

**COVID-19 associated hyperinflammation (COV-HI):
a longitudinal cohort study**

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Abstract (298 words)

Background

A subset of patients with severe COVID-19 infection develop a hyperinflammatory syndrome (COV-HI), which may contribute to morbidity and mortality. This study explores the phenotype of COV-HI, and associations with escalation of respiratory support and survival.

Methods

In this retrospective, cohort study 269 consecutive adult inpatients were enrolled at University College London Hospitals and Newcastle upon Tyne Hospitals in the UK, between 1st and 31st March 2020, during the first wave of COVID-19 community-acquired infection. Demographic data, laboratory tests and clinical status were recorded from the day of admission until death or discharge with minimum follow-up of 28 days. Initial and repeated measures of hyperinflammation were evaluated in relation to next day risk of maximal level of respiratory support and death using a multilevel logistic regression model.

Findings

Clear differences were observed between the CRP (C-reactive protein) trajectories of patients with severe disease (defined by death or requiring ventilatory support) compared to those with a milder disease course. An operational definition of COV-HI (CRP >150mg/L or CRP doubling in 24 hours from >50mg/L or ferritin >1500µg/L) was associated with poor outcome, as defined as the need for respiratory support or death. Of the whole cohort, 90 (33%) of patients met the COV-HI criteria at admission. Despite being younger, and having fewer comorbidities, 40% of these patients died compared with 26% of the non-COV-HI patients. In patients who were eligible for full respiratory support, 37% met the definition for COV-HI at presentation, and 75% met COV-HI criteria by the day of intervention.

Interpretation

Associations between elevated inflammatory markers, escalation of respiratory support, and survival in people with COVID-19 infection are consistent with the existence of a high-risk (COV-HI) inflammatory phenotype. COV-HI was often manifest on admission, followed a distinct trajectory, and may be useful to stratify patient groups in trial design.

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Research in context (279 words)

Evidence before this study

We searched PubMed on 23rd May 2020 for studies published in English using search terms ("novel coronavirus" OR "2019 novel coronavirus" OR "2019-nCoV" OR "COVID-19") AND ("hyperinflammation" OR "cytokine storm" OR "cytokine release" OR "HLH"). Four papers described differences in CRP and other inflammatory laboratory parameters in relation to outcome, one including longitudinal monitoring. A more recent study compared longitudinal changes in ferritin, D-dimer, and other tests between patients who survived or died, while a prospective cohort study of critically ill patients found an independent association between biomarkers of inflammation and in-hospital mortality. Numerous commentaries and review articles discussed hyperinflammatory syndromes in COVID-19 and the therapeutic potential of immunomodulation such as interleukin-6 blockade. Reservations have been expressed concerning appropriate selection criteria for intervention and potential risks of compromising anti-viral immunity and risk of secondary bacterial infection.

Added value of this study

A hyperinflammatory phenotype (COV-HI) defined by measurement of readily available routine clinical parameters was observed among a proportion of people admitted with COVID-19 infection. In the total cohort, meeting the COV-HI criteria on admission was associated with a higher mortality (40% versus 26%). Amongst patients eligible for full escalation of treatment, 37% fulfilled COV-HI criteria at admission, and 50% of these patients required escalation in respiratory support by 3 days. In total, 75% of eligible patients met the criteria by the day they needed respiratory support.

Implications of all the available evidence

COV-HI is associated with adverse outcomes. A more detailed definition is achievable and desirable through further research and validation to develop a prediction model. This will

facilitate targeted trials of intervention with immunomodulation and identify patients likely to require escalation of care.

(3780 words)

Introduction

COVID-19, caused by infection with SARS-CoV-2, is associated with severe respiratory compromise and mortality of up to 21% in hospitalized patients¹. Outcome is especially poor in patients requiring advanced respiratory support^{2,3} with recent UK data reporting a mortality rate of 54.4% in this group (<https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports>). Clinical deterioration often occurs 7-10 days after the onset of symptoms, in association with declining viral titres⁴. This suggests that pathology is driven by inflammation rather than direct viral injury and inflammatory markers are often significantly elevated in patients with severe COVID-19 infection^{3,5,6}. Uncontrolled, self-perpetuating and tissue-damaging inflammatory activity (hyperinflammation) has also been described in the pathogenesis of previous coronavirus infections⁷.

The term cytokine storm syndrome encompasses a number of overlapping, hyperinflammatory clinical syndromes. These include hemophagocytic lymphohistiocytosis (HLH), the macrophage activation-like syndrome (MALS) of sepsis, macrophage activation syndrome (MAS) and cytokine release syndrome^{8,9}. The reported sensitivity of these syndromes to cytokine-directed therapy has fuelled intense speculation¹⁰⁻¹² that outcome in a proportion of people with severe COVID-19 may also be ameliorated by immunomodulation of a hyperinflammatory response¹³⁻¹⁶.

Many trials using immunomodulatory/immunosuppressive drugs in COVID infection are now underway. Immunosuppression during infection incurs risk and the risk/benefit balance should be carefully accounted for in trial design. Previous experience from trials in sepsis for example demonstrate that lack of stratification may obscure positive results¹⁷. Therefore, improved understanding of hyperinflammation in COVID-19 is needed to inform trial design and ensure robust clinical research^{18,19}.

Diagnostic criteria for hyperinflammation are incompletely defined, especially in the context of COVID-19. Early studies of patients with COVID established independent associations between biomarkers of inflammation (such as C-reactive protein (CRP), IL-6 and ferritin) and severe disease (requiring respiratory support or resulting in death)^{2,3,5,20}. Subsequent prospective studies have confirmed this association in large cohorts of people admitted to hospital with COVID infection^{21,22} and proposed that high levels of inflammatory biomarkers (CRP>200 and D-Dimer> 2500) are more strongly associated with critical illness than age or comorbidity²¹. This evidence forms the basis for initial predictive models and decision aids for those at risk of poor outcome²³.

We agreed an operational definition of COVID-19 associated hyperinflammation (hereafter referred to as COV-HI) based on emerging evidence from the literature,^{3,12,15,18,24} from clinical observation and from extensive discussion with members of a UK group of specialists in hyperinflammation (the HLH Across Specialty Collaboration, HASC). Given that viruses are well known to cause HLH in a subgroup of patients, we also proposed to investigate the usefulness of the HLH diagnostic tool, the H-score, in the context of SARS-CoV-2 infection²⁵.

In this study, we aimed to test and assess hyperinflammation in COVID-19 by evaluating longitudinal associations between hyperinflammatory biomarkers, disease severity and survival. We applied proposed COV-HI criteria and the H-Score to our cohort. We sought to determine whether it was possible to identify patients with hyperinflammation on admission, or who developed hyperinflammation during their admission, and how hyperinflammation related to any deterioration in clinical status. We did not seek to develop an outcome prediction model based on hyperinflammation from this initial cohort as sample size calculations indicated 500-1000 patients would be needed.

Methods

Approval: The study COVID-19 hyperinflammation syndrome (COV-HI): protocol for a rapidly executed cohort study (REC ref 20/YH/0138 and IRAS ID 282626) received ethical approval from Yorkshire & The Humber - Leeds West Research Ethics Committee and approval by the Health Research Authority and Health and Care Research Wales (HCRW) on 15th April 2020. The study was registered at the Clinical Trials Gateway (NCT04385069), NIHR portfolio (ID45542) and HRA website (<https://www.hra.nhs.uk/covid-19-research/approved-covid-19-research/>).

Study population, eligibility and follow up: Consecutive patients ≥ 18 years of age with a positive PCR for SARS-CoV-2 admitted to University College London Hospitals (UCLH) or Newcastle Upon Tyne Hospitals (NUTH) for treatment of community-acquired COVID-19-related illness as defined by the WHO (WHO Department of Communications 2020) from 1st March to 31st March 2020 were considered for inclusion. The only exclusion criteria was the use of home NIV (non-invasive ventilation). Patients were followed until death, or hospital discharge or up to 28 days from admission.

Laboratory tests: SARS-CoV-2 was detected in nasal and throat swabs using RT-PCR²⁶. Routine blood tests that we recorded were those carried out in the usual clinical care of each patient and, where available, included full blood count, coagulation profile, renal and liver function, C-reactive protein (CRP), ferritin, D-dimer, lactate dehydrogenase, and troponin. All available patient data were collected daily from both sites until escalation of respiratory support or death, then continued daily at one site (London); and at least twice weekly at the other site, (Newcastle).

Clinical data and definitions:

Co-morbidity was recorded using the Charlson Comorbidity Index²⁷ from the patient record and categorised as none, single or multiple/severe comorbidities. Patients were designated as 'not for escalation' if any of the following statements were found in medical records within 24 hours of admission: a community DNA-CPR (do not attempt cardio-pulmonary resuscitation) order or a hospital treatment escalation plan of DNA-CPR; for ward-based care only; not for NIV (non-invasive ventilation); not for mechanical ventilation. In most cases these statements were highly overlapping, with the exception of a small number of patients who received NIV in a ward-based setting or who received escalated support but had advance directives not for CPR (both included in the subgroup "for escalation"). A 24-hour limit was chosen to identify those initially too frail or sick for escalation, and to avoid including decisions made later in the disease course after initial support and interventions had failed.

Respiratory support was categorised as: 'supplemental oxygen' when delivered by nasal cannulae or face mask; NIV when non-invasive pressure support was supplied by face mask; and 'intubation' when ventilation was delivered by endo-tracheal or tracheostomy tube. Escalation of respiratory support was defined as a transition from supplemental oxygen to either NIV or intubation.

We derived an operational definition of hyperinflammation from the literature on sHLH in sepsis, the H-score and the emerging reports that indicators of hyperinflammation including CRP and ferritin were significantly associated with poor outcome in COVID-19^{3,12,15,18,24}.

'Hyperinflammation' as a categorical variable was defined as any of the following: CRP >150mg/L; CRP doubling in 24 hours from >50mg/L; ferritin >1500µg/L. These cut-offs were agreed from the literature review^{3,12,15,18,24}, clinical observation and from extensive discussion with members of a UK group of specialists in hyperinflammation (the HLH Across Specialty Collaboration, HASC). including a subset of the authors of this work (RT, JJM, MC, PM, BG, MN, MB, MS).

From the clinically available information collected longitudinally during the study we calculated the H-score as defined according to Fardet *et al.*²⁵ but modified this to omit assessment of organomegaly and bone marrow cytology (difficult to ascertain in patients with COVID-19). Thus the new possible total score was 264, with the median score suggestive of sHLH used as cut-off of 132; following the model from Kyriazopoulou *et al.*²⁸

Data management: Demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records using a bespoke web-based REDCap database²⁹ developed by TD, BCL and MC at the Newcastle Joint Research Office. The data dictionary is available on request. Data were entered by members of the research or clinical care teams using a protocol jointly developed by the two centres. Anonymised data were downloaded from REDCap for statistical analysis by CC and JW. Outliers (implausible values) for variables and dates were identified and clarified with the data entry teams.

Statistical methods: Continuous and categorical variables are reported as median (IQR) and n (%), respectively. Escalation-free survival was estimated using Kaplan Meier curves with death or escalation to NIV or intubation as events and surviving patients censored at day 28. Scatter plots of daily results were plotted against time for longitudinal analysis. Missing data in baseline categorical values were included as a separate category. Missing daily values were imputed only for the repeated measures multivariate model below, by carrying forward results from the previous day. This reflects the reality of the information that would have been available to a clinician at any given time point. If more than one result was recorded on a given day, the most deviated result was selected at data entry. The moving average for each variable was overlaid using a LOESS curve showing 95% confidence intervals for the estimated daily mean. Depending on the analysis, time was centred on the date of first symptoms or the date of escalation, as described in figure legends. The other parameters in the LOESS models used

default settings with a polynomial of degree 2, interpolation on a cell size of 0.2, and a Gaussian (fitted least squares) kernel.

To interrogate factors associated with escalation of respiratory support or in-hospital mortality, we fitted a Cox proportional hazards model with time varying covariates for the repeated laboratory results with time measured from day of symptom onset. A forward step-wise model building approach was used from an initial model including three a priori variables: hyperinflammation as defined above; age and sex. Additional variables: lymphocyte count, comorbidity (Charlson index); steroids or immunosuppressants on admission; were selected for inclusion if they improved model fit as measured by a reduction in the Akaike Information Criterion. Where appropriate we log transformed variables to fit in the model. Age on hospital admission was included as a linear variable, but was also tested for a departure from this linear trend.

Sample size:

We did not plan any predictive modelling in this study as sample size calculations indicated the need for between 500 and 1000 patients. Instead we pragmatically decided to analyse the first tranche of data when it was complete and 28 days of follow up had occurred after the last patient's entry to the cohort.

Results

Patient demographics and baseline characteristics of COVID-19 patients stratified by escalation of care

Data were collected on 269 consecutive patients ≥ 18 years of age who presented to UCLH and NUTH between 1st and 31st March 2020 with a positive swab for SARS-CoV-2 PCR and who were followed up until death or discharge for a maximum of 28 days. Baseline demographics of the cohort are summarised in [Appendix page 1](#). The median age was 71 years, 62% were male and 26% were of Black, Asian or Minority Ethnic backgrounds. Except for ethnicity, no significant differences were seen in baseline characteristics between patients recruited in the two hospitals. These included proportions deemed not fit for escalation, rate of escalation to NIV or intubation, and overall mortality. Date of symptom onset preceding admission was recorded in almost all records; in 15 (6%) cases this was missing and the date of admission was used as the date of onset instead.

Treatment escalation plans indicating that patients were not for escalation of care above supplemental oxygen were recorded in 91 patients (33.8%). Of these, 50 (54.9%) patients survived until the end of the 28-day follow up. ([Appendix page 2](#)). On average, these patients were older and had higher Charlson scores than those eligible for escalation of respiratory support ([Appendix page 3](#)). Of those eligible for escalation, 137 (77.0%) survived; however only 56.7% of patients needing non-invasive or invasive ventilation remained alive at the end of follow up compared to 97.7% who did not require escalation of care ([Appendix page 2](#)).

Baseline laboratory results of the cohort are summarized in [Appendix page 4](#). In patients who were eligible for escalation and subsequently died, lymphocyte count was lower and CRP higher, compared with those who were escalated and survived. Missing data were low for routine blood tests. Of inflammatory markers, only CRP was recorded reliably (90% of patients)

whereas ferritin, D-dimer, LDH and other measures were reported on $\leq 50\%$ of patients at admission ([Appendix page 4](#)).

Patients eligible for escalation who did not survive had a high CRP trajectory

To synchronise the course of COVID-19 in patients presenting at different stages in their illness we plotted mean daily blood test values versus elapsed time since the onset of symptoms using the onset of symptoms as a datum ([Figure 1](#)). As expected, a higher level of inspired oxygen (FiO_2) was required by patients who required NIV or intubation. Divergent CRP trajectories were apparent between patients not for escalation or receiving oxygen only, those escalated to NIV, and those who required mechanical ventilation. People who required mechanical ventilation showed a higher mean CRP, peaking at 247mg/L (day 13), compared to a peak of 153mg/L (day 10) in the group requiring NIV only. The bar chart of daily status and [Appendix page 6](#) show that the early trends in CRP were mainly related to the mean values of patients, with the possibility of survivor bias from loss to discharge and death mainly arising at the time of the peak values.

Levels of creatinine, neutrophils and lymphocytes also varied between one or more subgroups, with lower lymphocyte counts being seen in the groups with worse clinical outcomes, and highest neutrophil counts seen late in the disease process in patients requiring mechanical ventilation.

Among the 89 patients whose care was escalated, the daily means of sequential tests were compared in survivors and non-survivors indexing their clinical course at the point of escalation ([Figure 2](#)). Although this showed similar trajectories of CRP, neutrophils and lymphocytes before the intervention, a delayed, higher peak CRP, and a greater degree of neutrophilia and more marked lymphopenia were observed in patients who eventually died. The most noticeable

changes occurred in the first 5 days before the possibility of bias increased from loss to death and discharge ([Appendix page 6](#)).

Insufficient data were collected to perform an H-score in the majority of patients in this cohort reflecting a lack an awareness of the score and clinical practice in a pandemic. Of the 47 patients who had sufficient data to calculate an H-score, the median was well below the cut-off indicating sHLH in the proposed modified score. ([Appendix page 7](#)).

Hyperinflammation was associated with inferior escalation-free survival – admission data

Admission definition for COV-HI was CRP >150mg/L or ferritin >1500µg/L, as doubling of CRP was not possible with single measures. Of the whole cohort, 90 (33%) of patents met the COV-HI criteria at admission. Despite being younger (66 versus 71 years), and having fewer comorbidities (Charlson Score 1 versus 2), 40% of these patients died compared with 26% of the non-COV-HI patients ([Appendix page 8](#)). The majority of people meeting the criteria for COV-HI on their admission to hospital did so by virtue of having a CRP>150mg/ml. However 16/90 (18%) met the definition on the basis of ferritin 1500µg/L or greater ([Appendix page 9](#)).

Of the 91 patients in the whole cohort who were not eligible for escalation, 25 met the COV-HI (27%) criteria on the day of admission and of these 17 died by 28 days (68%) ([Table 1](#)).

Looking at patients with no ceiling of care, escalation-free survival was worse among those with hyperinflammation at admission after adjusting for age, sex and Charlson co-morbidity (likelihood ratio test, $p < 0.0001$) ([Figure 3A](#)). Admission CRP and ferritin (where recorded) were higher in patients eligible for escalation who did not survive, compared with those who remained alive ([Appendix page 4](#)).

Hyperinflammation was associated with inferior escalation-free survival – longitudinal data

On the day of admission, 65/178 (37%) patients eligible for escalation met the criteria for COV-HI, of whom 19 subsequently died (26%) (**Table 1**). 50% of patients meeting criteria for COV-HI at admission required escalation of respiratory support by 3 days (95% CI 1-4) (**Figure 3A**). In patients without hyperinflammation (i.e. not meeting COV-HI criteria throughout their admission), (95/178), or those with missing data (18/178), the endpoint of escalation to respiratory support was not reached by 28 days (therefore it is not possible to calculate a median escalation-free survival). Furthermore, the association between any increased CRP or ferritin measurement, and the need for next day escalation remained significant (Hazard Ratio 2.2 (1.6 - 2.9) on a daily basis after adjustment for age, sex, and co-morbidity (**Table 2** and **Appendix page 10** for additional adjustments). In the fitted time varying Cox model there was no clear systematic pattern in the residuals for the key predictors, and a fitted line was approximately horizontal, so given the number of data points the proportional hazard assumption was appropriate (Schoenfeld residual plots and log(-log) plots are shown in **Appendix page 12**). Within this model there was no evidence to support a direct association of escalation with site ($p = 0.95$) and no evidence for an interaction by site of the association of COV-HI with escalation ($p=0.8$). 75% of patients who were eligible for escalation met the criteria for COV-HI by the time they needed respiratory support (**Figure 3B**).

Discussion

By longitudinal observation of a cohort of patients admitted with COVID-19 to two hospitals in the UK, this study supports the concept that a proportion of patients have a hyperinflammatory phenotype (COV-HI) and that meeting the criteria for this phenotype is associated with a poor clinical outcome. Striking differences were observed between the CRP trajectories of patients whose disease was severe, as defined by death or requiring ventilatory support, and those whose disease followed a milder course.

In patients who were eligible for escalation of care, we found an independent association between patients meeting COV-HI criteria and their need for ventilatory support or death, once we had accounted for age, sex and comorbidity. Furthermore, by applying criteria for COV-HI to this patient cohort, we showed that 37% could be identified at presentation, and 75% of patients who went on to need ventilatory support met these criteria before the point for escalation was reached. Our work builds on, and contributes to, the evidence enabling risk prediction models for people with COVID infection.

In patients who had a ceiling of care determined at admission and were therefore not for escalation to respiratory support, meeting COV-HI criteria was associated with a mortality of 68%. In those patients for whom respiratory support was an option mortality was 29%. The cause of the higher mortality in the former group cannot be extrapolated from our data, but may relate to confounders such as frailty/multi-morbidity, or suggest that respiratory support can improve outcome in patients with a hyperinflammatory response to COVID-19.

The thresholds we used to define COV-HI (CRP >150mg/L or CRP doubling in 24 hours from >50mg/L or ferritin >1500µg/L) were in line with, or more stringent than, reported elsewhere

^{3,15,18,24}. The use of CRP and ferritin, both readily available and inexpensive, were routinely and reliably collected in the majority of patients; by contrast in this real-world study, some key data required for calculating an H-score were only available for a minority of patients. We therefore could not draw firm conclusions about the role of the H-score as so few patients had the required clinical data to complete the score. In the small minority where an H-Score could be calculated, the result did not suggest a high probability of sHLH.

There is an emerging body of evidence that hyperinflammation in COVID infection is distinct ³⁰ from other recognised hyperinflammatory states, and this is part of a wider debate regarding the definition and aetiopathogenesis of cytokine storm syndromes. CRP appears to be an important marker of poor outcome in COVID-19 infection in particular and the majority of patients who met the COV-HI criteria in this study did so on the basis of the CRP criteria. The role that CRP plays in predicting outcome in COVID-19 is in contrast to studies in other conditions leading to pneumonia/ARDS in the literature where CRP is not found to be prognostically useful in predicting deterioration ^{31,32}.

Elevated ferritin has been used in risk models for the hyperinflammatory subtype of sepsis, (so called macrophage activation like syndrome, or MALS), defined as a ferritin of $>4420\text{ng/ml}$ ²⁸. Although we have shown median ferritin levels in this cohort of people with COVID-19 infection were significantly lower than those in MALS, an on-going study with a larger cohort will hope to address the question of whether there are subtypes of hyperinflammatory disease caused by SARS-CoV-2 infection defined by different biomarker thresholds. Previous work in sepsis and ARDS³³ may help inform that analysis.

The highly elevated CRP results in our study raise the question of superadded bacterial infection, but a recent review of the literature supports our clinical experience that very little bacterial (or fungal) infection was seen³⁴. We also demonstrated a late spike in CRP associated with raised neutrophils in the group in our study requiring ventilation which may represent ventilator associated pneumonia. This potential phenomenon would not affect the validity of our proposed COV-HI definition because in our methodology this was applied before escalation to respiratory support.

In contrast to many recent studies, which rely on single data points, we have been able to estimate the association between longitudinal, repeated measurements of laboratory markers and clinical outcome. The main limitation of this dataset is that 'last value carried forward' was used in our modelling, which is a known source of potential bias. This was the only option available to us for the purposes of modelling risk of escalation (to be able to include the longitudinal repeated measurements) and partly reflects the real-world situation when a doctor is assessing a patient clinically. Of note, we had complete follow up until 28 days post-admission including out of hospital deaths. This is a longer and more complete follow up than many recent reports³⁵.

There is an emerging literature which supports our findings that inflammatory markers are strongly associated with critical illness and mortality²¹ in people with COVID-19 infection and suggests that clinicians should measure such markers routinely. Such emerging evidence also mandates further study to inform the understanding of inflammation and hyperinflammation in COVID-19. While some prognostic models for COVID-19 have been published, either in preprint form or fully, all those considered in a recent systematic review and meta-analysis were found to be at high risk of bias³⁵. We have not attempted to create a prognostic score using our data; instead we have simply estimated the association between hyperinflammation and outcome.

This study was not appropriately powered to examine thresholds via a derivation and validation approach, or to define a risk prediction model. However, using simple biomarkers associated with hyperinflammation (CRP and ferritin), we have identified a potential clinical phenotype (COV-HI) associated with poor outcome in severe COVID-19 infection.

In conclusion, we have shown there is an association between readily available and commonly tested inflammatory biomarkers, the need for escalation of respiratory support, and risk of death in people with COVID-19 infection. This supports the concept that a high-risk inflammatory phenotype, COV-HI, exists, and may be associated with higher mortality. The COV-HI criteria need to be validated in a larger cohort but have the potential to be developed as an easy bedside risk tool, and be important in patient stratification for optimal trial design.

Contributors: Design of research study; JJM, RT, MC, JW, CC, ECJ, PM, TL, ADS. Acquiring data; AL, TL, MN, BG, EK, LMG, KEW, GAR, LSR, EMc, HJ'B, MG, HP, EH, AS, CA, ISVDL, KFB, CJAD, ATH, BCL, TR, AL. Analyzing data; CC, JW, JP, JJM, MC, RT. Writing the manuscript; JJM, RT, MC, JW, CC, MN, BG, PM, ECJ. Review of the manuscript; MB, MM, MS, BW. All authors approved the final version.

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Declaration of interest:

We declare no competing interests.

Data sharing statement:

The study protocol and data dictionary are available upon request to the corresponding authors. Requests for access to the individual participant data that underlie the results reported in this article may be made to the Access Committee via the corresponding authors. De-identified data will be available from the date of publication for 36 months, subject to approval of a proposal with a signed data access agreement

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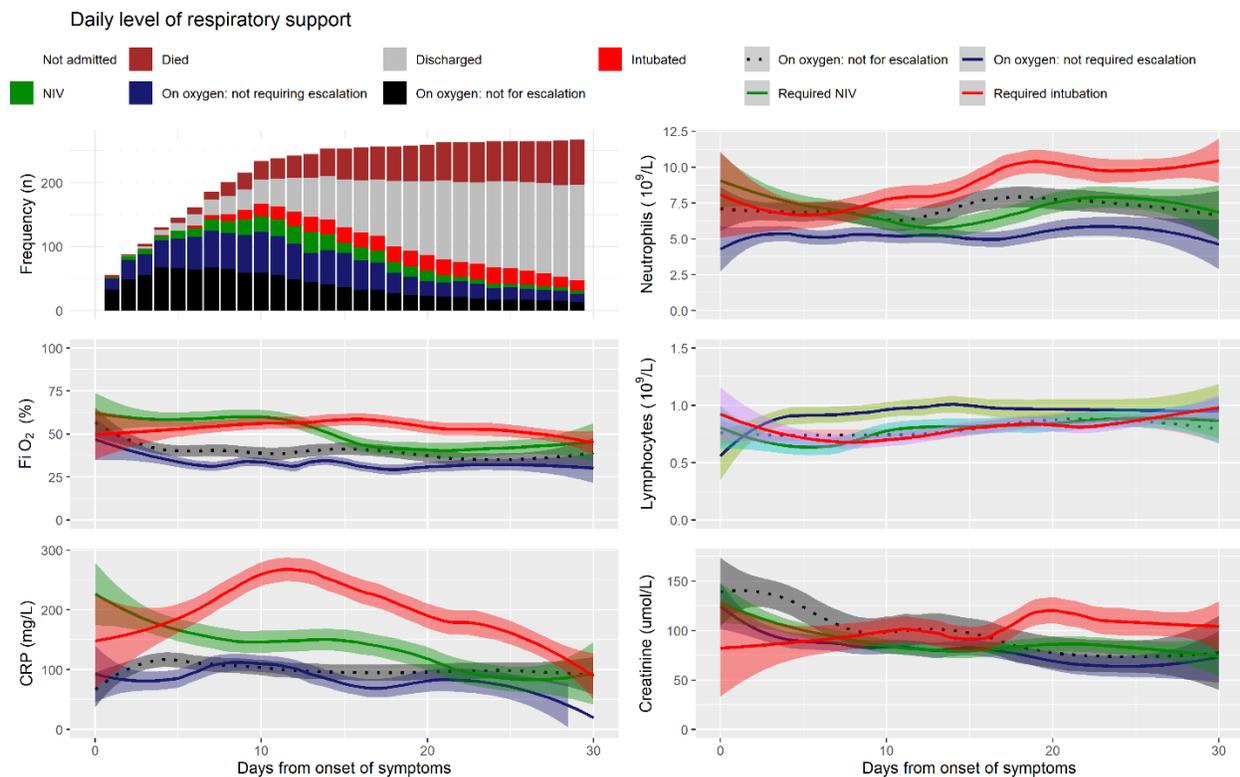


Figure 1: Longitudinal monitoring and escalation of respiratory support. Laboratory results were plotted against time. LOESS curves are shown fitted from mean daily worst values from day of symptom onset for all patients plotted by highest required respiratory support during admission (fitted loess curve showing mean and 95% CI-shaded area, missing data imputed from last value carried forward, the other parameters in the models used default settings with a span = 50%, polynomial of degree 2, interpolation on a cell size of 0.2, and a Gaussian (fitted least squares) kernel). These plots were stratified as follows: Among all patients, longitudinal mean values were stratified by the highest level of respiratory support during the admission. Those with a clinical decision to not attempt cardiopulmonary resuscitation (DNACPR) nor to escalate support beyond ward-based care were included as a separate category. NIV, non-invasive ventilation. Daily numbers in each category are shown and discussed in Appendix page 6.

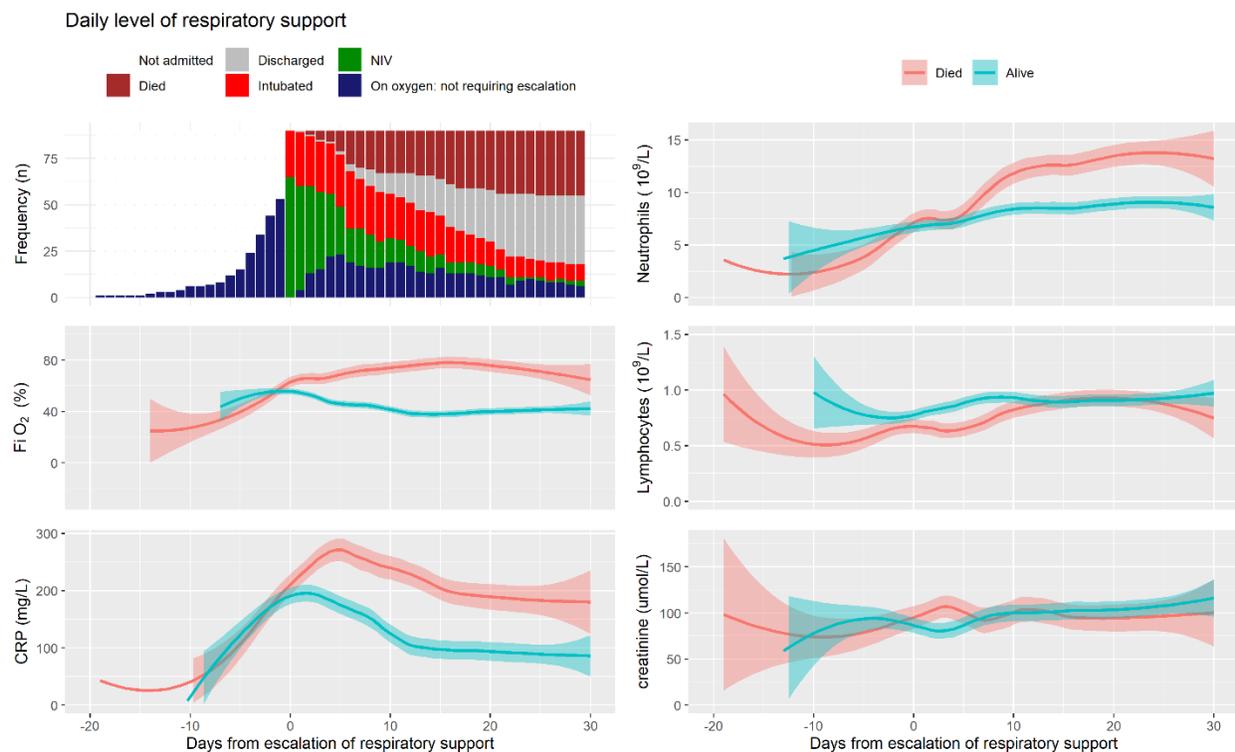
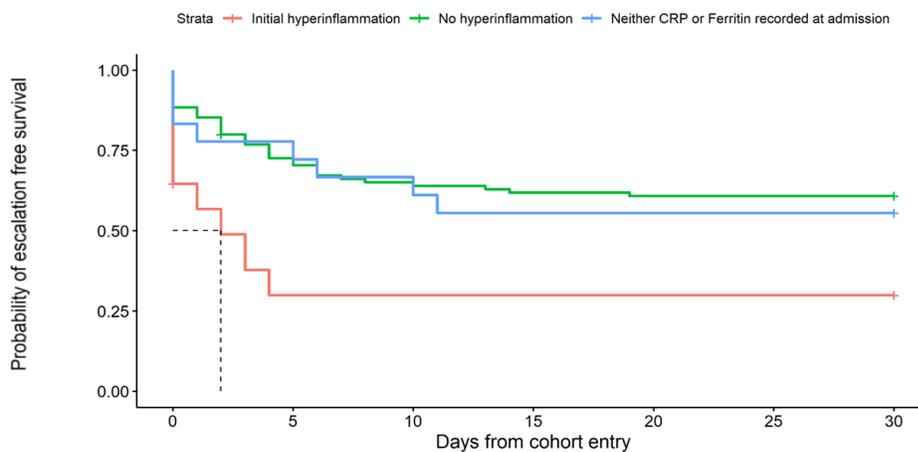


Figure 2: LOESS curves fitted from worst daily mean values stratified by overall survival centred on day of increased respiratory support, only patients eligible for escalation who received increased respiratory support (fitted loess curve with mean and 95% CI-shaded area, the other parameters in the models used default settings with a span = 50%, polynomial of degree 2, interpolation on a cell size of 0.2, and a Gaussian (fitted least squares) missing values imputed by last value carried forward). Daily numbers in each category are shown and discussed in Appendix page 6.

A

Kaplan Meier plot of crude probability of survival without respiratory support (NIV/intubated) by CRP>150 or Ferritin>1500 on cohort entry date
 Median survival shown for hyperinflammation group (Log rank test $p < 0.0001$)



(Only patients eligible for escalation, includes out of hospital death, follow up censored at 30 days)

| | 0 | 5 | 10 | 15 | 20 | 25 | 30 |
|---|----|----|----|----|----|----|----|
| Initial hyperinflammation | 65 | 19 | 19 | 19 | 19 | 19 | 19 |
| No hyperinflammation | 95 | 68 | 61 | 58 | 57 | 57 | 57 |
| Neither CRP or Ferritin recorded at admission | 18 | 14 | 12 | 10 | 10 | 10 | 10 |

B

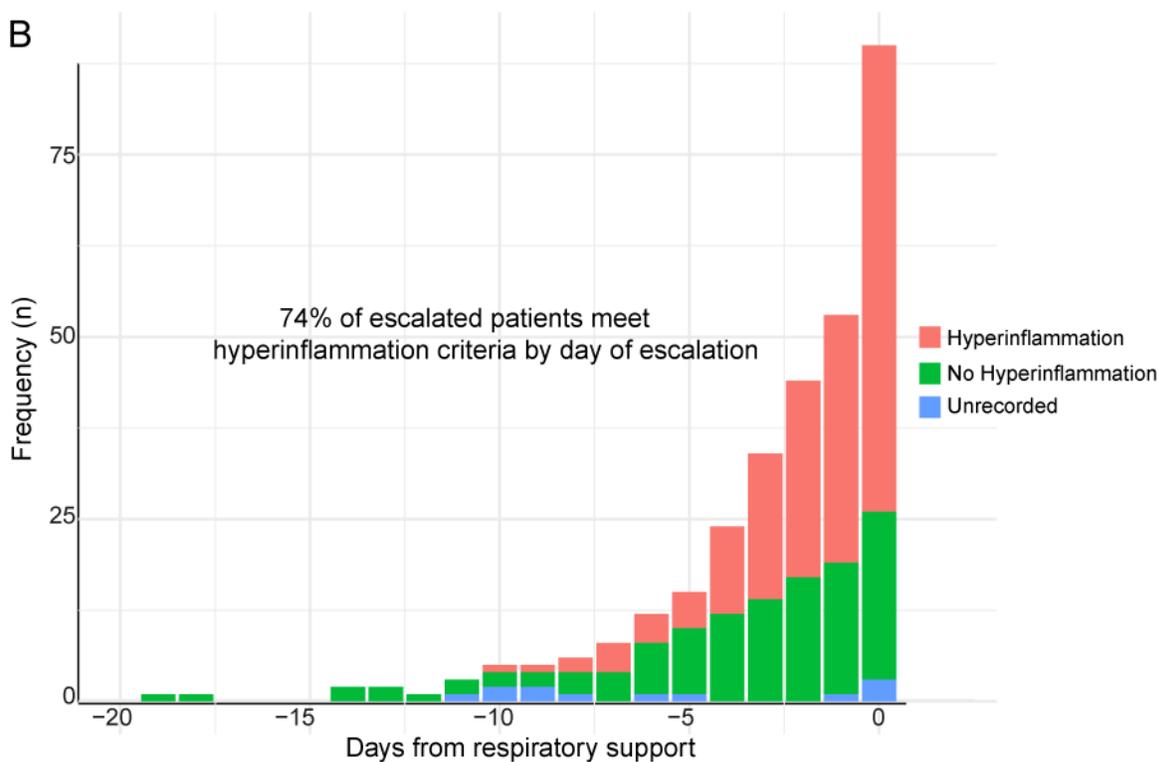


Figure 3: Hyperinflammation was associated with inferior escalation-free survival

(A) The combined outcome of death or need for ventilation support was defined in patients eligible for respiratory support (patients censored ~~at 30 days on end-of-study follow-up~~). Kaplan Meier curves are plotted from the first day of data collection for each patient. These were stratified by whether hyperinflammation criteria were met (CRP >150mg/L or ferritin >1500ug/L) on the day of cohort entry. Patients without CRP or biochemistry recorded on admission day were included as a missing category. The difference in ventilation free survival between those who met or did not meet hyperinflammation criteria was tested with a log rank test. Predicted median survival is indicated by the dashed line for the hyperinflammatory group only.

(B) Daily percentage of patients meeting the criteria for hyperinflammation (CRP >150mg/L or CRP doubling in 24 hours from >50mg/L or ferritin >1500µg/L) from the day of their symptom onset until the day that they needed ventilatory support – 74% of the total population for whom escalation could be considered had met the criteria by the day that they do need support.