, CL, MP, AG, JA, TP and RTK. Data analysis was conceived and performed by CLS, and data interpretation was performed by MPV and CLS. Figures were generated by CLS. The manuscript was written by CLS, and revised by MPV, MH, RD, AM, and RTK. All authors reviewed and approved the final manuscript.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare. All authors have access to all the data in the study and shared final responsibility for the decision to submit for publication.

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**Ethics Committee Approval:** This work was approved by the Chelsea & Westminster NHS Foundation Trust Clinical Governance team and the Data Protection Officer, Head of Information Governance. As we report on routinely collected non-identifiable clinical audit data, no ethical approval was required under the UK policy framework for health and social care.

**Data Availability:** Fully anonymised data will be available post peer review publication on reasonable request, in accordance with institutional protocols above.

**References:**

1 Zhu N, Zhang D, Wang W et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733.

2 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395(10229):1054–10

3 Grasselli G, Zangrillo A, Zanella A et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA*. 2020 Apr 6. doi: 10.1001/jama.2020.5394. [Epub ahead of print]

4 Intensive Care National Audit and Research Centre (ICNARC). ICNARC report on COVID-19 in critical care. 05 June 2020 available at https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports.

5 Chen C, Zhang XR, Ju ZY, He WF. [Advances in the research of cytokine storm mechanism induced by Corona Virus Disease 2019 and the corresponding immunotherapies]. *Zhonghua Shao Shang Za Zhi*. 2020 Mar 1;36(0):E005. Chinese. doi: 10.3760/cma.j.cn501120-20200224-00088. Epub ahead of print. PMID: 32114747.

6 Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, Vander Heide RS. Pulmonary and Cardiac Pathology in Covid-19: The First Autopsy Series from New Orleans. Published online 2020 Apr 10; https://www.medrxiv.org/content/10.1101/2020.04.06.20050575v1.

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7 Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, Baxter-Stoltzfus A, Laurence J. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Transl Res.* 2020 Apr 15. doi: 10.1016/j.trsl.2020.04.007. [Epub ahead of print]

8 Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med.* 2020 May 6. doi: 10.7326/M20-2003. [Epub ahead of print]

9 Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haem 2020 March 25 [Epub ahead of print] https://doi.org/10.1111/jth.14810

10 World Health Organisation. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. https://apps.who.int/iris/bitstream/handle/10665/331446/WHO-2019-nCoV-clinical-2020.4-eng.pdf?sequence=1&isAllowed=y 13th March 2020, accessed 07/06/2020.

11 Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). Blood Transfus 2020; DOI: 10.2450/2020.0083-20. [Epub ahead of print] , accessed 07/06/2020.

12 Casini A, Alberio L, Angelillo-Scherrer A, et al. Thromboprophylaxis and laboratory monitoring for in-hospital patients with COVID-19 - a Swiss consensus statement by the Working Party Hemostasis. Swiss Med Wkly. 2020 Apr 11;150:w20247. doi: 10.4414/smw.2020.20247, accessed 07/06/2020.

13 Zhai Z, Li C, Chen Y, et al. Prevention and Treatment of Venous Thromboembolism Associated with Coronavirus Disease 2019 Infection: A Consensus Statement before Guidelines. Thromb Haemost. 2020 Apr 21. doi: 10.1055/s-0040-1710019. [Epub ahead of print], accessed 07/06/2020.

14 Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. *J Am Coll Cardiol*. 2020 Apr 15:S0735-1097(20)35008-7. doi: 10.1016/j.jacc.2020.04.031. Epub ahead of print. PMID: 32311448; PMCID: PMC7164881.

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15 Condliffe R, Bunclark K, Hurdman J, et al. BTS Guidance on Venous Thromboembolic Disease in patients with COVID-19. 2020 Apr 23 available at https://www.brit-thoracic.org.uk/about-us/covid-19-information-for-the-respiratory-community/#bts-guidance-on-venous-thromboembolic-disease-in-patients-with-covid-19, accessed 07/06/2020.

16 Spyropoulos AC, Levy JH, Ageno W, et al. Clinical Guidance on the Diagnosis, Prevention and Treatment of Venous Thromboembolism in Hospitalized Patients with COVID-19. J Thromb Haemost. 2020 May 27. doi: 10.1111/jth.14929. Epub ahead of print. PMID: 32459046, accessed 07/06/2020.

17 Kollias A, Kyriakoulis KG, Dimakakos E, Poulakou G, Stergiou GS, Syrigos K. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. Br J Haematol. 2020 Jun;189(5):846-847. doi: 10.1111/bjh.16727. Epub 2020 May 4, accessed 07/06/2020.

18 Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19: CHEST Guideline and Expert Panel Report [published online ahead of print, 2020 Jun 2]. Chest. 2020;S0012-3692(20)31625-1. doi:10.1016/j.chest.2020.05.559, accessed 07/06/2020.

19 Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020 May;18(5):1094-1099.

20 Paranjpe I, Fuster V, Lala A, et al. Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19. J Am Coll Cardiol. 2020 May 5:S0735-1097(20)35218-9. doi: 10.1016/j.jacc.2020.05.001. Epub ahead of print, accessed 07/06/2020.

21 Shovlin CL, Vizcaychipi MP. Implications for COVID-19 triage from the ICNARC report of 2,204 COVID-19 cases managed in UK adult intensive care units. *Emerg Med J* 2020 Jun;37(6):332-333.

22 Heng JS, Atkins J, Clancy O, et al. Geographical analysis of socioeconomic factors in risk of domestic burn injury in London 2007-2013. *Burns* 2015 May;41(3):437-45.

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23 Shovlin CL, Vizcaychipi MP. Definition of COVID-19 genomic susceptibility: ACE2 variants relevant to human infection with SARS-CoV-2 in the context of ACMG/AMP Guidance. 2020. Available at https://www.medrxiv.org/content/10.1101/2020.05.12.20098160v3, accessed 07/06/2020.

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**TABLE 1: INITIAL ELEMENTS EXAMINED FOR COVID-19 TRAFFIC LIGHTS**

| | |
|---|---|
| **Symptoms** | Fever, dry cough, fatigue, dyspnea, diarrhoea, tachypnoea, thirst, loss of appetite. |
| **Observations** | Temperature, heart rate; blood pressure; respiratory rate; oxygen saturation ($SpO_2$) |
| **Blood tests including** | |
| Full blood count | Red and white cell counts (with differential for e.g. lymphocytes, neutrophils, monocytes, eosinophils); haemoglobin, haematocrit, platelet; |
| Coagulation screen | including fibrinogen, prothromin time and activated partial thromboplasin time (APTT); D-dimer, and anti-factor Xa where appropriate |
| Biochemistry | Electrolytes (sodium, potassium), renal function (urea, creatinine), and liver function (bilirubin, alkaline phosphatase, albumin, aspartate transaminase, alanine transaminase, gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH)) |
| Iron studies | Serum iron, transferrin saturation index, ferritin |
| Other | Additional acute phase response markers including C-reactive protein; procalcitonin (PCT)[a]. |
| **Therapeutics including** | |
| Oxygen delivery | Fraction of inspired oxygen ($FiO_2$, from 21% [room air] to 100%); and delivery method (nasal cannulae, face mask and type) |
| Ventilatory support | Continuous positive airway pressure (CPAP) and invasive ventilation. Ventilation pressures and volumes, positive end expiratory pressure (PEEP) |
| Circulatory support | including noradrenaline, and renal replacement therapies |

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**TABLE 2: FINAL ELEMENTS USED IN COVID-19 TRAFFIC LIGHTS**

| | Pathology marker | No Flag | Mild Risk | Medium Risk | High Risk | Suspected Risk |
|---|---|---|---|---|---|---|
| **Thromboembolic event** | [1]CRP (mg/L) and/or D-Dimer (ng/mL) | <1.1 | >1.11 to 100 | >101 to 200 And/or >1,000 to 3,000 | >201 to 250 and/or >3,001 to 5,000 | >251 and/or >5,001 |
| **Cytokine storm** | Ferritin (µg/L) | <300 ♂ & <200 ♀ | >300 to 1,000 | >1,001 to 2,000 | >2,501 to 4,000 | >4,001 |
| **ARDS/Secondary Infection*** | $SpO_2$ (%)** and PCT (µg/L) | >96 and/ <0.05 | 96-94 >0.051 to 0.25 and | 92-94 0.25 to 0.5 | 90-92 0.5 to 1.0 | <90 and >1.01 |

*[1] *In the initial analyses, based on pattern of disease in patients with proven PE on CT scan, a D-dimer >10,000 ng/mL was used to indicate thromboembolic disease. The single biggest predictor was that of CRP which preceded a subsequent spike in D-dimer: 22% of the patients with a CRP >200mg/L later developed a D-dimer>10,000ng/mL, rising with a CRP >250mg/L. Conversely, of the 30 patients with a pulmonary embolus and CRP exceeding 200mg/mL, 13 (43%) had an initial D-dimer >3,000ng/mL, suggesting that CRP may help as an early warning sign of a future high spike in D-dimer.Acute Respiratory Distress Syndrome (ARDS )/ Secondary Infection was iterated several times throughout the first COVID-19 infection outbreak. For simplicity and modelling* $SpO_2$ <90% on *arrival to the emergency department (on room air) was used as a predictive marker for ARDS as identified on neuronal network predictive modelling.*

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## FIGURE LEGENDS

**Figure 1. Real time decision support tool**

The 3 patterns of disease that were recognised early in the outbreak to be causing mortality. In pattern 1, the disease remained single-organ, usually respiratory but progressed from a viral pneumonia to a severe adult respiratory disress syndrome (ARDS) +/- superimposed bacterial pneumonia. Pattern 2 was characterised by circulatory collapse (cytokine storm), and pattern 3 by thromboembolic disease. To facilitate review across all flags, the decision support is set up as a 'favourite' tool in computers shared in communal areas such as nurses' stations in the emergency department, acute admission unit and adult intensive care unit.

***Figure 2:*** **Distinctive patterns and overlaps of critically ill patients**

**A)** Relative proportions of patients falling into dashboard-flagged categories, and a general respiratory flag, are drawn to scale by area. The ARDS component is not fully to scale since due to delays in set up, only 122 patients had procalcitonin results and therefore the total number was estimated for a population of 923 cases. **B)** Subcategory overlaps for cytokine storm and thromboembolic disease. These document all patients reaching the category criteria, so that "suspected" and "high-risk" groups are subgroups of "medium risk".

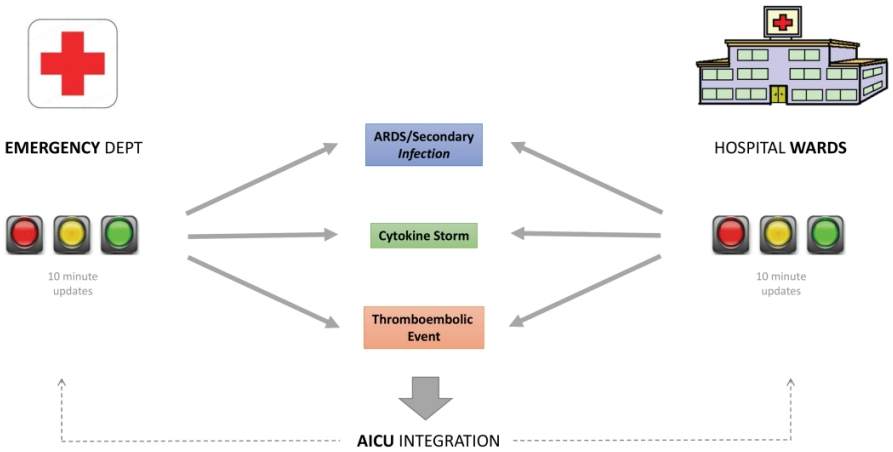
**Figure 3. Flag subcategories and dynamic progression.** Patients are classified by the most severe flag received for thromboembolism (upper panel) and cytokine storm (lower panel). Symbols are drawn to scale by area, and indicate the final numbers and percentages within each of the 3 categories (bold black text); the number of cases where the flag was the first the patient received (red or grey numbers above horizontal white lines), and the number of times the flag was preceded by one of the lower risk flags (red or grey numbers below horizontal white lines). Arrows indicate the number of patients progressing from a lower risk category, and indicate the median number of days (and interquartile range, IQR) spent in the lower risk category.

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**Figure 4**. **Heat map of interim mortality rates according to dynamic progression between thromboembolic risk categories**.

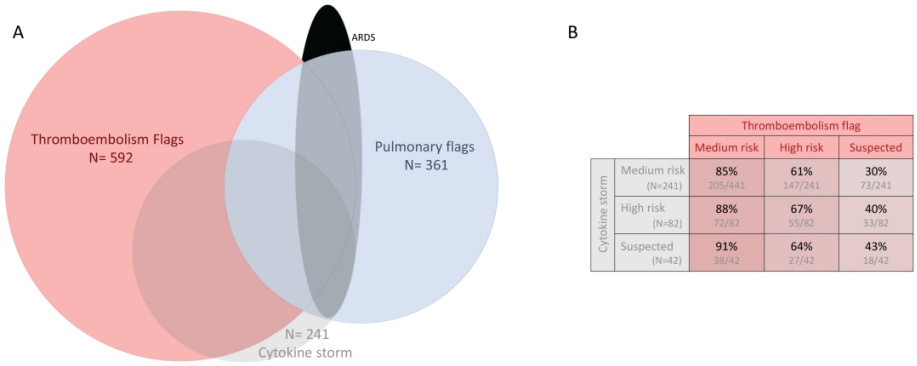
The upper row indicates the cases reaching the stated column thromboembolic flag with no previous flag. The middle row indicates cases with the "high-risk" and "suspected thromboembolism" flags that were reached after a previous "medium-risk" flag. The lower row indicates cases with the "suspected thromboembolism" flag reached after a previous "high-risk" flag. Dunn's multiple comparison test was used to derive the multiple comparison-adjusted p values.

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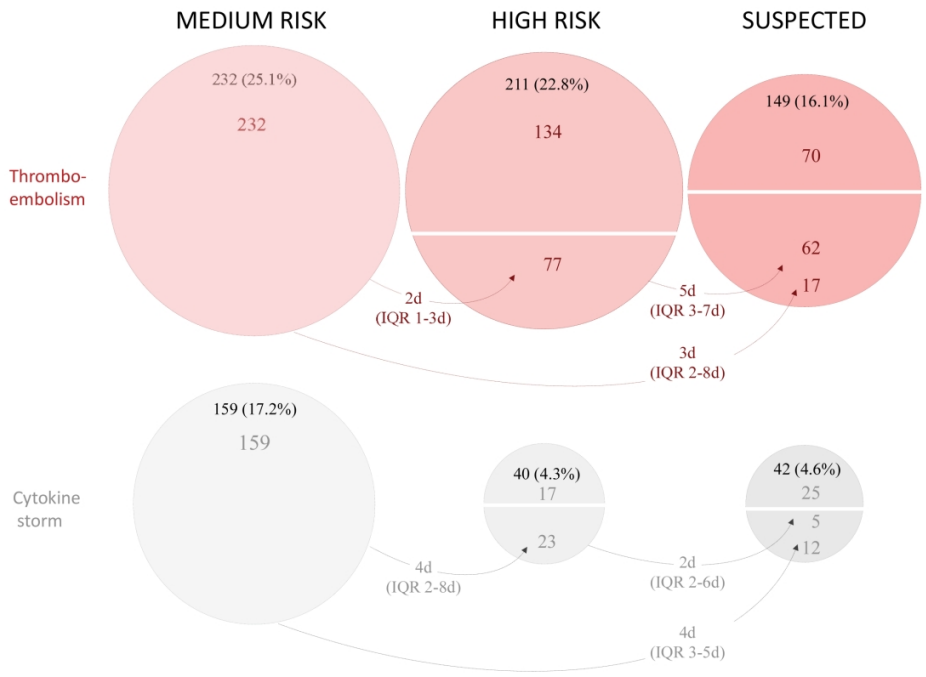

**Real time decision support tool**

The 3 patterns of disease that were recognised early in the outbreak to be causing mortality. In pattern 1, the disease remained single-organ, usually respiratory but progressed from a viral pneumonia to a severe adult respiratory disress syndrome (ARDS) +/- superimposed bacterial pneumonia. Pattern 2 was characterised by circulatory collapse (cytokine storm), and pattern 3 by thromboembolic disease. To facilitate review across all flags, the decision support is set up as a 'favourite' tool in computers shared in communal areas such as nurses' stations in the emergency department, acute admission unit and adult intensive care unit.

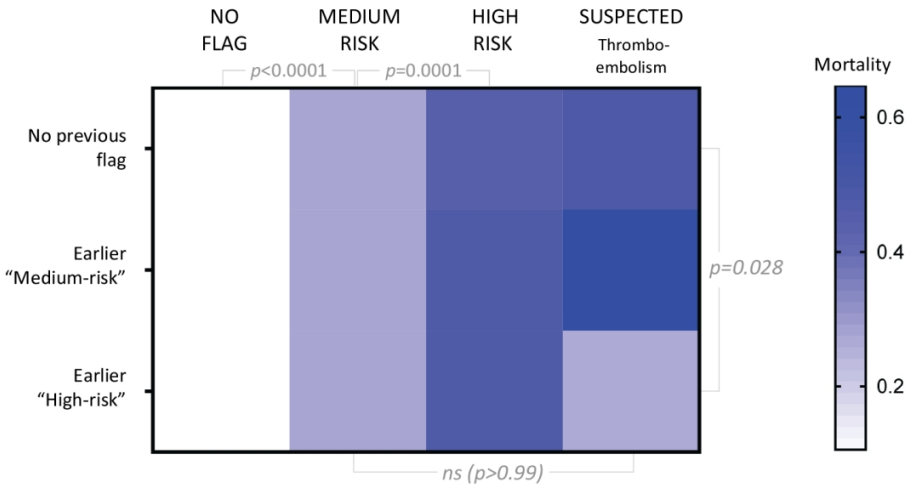



**Distinctive patterns and overlaps of critically ill patients**

A) Relative proportions of patients falling into dashboard-flagged categories, and a general respiratory flag, are drawn to scale by area. The ARDS component is not fully to scale since due to delays in set up, only 122 patients had procalcitonin results and therefore the total number was estimated for a population of 923 cases. B) Subcategory overlaps for cytokine storm and thromboembolic disease. These document all patients reaching the category criteria, so that "suspected" and "high-risk" groups are subgroups of "medium risk". There were smaller overlaps between the pulmonary flags and these categories (data not shown).




**Flag subcategories and dynamic progression.** Patients are classified by the most severe flag received for thromboembolism (upper panel) and cytokine storm (lower panel). Symbols are drawn to scale by area, and indicate the final numbers and percentages within each of the 3 categories (bold black text); the number of cases where the flag was the first the patient received (red or grey numbers above horizontal white lines), and the number of times the flag was preceded by one of the lower risk flags (red or grey numbers below horizontal white lines). Arrows indicate the number of patients progressing from a lower risk category, and indicate the median number of days (and interquartile range, IQR) spent in the lower risk category.




**Heat map of interim mortality rates according to dynamic progression between thromboembolic risk categories.** The upper row indicates the cases reaching the stated column thromboembolic flag with no previous flag. The middle row indicates cases with the "high-risk" and "suspected thromboembolism" flags that were reached after a previous "medium-risk" flag. The lower row indicates cases with the "suspected thromboembolism" flag reached after a previous "high-risk" flag. Dunn's multiple comparison test was used to derive the multiple comparison-adjusted p values.

# A COVID-19 near real time traffic light system defines patterns of disease in an acute hospital setting

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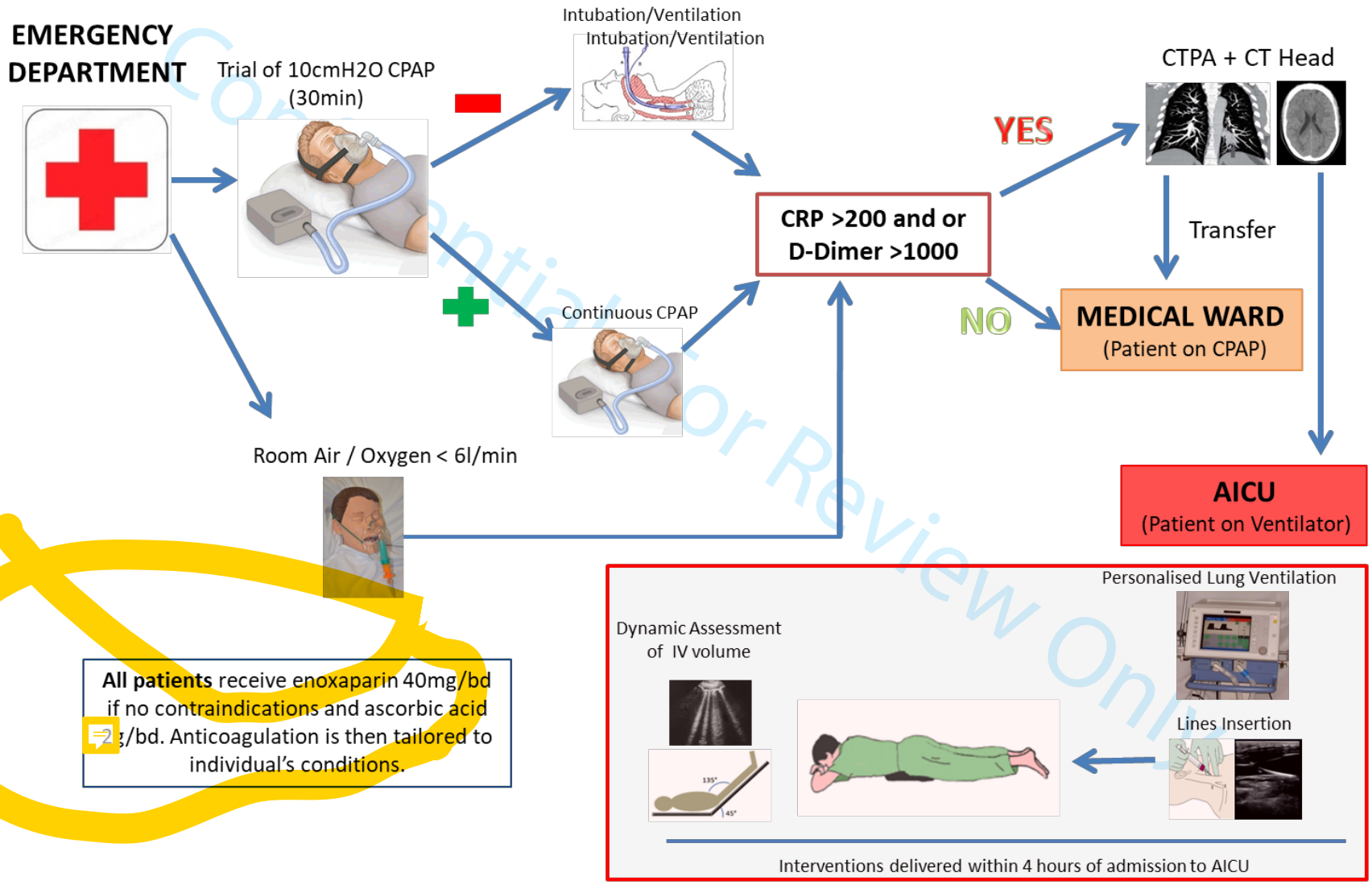
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## DATA SUPPLEMENT

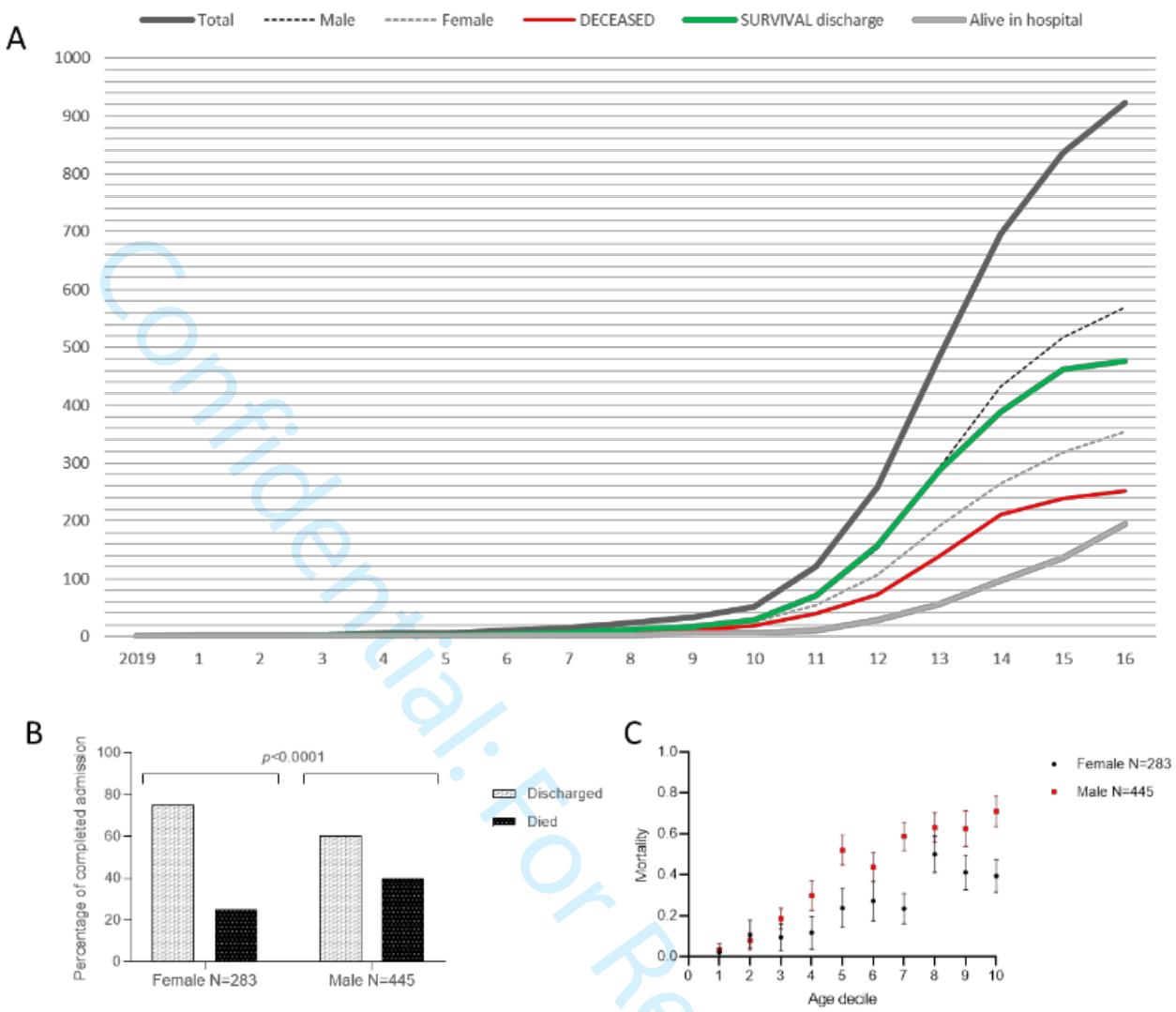
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Supplementary Figure 2: COVID-19 cases in institution. ..... 3
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Chelsea and Westminster Hospital NHS
NHS Foundation Trust

# Clinical Pathway for Thromboembolic Events on arrival to the Emergency Department




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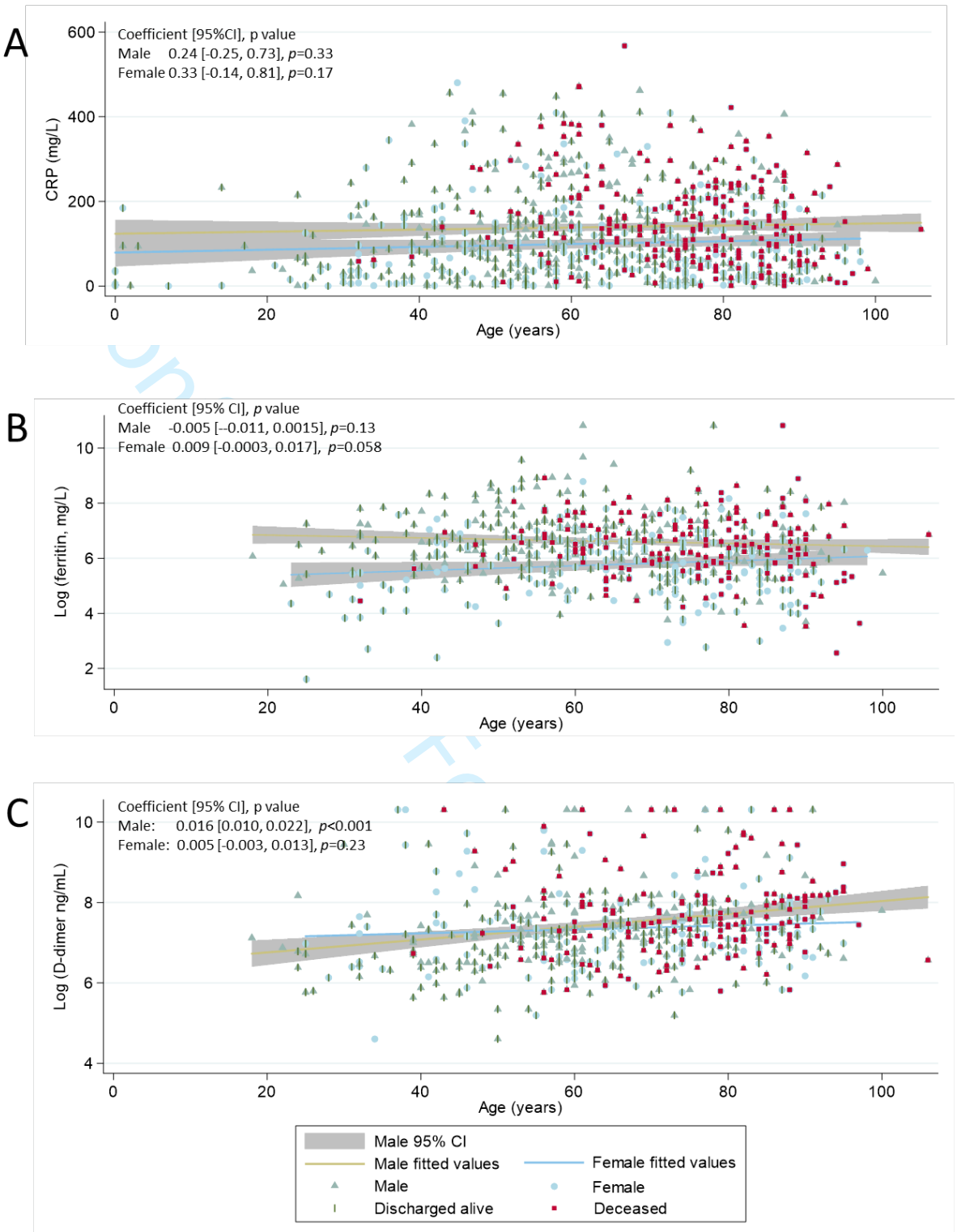

**Supplementary Figure 2: COVID-19 cases in institution.**
**A**) Cumulative cases across the first 16 weeks of 2020 until 22 April 2020. Total COVID-19 cases are plotted in thick black, males by black dotted line, females by grey dotted line, cases who survived to discharge in green, cases who died in red, and cases still in hospital by thick grey line. **B)** Comparison of male and female outcomes across all ages, using cases restricted to known outcomes (p value calculated by $\chi 2$ with 1 degree of freedom). **C)** Comparison of male and female outcomes across age deciles (age range 0-106 years, decile boundaries at 39, 50, 56, 61, 67, 73, 77, 82 and 87 years). The p value was <0.001 calculated by logistic regression using absolute age (years), or age deciles as illustrated.

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| | All COVID-19 CASES | | | | Males | | | Females | | | | | *p-values calculated by multivariate linear regression* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | ***Sex*** | ***Age*** | |
| | Normal range | **Total** | **Median** | **IQR** | **Total** | **Median** | **IQR** | **Total** | **Median** | **IQR** | ***P* value for sex** | | *Age-adjusted* | *Crude* | *Sex-adjusted* |
| Age, year | | 923 | 67 | 53-80 | 569 | 65 | 54-78 | 354 | **72** | 52-82 | 0.037 | | /- | /- | /- |
| Temperature, °C | 36.6-38.1 | 672 | 36.9 | 36.3-37.4 | 417 | **36.9** | 36.3-37.5 | 275 | 36.8 | 36.2-37.4 | 0.13 | | 0.31 | <0.001 | 0.13 |
| Respiratory rate, $min^{-1}$ | 14-20 | 878 | 24 | 20-28 | 556 | **24** | 20-30 | 322 | 22 | 18-28 | 0.0001 | | 0.001 | 0.001 | 0.002 |
| Diastolic BP, mmHg | 60-90 | 871 | 77 | 66-86 | 555 | **78** | 68-87 | 316 | 74 | 64-84 | 0.0008 | | 0.017 | 0.016 | 0.032 |
| Heart rate, $min^{-1}$ | 60-100 | 878 | 96 | 82-110 | 556 | **96** | 83.5-111 | 322 | 94 | 80-109 | 0.051 | | 0.195 | <0.001 | <0.001 |
| $SpO_2$, % | Age* | 879 | 95 | 92-98 | 556 | **95** | 92-98 | 323 | 96 | 93-98 | 0.012 | | 0.007 | 0.046 | 0.026 |
| C-reactive protein, mg/L | <5 | 887 | 102.1 | 44.9-179 | 555 | **122.9** | 54.9-205.8 | 332 | 75.25 | 31.8-153.2 | **<0.0001** | | <0.001 | 0.17 | 0.11 |
| D-dimer, ng/mL | <500 | 629 | 1920 | 1070-3802 | 417 | **2020** | 1100-4584 | 212 | 1710 | 989-3369 | 0.30 | | 0.122 | 0.28 | 0.122 |
| Ferritin, µg/L | 20-300 | 658 | 566 | 261-1208 | 420 | **725.5** | 390.5-1411 | 238 | 319.5 | 156-762 | **<0.0001** | | 0.025 | 0.65 | 0.49 |
| Creatinine, µmol/L | 60-125 | 822 | 86 | 69-117 | 513 | **94** | 76-126 | 309 | 71 | 58-96 | **<0.0001** | | <0.001 | <0.001 | <0.001 |
| Procalcitonin, µg/L | <1 | 59 | 0.16 | 0.08-0.64 | 38 | **0.275** | 0.09-0.87 | 21 | 0.1 | 0.08-0.47 | 0.15 | | 0.16 | 0.24 | 0.22 |

**Supplementary Table 1: Comparison of dashboard indices on admission, by sex.**
Bold face indicates the more abnormal variable between the sexes, and for *p*-values, those meeting p<0.0001. Females were older, there was no difference in the percentage of males and females by ethnicity, but all dashboard variables tended to be more abnormal in males, particularly CRP (illustrated in main manuscript *Figure 3*), ferritin, creatinine (*p*-values <0.0001); respiratory rate and diastolic blood pressure (p<0.0001). BP, blood pressure, $SpO_2$, oxygen saturation, IQR, interquartile range. P values for sex calculated by Mann Whitney rank sum. * Age dependent, $SpO_2$ normal low 92% (for older patients), normal high 98.5%. The final columns indicates the *p*-values following exploratory multivariate regression analyses (regression coefficients not indicated for clarity).

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**Supplementary Figure 3. Comparison of key dashboard indices on admission by age and sex.** Individual values are plotted for males (green triangles/ khaki regression line), and females (blue circles/blue regression line). Superimposed for completed encounters, are whether the patient was discharged alive (green pipe), or died (red square). **A)** Admission CRP values including 95% confidence intervals [CI] for males and females, and illustrating higher values in males that becomes less pronounced at older age as female ferritin tends to increase. **C)** Natural log-transformed D-dimer. Note there was again no relationship with age for females (95% CI not shown for clarity), and that D-dimer increased with age in males, though the regression coefficient for ln (D-dimer) predicted an averaged increase in the order of only 10ng/mL per decade which we considered unlikely to have a clinical impact given the values presented in Supplementary Table 1.