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Simple hyperinflammation scores predict mortality in hospitalized patients with COVID-19 and offer a personalized medicine approach to dexamethasone intervention

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ABSTRACT

Background: Dexamethasone is recommended for use in all patients with COVID-19 requiring supplemental oxygen, however, only some patients develop hyperinflammation (COV-HI) potentially influencing their response to corticosteroids. This study tested the ability of criteria defining COV-HI to predict response to dexamethasone.

Methods: A retrospective, multicentre, observational cohort study of 1313-patients with PCR-confirmed COVID-19 during first and second waves of community-acquired infection including 212 patients who received dexamethasone monotherapy. Demographic data, laboratory tests and clinical status were recorded from admission until death or discharge, with minimum 28-days follow-up. Patients were stratified at admission as COV-HI-YES/COV-HI-NO based on three published COV-HI definitions.

Results: Patients with COV-HI shared a biological phenotype of hypoalbuminemia/anemia, and elevated D-dimer/lactate dehydrogenase/alanine transaminase/respiratory rates. Combining these features predicted 28-day mortality and stratified COV-HI-YES from COV-HI-NO more effectively compared to individual markers/demographic features alone. In COV-HI-YES patients, dexamethasone treatment halved mortality-risk (relative risk = 0.50) compared to untreated patients. However, in COV-HI-NO patients mortality-risk was 3.03x higher (CI = 1.3-7.0) in treated versus untreated patients during a 28-day admission period.

Conclusions: We present a framework for a new machine-learning based scoring system for COV-HI combining clinical assessment with laboratory markers for prediction of mortality and targeting glucocorticoids in hospitalized COVID-19 patients.

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Introduction

COVID-19, caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused ~7 million deaths to date [1]. Early in the pandemic, it was observed that some patients experience clinical deterioration 7-10 days after symptom onset coinciding with diminishing viral titres, but high levels of ferritin and inflammatory cytokines. This suggests that rather than direct viral insult, pathology is driven by a host hyperinflammatory response [2]. Identifying and defining these patients is important to understand the pathogenesis, and to target immunomodulatory therapy.

Disease scores based on clinical and biochemical parameters can offer an important means to diagnose conditions that are clinically challenging. An example of this is the HScore, a scoring system for the prototypic hyperinflammatory syndrome hemophagocytic lymphohistiocytosis (HLH). It has been shown, however, that the HScore does not capture all patients who appear clinically to have a COVID-19-associated hyperinflammatory syndrome (COV-HI), nor does it have clinical use in predicting COVID-related mortality [3,4]. Instead, novel criteria to identify COV-HI have been defined [4–7]. Manson et al. [5] classified COV-HI as C reactive protein (CRP) >150 mg/dL, CRP doubling >50 mg/L in 24 h, and/or ferritin >1500 μg/L. A higher proportion of patients with COV-HI on admission died during follow-up (40%) compared with the patients without COV-HI on admission (26%) and meeting this threshold increased risk of next-day escalation to respiratory support or death [5]. Ardern-Jones et al. [7] developed the Hyperinflammation-5 National Early Warning Score-2 (HI5-NEWS2) tool assessing COV-HI, using the parameters CRP, ferritin, neutrophils, lymphocytes and platelets (HI5) combined with a validated measure of generalized medical deterioration (NEWS2). Twenty-eight day mortality in patients with elevated HI5-NEWS2 scores was higher compared to those with low scores (36.0% vs 7.8%; $P < 0.001$) [7]. We chose to focus on these definitions because of their simplicity and availability in most clinical settings.

Reflecting the role of the host response in SARS-CoV-2 infection, immunosuppression is now part of routine treatment of selected patients with COVID-19, with guidelines including the use of corticosteroids [8] and IL-1, IL-6 and JAK antagonists/inhibitors [9–12]. However, immune suppression may be associated with poorer outcomes in some subgroups; thus, there is a need for simple measures of hyperinflammation to aid targeted drug intervention [7,10,13,14]. This study aimed to investigate the role of hyperinflammation in patients with COVID-19 by validating definitions of hyperinflammation in new cohorts, exploring the biological plausibility of these models and then using them to further scrutinize the risks and benefits of dexamethasone treatment.

Methods

Patient cohort

Daily clinical, laboratory features, immunosuppressive medication and level of respiratory support were collected from 3163 patients admitted to UK hospitals with confirmed COVID-19 during the first and second waves (01/03/2020—09/05/2021) of community-acquired infection (Figure 1, Table S1). Participating trusts were University College London Hospitals NHS Foundation Trust (UCLH), University Hospitals Southampton NHS Foundation Trust, Sheffield Teaching Hospitals NHS Foundation Trust, Newcastle upon Tyne Hospitals NHS Foundation Trust and The Royal Wolverhampton NHS Trust. Patients were included if they had a positive respiratory swab PCR result for SARS-CoV-2. Patients were followed up until death, hospital discharge, or for a minimum of 28 days from admission. Data was stored on the REDCap database hosted at the Newcastle Joint Research Office (see Manson et al. [5] for protocol and initial report based on the first 278 recruited patients). All extracted data were anonymized.

Ethical approval was obtained from the Yorkshire & The Humber–Leeds West Research Ethics Committee (reference 20/YH/0138), as well as approval from the Health Research Authority (IRAS ID 282,626) and Health and Care Research Wales on April 15, 2020. The study was registered with the Clinical Trials Gateway (NCT04385069), the National Institute for Health Research portfolio (ID45542), and the Health Research Authority website.

Criteria for patient stratification

COV-HI: Patients were stratified according to different published criteria: Manson et al. (Manson criteria) [5] (see Supplemental Methods); Ardern-Jones et al. (HI5-NEWS2) [7]; and HI4O2 a modified version of HI5-NEWS2 where oxygen saturation replaces ferritin within its definition) (Table S2). Patients with and without hyperinflammation were designated “COV-HI-YES” and “COV-HI-NO,” respectively.

Data processing

Routinely measured clinical and laboratory markers

Measurements of routine markers were taken at baseline—considered as the first day data was available (cut off at day 5) and included respiratory rate, temperature, neutrophils, creatinine, alanine transaminase (ALT), C reactive protein (CRP), ferritin, triglycerides, D-dimer, troponin, urea, urine protein creatinine ratio, lactate dehydrogenase (LDH), chest x-ray infiltrates, interleukin (IL)-6, oxygen (O_2) saturation, hemoglobin, lymphocytes, platelets, albumin, monocytes, fibrinogen, and ejection fraction. Only routine markers collected prior to invasive mechanical ventilation were included in the analysis (see Supplemental Methods).

Data exclusion

To assess the validity of COV-HI criteria, we created a final patient cohort of 1313 patients who had sufficient information on 16 variables (Table S1, Table S3). Routine markers and demographic information with ≥10% missing data were excluded from the initial analysis (Table S3). A secondary patient cohort ($n = 699$) was created from those with more clinical data available to explore additional laboratory markers: D-dimer, LDH and troponin (Table S3). To utilize the full extent of the patient cohort, markers with ≤10% missingness and not used within the COV-HI definitions were imputed using k nearest neighbors (kNN). To create the 1313- and 699-patient cohorts, we excluded patients from the original 3163 patient cohort who received invasive mechanical ventilation on their first day of admission; were treated with antivirals and/or any immunosuppressive medication (including dexamethasone); with missing measurements needed to assign COV-HI status using the various criteria (Figure 1). Patients included within the 699-cohort are derived from the larger 1313-patient cohort.

Finally, a separate dataset of 212 patients was created to explore the effects of dexamethasone treatment using survival analysis. None of the patients treated with dexamethasone included in the survival analysis were recruited prior to the RECOVERY Trial (prior to March 19th 2020). All patients in this cohort met the inclusion criteria (except for immunosuppressive medication i.e., dexamethasone) that was applied to the other two cohorts that were generated (Table S1). Further processing steps shown in Supplementary Methods.

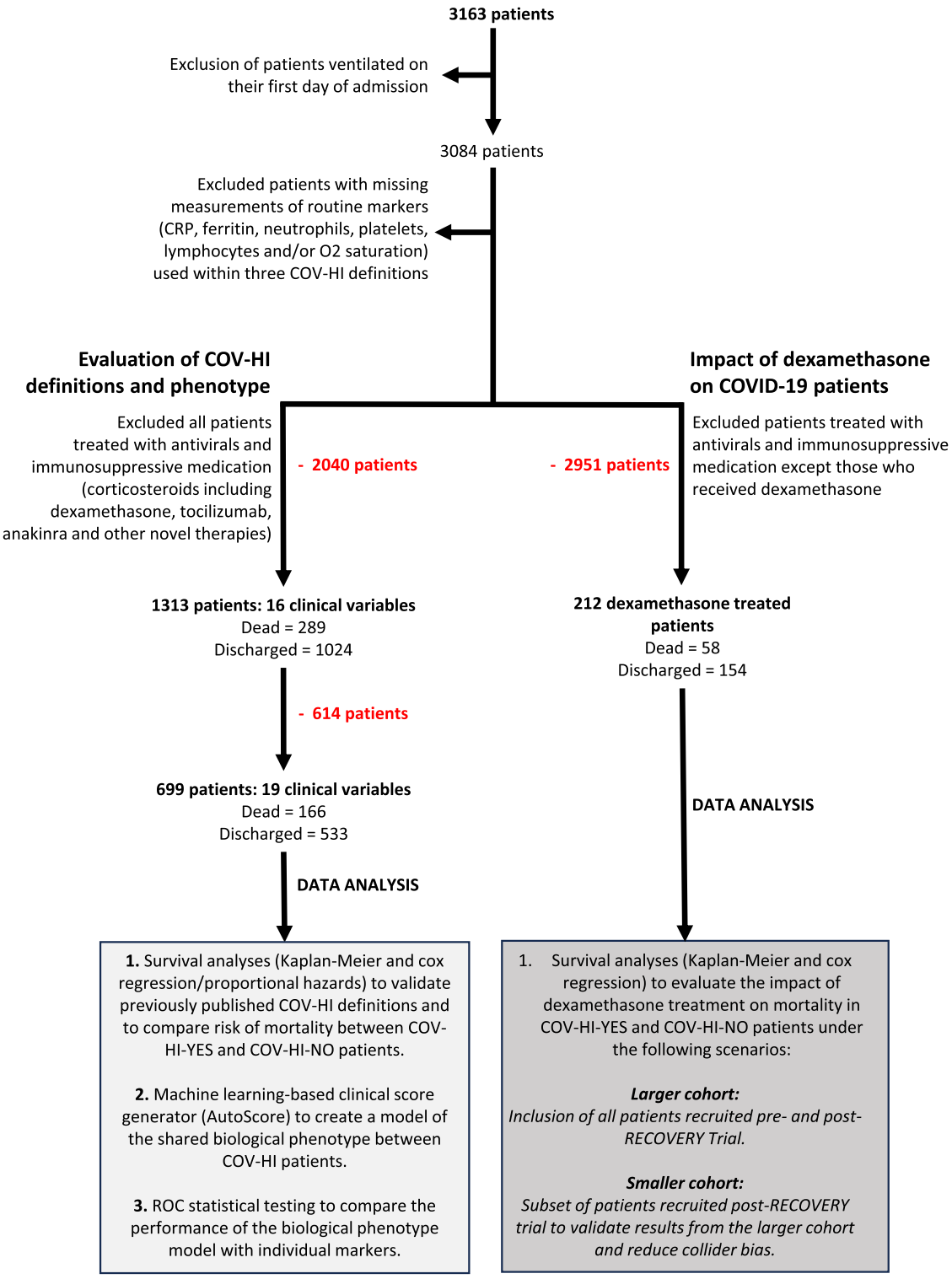

Figure 1. Data processing pipeline. The initial cohort consisted of 3163 patients. After exclusion of patients who were ventilated from admission, patients treated with antivirals and immunosuppressive medication and patients with missing values for CRP, ferritin, neutrophil, lymphocyte, platelet and O_2 saturation measurements (used within the Manson, HI5-NEWS2 and HI4O2 definitions) a reduced cohort of 1313 patients were available in which 16 routine markers with ≤10% missingness could be used within the analysis. A secondary cohort of 699 patients was generated from the original 1313 cohort, where 19 variables (additional markers: D-dimer, troponin and lactate dehydrogenase) with ≤10% missingness could be analyzed. Lastly, a tertiary cohort of 212 patients treated with dexamethasone was created using the same exclusion criteria with a smaller cohort restricted to patients recruited post-RECOVERY trial.

Data analysis

Survival analyses—admission to 28-day mortality

The probability of in-hospital mortality and the ability of the Manson, HI5-NEWS2 and HI4O2 criteria to predict this was estimated using Kaplan-Meier curves (see Supplemental Methods). Surviving patients and patients who did not experience mortality by day-28 were censored. The log-rank test was used to compare the survival distribution between COV-HI-YES and COV-HI-NO patients. The impact of dexamethasone treatment on patients with and without hyperinflammation was analyzed through multivariate Kaplan-Meier curves. Log rank test was used for pairwise comparisons between COV-HI-YES and COV-HI-NO, with and without dexamethasone treatment. For all comparisons, the relative risk (RR) was also calculated (formula: mortality risk in COV-HI-YES/mortality risk in COV-HI-NO; Dex-treated/Dex-Untreated).

To interrogate routine markers most predictive of 28-day mortality, a Cox proportional hazards model with time-varying covariates for the repeated laboratory results, with time measured from date of admission being used. A forward stepwise model-building approach was used (as less than 15 variables were being evaluated) from an initial model including the following a-priori variables: hyperinflammation (defined above for each criterion), age, sex at birth, ethnicity and Charlson comorbidity index. Additional markers (outlined in Table S3) were included if they improved model fit, as measured by a reduction in the Akaike Information Criterion (AIC). For the comparison on COV-HI-NO patients treated with and without dexamethasone, the covariates: age; sex at birth; ethnicity; Charlson comorbidity index and time from admission to dexamethasone treatment initiation was included with the COV-HI definition. The Schoenfeld test was used to validate the proportional hazards assumption for all Cox models. Where appropriate variables were log or square root transformed if this improved model fit i.e., improved a variables compliance with the proportional hazard assumption. R packages used was “Survival,” “Survminer,” “ggsurvfit,” “finalfit,” “MASS” and “leaps.” This methodology was also used by Manson et al. [5] and Ardern-Jones et al. [7]. Lastly, forest plots of hazard ratios (95% confidence intervals) were generated using SRplot [15]. Lastly, to reduce confounding and avoid collider bias as much as possible, we performed a secondary analysis that used the same analytical pipeline (Kaplan-Meier and Cox proportional hazards) and covariates, with the analysis restricted to patients admitted after the publication of the RECOVERY trial [8], when dexamethasone use became standardized based on oxygen requirement.

Machine learning-based clinical score generator (AutoScore)—Biological phenotype

AutoScore consists of 6 modules (variable ranking, variable transformation, score derivation, model selection, score fine-tuning and model evaluation) for developing interpretable point-based scores [16]. Compared to complex models, point-based scores are more explainable and interpretable and can be easily implemented and validated in clinical practice.

A dataset of 446 patients (collectively identified by the Manson, HI5-NEWS2 and HI4O2 as patients with and without hyperinflammation) was randomly divided into nonoverlapping training (70%: 312 patients) and testing (30%: 134 patients) datasets. The training set was used to develop the biological phenotype model, and the testing set was used to evaluate the best score/cut-off. Markers not used within the Manson, HI5-NEWS2 and HI4O2 criteria but collectively identified as features associated with hyperinflammation were used within the analysis. These variables were ranked by random forest (parameter—ntree = 100) and parsimony plot analysis identified that using eight or nine variables within the biological model achieved area under the curves (AUCs) of 0.8020 and 0.8180, respectively. Parsimony plot analysis aims to identify the optimum number of variables to include within a model by balancing model complexity (i.e., number of variables) with model performance (measured by AUC). To build the biological model and produce scores, AutoScore uses multivariable logistic regression. Continuous variables were categorized, and quantiles were used to determine cut-off values of the data points. Initial AutoScore-generated scores were fine-tuned and an optimum threshold for stratifying COV-HI-YES from COV-HI-NO patients was evaluated on the test dataset. Lastly, the biological model was applied to the 699-patient cohort and its ability to predict 28-day mortality was evaluated through Kaplan-Meier analysis.

Results

Manson, HI5-NEWS2 and HI4O2 definitions of COVID-19 hyperinflammation effectively predicted 28-day mortality

Patients were assessed for hyperinflammation associated with COVID-19 according the criteria published by Manson et al. (Manson) [5] and Ardern-Jones et al. (HI5-NEWS2 and HI4O2) [7] using clinical measure established at baseline (day 0 + 5 days) (Table S2). All definitions were able to predict 28-day mortality in the combined cohorts (Manson: $P = 4.42\times10^{-6}$; HI5NEWS2: $P = 3.72\times10^{-5}$; HI4O2, $P = 1.13\times10^{-5}$) and demonstrated that COV-HI-YES (Manson: 52.36%; HI5-NEWS2: 52.53%; HI4O2: 54.68%) patients had a higher risk of mortality compared to COV-HI-NO patients (Manson: 45.26%; HI5-NEWS2: 40.47%; HI4O2: 36.36%) (Table S1, Fig 2A).

The published COV-HI definitions were further validated by dividing the cohort according to recruiting site (Table S1 for cohort demographics). The Manson criterium (developed using UCLH and Newcastle upon Tyne Hospital cohorts) predicted 28-day mortality using data from the Southampton cohort ($P = 3.05\times10^{-3}$) (Fig 2B) and the HI5NEWS2/HI4O2 criteria (developed using the Southampton cohort) were able to predict 28-day mortality ($P = 2.44\times10^{-3}$ and $P = 1.71\times10^{-4}$, respectively) in the combined UCLH/Sheffield/Wolverhampton/Newcastle cohorts (Fig 2C-D).

Lastly, all COV-HI definitions (Manson, $P = 0.0013$; HI5-NEWS2, $P = 0.0032$; HI4O2, $P = 3.02E-05$) were significantly associated with 28-day mortality (Figure S1A-C). Patients who met the HI4O2 criteria had the highest mortality risk (Hazard ratio (HR) = 1.805, 95% CI: 1.368-2.383) compared to patients who met the Manson (HR = 1.553, 95% CI: 1.188-2.030) or HI5-NEWS2 (HR = 1.492, 95% CI: 1.143-1.947) criteria. Other features that were consistently associated with elevated risk of 28-day mortality included older age, increased number of comorbidities and elevated creatinine (Figure S1A-C). Respiratory rate and temperature were not significantly different between COV-HI-YES survivors and nonsurvivors across COV-HI definitions (Table S4), despite being identified in the Cox regression models. Taken together, these results validated that COV-HI criteria applied to baseline/admission values could predict 28-day mortality effectively.

COV-HI patients share a common biological phenotype, irrespective of diagnostic criteria

The characteristics of patients designated as “COV-HI-YES” ($n = 316$) and “COV-HI-NO,” ($n = 550$) respectively by all three definitions for hyperinflammation (Manson [5] HI5-NEWS2 [7] and HI4O2) were as previously reported (Table S2). Patients stratified as COV-HI-YES were more likely to be male, older and have higher Charlson comorbidity indexes. There was also a higher proportion

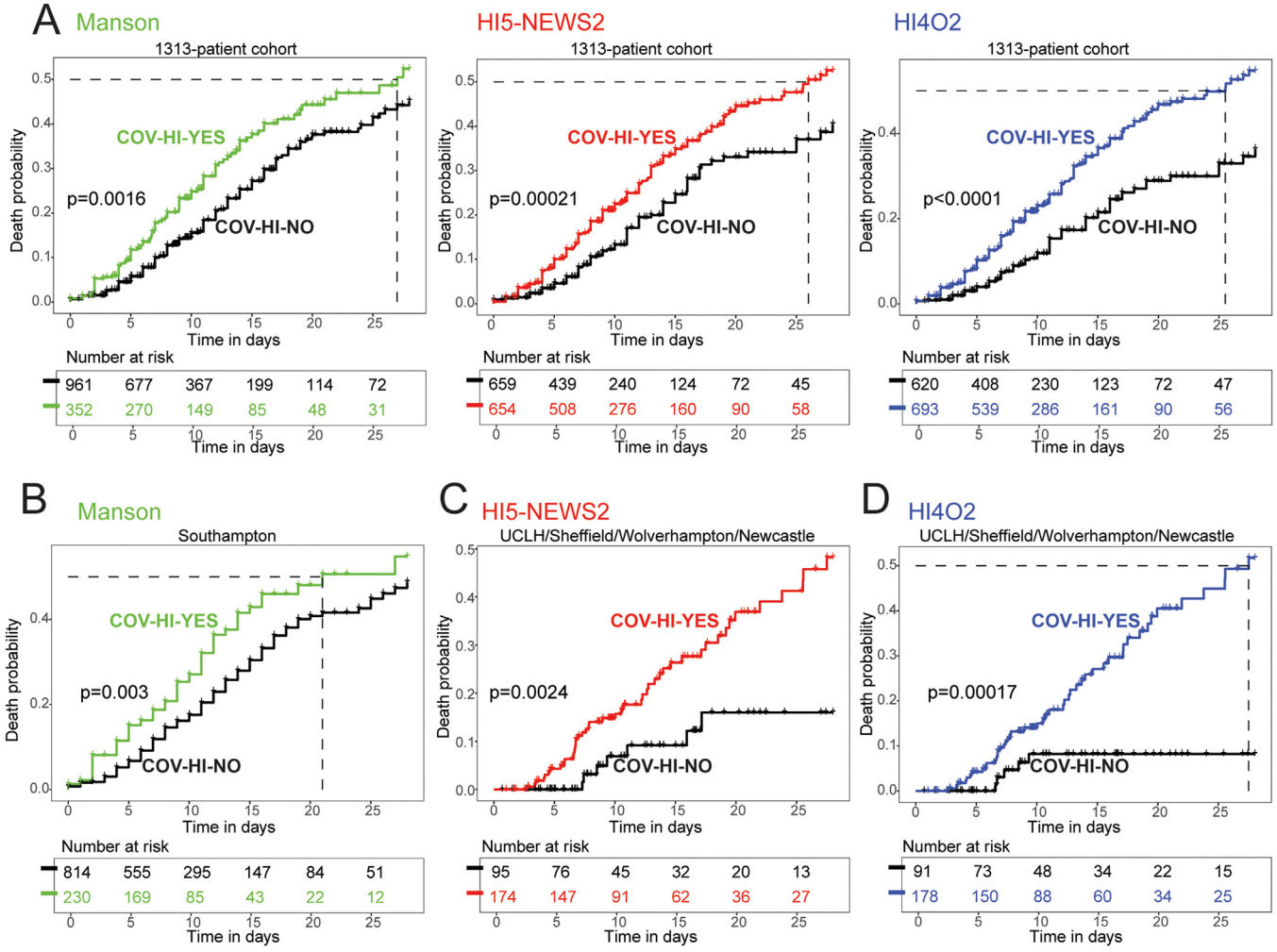

Figure 2. Previously published definitions of COV-HI could effectively predict mortality in larger and independent cohorts. Patients (n = 1313, Table S1) were assessed for COVID-19 associated hyperinflammation according to (A) Manson, HI5-NEWS2 and HI4O2 criteria using routine measures at baseline (Day 0 + 5 days) (Table S2) and Kaplan-Meier analysis was used to evaluate whether these definitions could predict 28-day mortality in a larger cohort. The published COV-HI definitions were validated by dividing the 1313 cohort (Table S1) according to recruitment site. (B) The Manson criterium (developed using UCLH and Newcastle cohorts) was validated using data from the Southampton cohort and the (C) HI5NEWS2 and (D) HI4O2 criteria (developed using the Southampton cohort) were validated using the UCLH/Sheffield/Wolverhampton and Newcastle combined cohorts.

of Black-African/Caribbeans in the COV-HI-YES group compared to the COV-HI-NO (Table S5).

To explore the biological phenotype associated with COV-HI in more detail, all routine markers (excluding the markers within each of the COV-HI definitions) (Table S3) were analyzed using the autoscore ML-based automatic clinical score generator [16]. Low albumin and hemoglobin and elevated D-dimer, LDH, ALT, creatinine, troponin and respiratory rate were the most important additional markers associated with hyperinflammation (Fig 3A-B, Table S6). Optimum cut-off values for patient stratification into COV-HI-YES vs COV-HI-NO were calculated for each of the routine markers identified, and a composite score was generated. COV-HI patients had scores ≥43-points (testing set: AUC-ROC = 0.7994; sensitivity = 0.7500 and specificity = 0.7246) (Fig 3C, Table S6). This eight-variable model (that excludes temperature) predicted 28-day mortality ($P = 4.99\times10^{-3}$) effectively and demonstrated that COV-HI-YES patients had an elevated risk of mortality (54.04%) compared to COV-HI-NO patients (39.73%) (Fig 3D). Lastly, ROC statistical testing demonstrated that the biological phenotype model outperformed individual laboratory, clinical and demographic markers (Table S7).

In summary, this approach showed that patients with COV-HI have global derangements in routinely measured markers beyond those used in COV-HI definitions. Furthermore, this clinical phenotype model had biological plausibility since it could predict 28-day mortality and further supports the proposal that routinely measured features can be combined and used to identify patients likely to develop COV-HI.

The benefits of dexamethasone treatment are specific to patients with COV-HI

The relationship between outcome and the use of dexamethasone was also assessed in patients with and without hyperinflammation who were recruited post-RECOVERY trial (Table S1, Figure 1). Dexamethasone treatment was associated with a significantly reduced risk of death in patients with COV-HI when compared to COV-HI patients who did not receive dexamethasone; and this held true across all three definitions of hyperinflammation (Manson: 22.87% vs 50.49%, RR = 0.45, $P = 1.53\times10^{-3}$; HI5-NEWS2: 31.24% vs 49.99%, 49.99%RR = 0.62, $P = 5.16\times10^{-3}$;

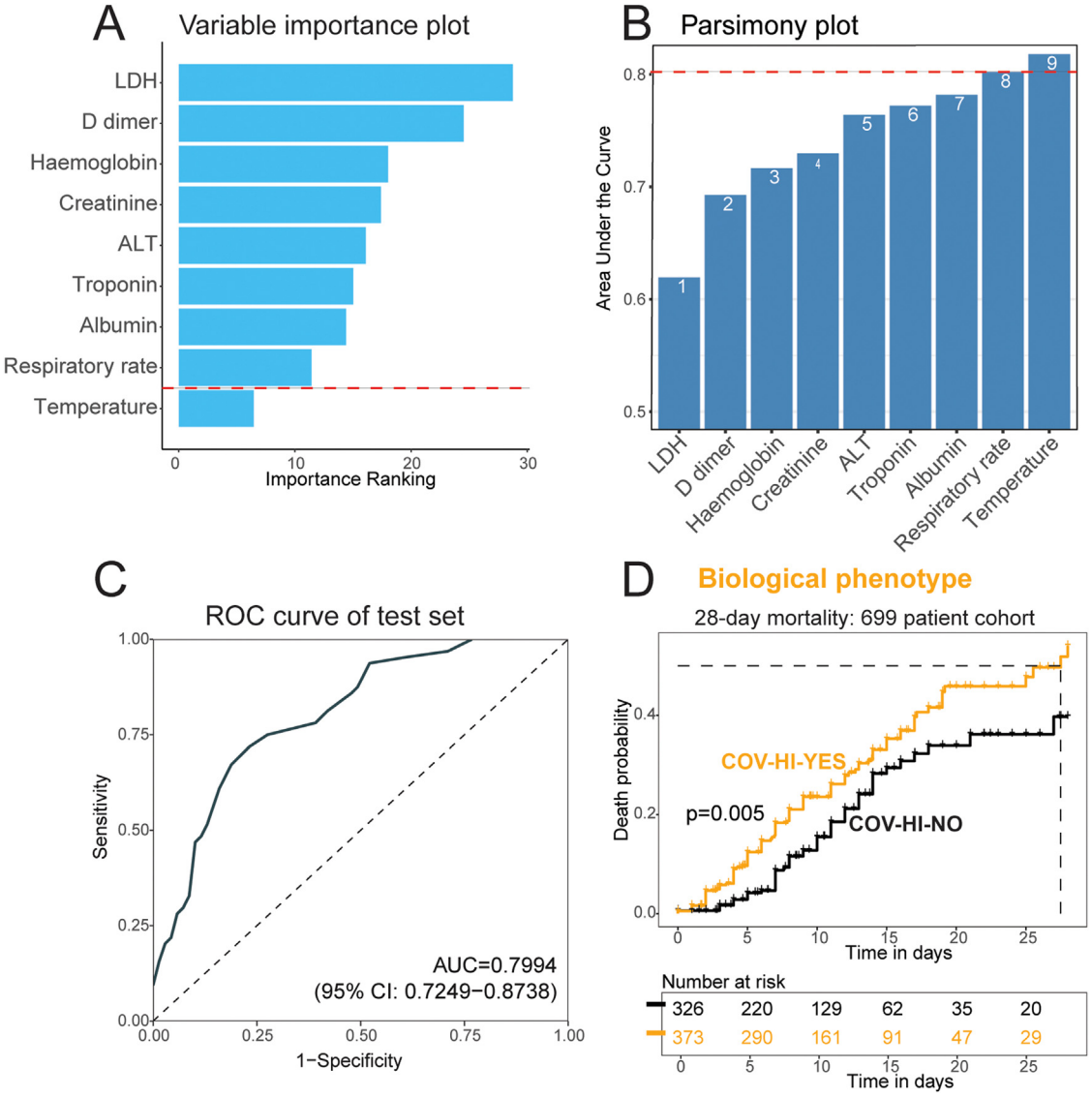

Figure 3. Biological phenotype of COV-HI patients. (A) Variable importance plot showing how important each marker is at stratifying COV-HI-YES and COV-HI-NO patients. (B) Parsimony plot which balances model complexity (no. of features) with accuracy, identified that eight and nine variables could achieve AUCs of 0.8020 and 0.8180, respectively. (C) Performance of the biological phenotype model based on 8-features (built on the train set: 312 patients) on an unseen group of patients (test set: 134 patients). (D) Kaplan-Meier curves evaluating the ability of the eight-variable clinical model (built on baseline values) to predict risk of mortality over a 28-day admission period using the 699-patient cohort. The nine-variable model (including temperature) was not considered as it was unable to predict mortality indicated by red dotted line in (A-B). ALT, Alanine transaminase; LDH, Lactate dehydrogenase.

HI4O2: 25.76% vs51.39%, RR = 0.50, $P = 2.09\times10^{-4}$) (Figs. 4A, S2A-B).

However, in patients stratified as COV-HI-NO by the Manson and HI5-NEWS2 definitions of hyperinflammation, treatment with dexamethasone showed no benefit compared to patients who did not receive dexamethasone (Manson: 40.94% vs 44.26%, $P = 8.23\times10^{-1}$; HI5-NEWS2: 39.54% vs 41.00%, $P = 9.31\times10^{-1}$, Figure S2C-D). In patients classified as COV-HI-NO by the HI4O2 criteria, a trend towards harm (HI4O2: 56.09% vs 37.32%, RR = 1.50, $P = 6.21\times10^{-2}$) was identified in the dexamethasone treatment group by Kaplan-Meier analysis (Figure 4B). To explore the HI4O2 definition in more detail using Cox regression analysis after adjusting for age, sex at birth, ethnicity, comorbidities and time from admission to treatment initiation, it was found that use of dexamethasone in COV-HI-NO patients was associated with a HR of 3.03 (95% CI: 1.315-6.961, $P = 9.21\times10^{-3}$) for 28-day mortality, indicating that COV-HI-NO patients treated with dexamethasone had a 203% higher risk of death compared to untreated patients (Figure 4C). The same results were observed when all COVID-19 patients (recruited pre- and post-RECOVERY trial) were included (Figure S3A-C). Taken together, these results suggest that dexamethasone benefit is specific to patients with COV-HI and treating patients without hyperinflammation (based on the HI4O2 definition) may be associated with poor outcome.

Discussion

This retrospective analysis confirmed that established criteria used to define hyperinflammation in COVID-19 (COV-HI criteria: Manson, HI5-NEWS2 and HI4O2) [5–7] continued to have significant clinical relevance in independent/validation cohort, and were effective at predicting 28-day mortality and impact of dexamethasone treatment on COV-HI patients. We also showed that by using COV-HI criteria (such as HI5-NEWS2 and HI4O2) that use weighted and combined routinely measured markers, we can better predict these outcomes compared to the Manson criteria which used lab-

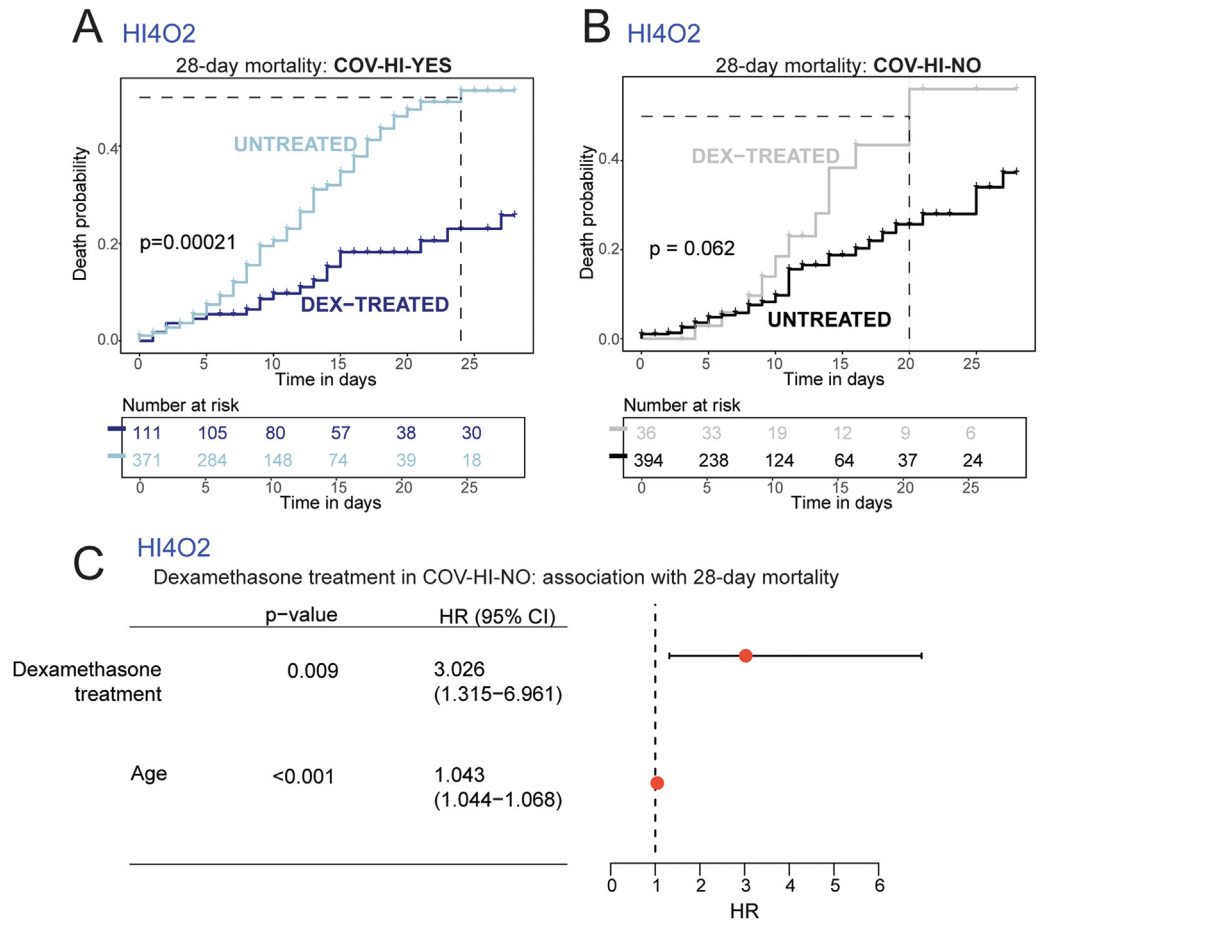

Figure 4. The impact of dexamethasone on mortality in patients with and without COV-HI who were recruited post the RECOVERY trial. Patient cohorts defined in Table S1 were assessed: dexamethasone-treated cohort (n = 212) and untreated cohort (n = 1313). (A-B) Kaplan-Meier curves measuring the HI4O2 definition ability to predict the impact of dexamethasone on 28-day mortality for (A) COV-HI-YES and (B) COV-HI-NO patients from date of admission (see also Figure S2A-D for Manson and HI5-NEWS2 criteria) (C) Cox proportional hazards analysis was implemented to measure the association of dexamethasone treatment in patients without hyperinflammation with mortality. Red (right-hand panel) denote variables that significantly increase the risk of mortality. The metrics for the Cox regression results are as follows: AIC=944.59; concordance=0.710; likelihood ratio test P-value = 4×10^{-10} and the global Schoenfeld P-value = 0.64. HR, hazard ratio. See Figure S3A-C for analysis of all patients (pre and post RECOVERY).

oratory markers alone. Furthermore, by combining these criteria, a shared biological phenotype associated with COV-HI was identified (irrespective of the criteria used to initially define COV-HI), giving scientific plausibility to the concept. As this phenotype was based on routinely available measurements, even those available on point-of-care testing analyzers, COV-HI can be readily identified in most clinical settings including resource poor environments.

Data from the RECOVERY Collaborative Group showed an overall reduction in mortality for people hospitalized with COVID-19 who received dexamethasone treatment (22.9%) versus those who received usual care (25.7%) [8]. Our retrospective analysis of outcomes suggests that the benefit of dexamethasone may be restricted to COV-HI patients. Treating patients without hyperinflammation was associated with a significantly increased risk of death (56.09% vs 37.32%) compared to receiving supportive care (with no immune modulation). This could be explained by dexamethasone impairing type I interferon/antiviral responses, thus abolishing the beneficial impact of an anti-inflammatory effect in patients with little evidence of hyperinflammation. This observation is borne out by the poor efficacy of steroid therapy in other viral conditions [17,18]. Furthermore, in COVID-19, there are some well-known adverse outcomes from dexamethasone and/or high-dose steroid therapy, with complications related to diabetes and secondary fungal infections [19–22]. Another possibility to consider for poor outcomes with dexamethasone in the COV-HI-NO group is that these patients were generally more unwell (and were on supplemental oxygen as a result) despite not meeting COV-HI criteria. In this case, it may not be unexpected that these patients did worse on dexamethasone. Taken together, the potential adverse outcomes associated with steroid therapy highlight the importance of identifying patients who truly have COV-HI where the benefit is more likely to outweigh the risk as suggested by previous studies [7].

Beyond elevated CRP, hyperserotonemia and neutrophilia, this analysis highlights a shared biological phenotype of hypoalbuminemia, anemia, and elevated D-dimer, LDH, ALT, creatinine, and elevated respiratory rates amongst COV-HI patients. A relationship between these markers and COVID-19 has been described previously in the literature. For instance, raised D-dimer fits the concept of COVID-related coagulopathy [23] and thromboinflammation, perhaps exacerbated by a low albumin; a raised D-dimer/albumin ratio (>56.56) predicted in-hospital mortality of COVID-19 patients with an AUC-ROC and odds ratio of 0.773 and 6.216, respectively [24]. Albumin supplementation in COVID-19 patients reduced D-dimer by >50%. Markers of organ dysfunction/damage (elevated ALT, LDH and creatinine) observed within this biological phenotype directly correlate with markers of systemic inflammation (indicated by CRP, ferritin and IL-6) [25]. Lastly, our results demonstrated that COV-HI patients are more likely to be male, older and have more comorbidities. Biological factors such as im-

munosenescence and inflammaging often affect the elderly, and there is a greater incidence of comorbidities such as diabetes mellitus, obesity and cardiovascular disease in men and individuals from ethnic backgrounds such as Black-African/Caribbean individuals. Collectively, these factors can lead to elevated levels of background/systemic inflammation compared to the rest of the general population. Therefore, the risk of perpetuating a hyperinflammatory response to SARS-CoV-2 infection is likely increased within these patients [26–33].

This study should be interpreted in the context of important limitations. Unfortunately, we had to exclude 58.49% of patients from the 3163-patient cohort for reasons such as a large proportion of patients receiving immunosuppressive medication. Only looking at a subset of patients may not be completely representative of the recruited cohort. Secondly, not all patients had recorded measurements for markers used within the COV-HI definitions at baseline. This meant it was not possible to classify these patients despite them meeting all other inclusion criteria from our study. Furthermore, we could not explore all markers (e.g., fibrinogen, BMI, triglycerides, monocytes etc.) in detail, as the degree of missingness was too high and imputation would introduce a certain level of bias into our results. This was a particular issue as these markers have been previously associated with COV-HI in the literature. The same issue was present concerning treatment. Besides dexamethasone, we were unable to explore the impact of other individual immunosuppressive therapies (e.g., tocilizumab, $n = 24$; prednisolone, $n = 12$; methylprednisolone, $n = 53$) that were given to patients post-RECOVERY trial due to low recorded numbers.

Whilst our study demonstrated a statistically significant result that dexamethasone increases the mortality risk 3.03 times in patients who do not meet the HI4O2 criteria, the confidence interval (1.315-6.961) for this HR is relatively wide. This occurred because the sample size is small, leading to reduced precision of this estimate. Further studies with larger sample sizes of this dexamethasone-treated group are needed to confirm the true magnitude of this effect and to optimize dexamethasone dose, treatment duration and response biomarkers. Another limitation was the presence of collider bias when using the larger patient cohort, particularly when combining patients treated both before and after the RECOVERY trial.

Before the RECOVERY trial, dexamethasone allocation in COVID-19 patients was unstandardized and often influenced by evolving clinical judgment, disease severity, and local protocols. This variation introduces the risk of collider bias when conditioning on COV-HI status, which may itself be associated with both treatment and outcome. To minimize this bias, our study incorporated an additional analysis that was restricted to a subset of patients recruited after the RECOVERY trial publication, during a period when dexamethasone prescribing was more standardized and predominantly administered to patients requiring supplemental oxygen regardless of inflammatory status, and we continued to adjust for key confounders. Whilst this analysis helped to reduce the risk of collider and confounding bias, some limitations remain. These include potential unmeasured confounding related to clinician decision-making and the possibility of minor selection bias if treatment timing or eligibility varied within the post-RECOVERY period. It should also be noted that the original Manson score was generated early in the pandemic (patients recruited between March 1 and March 31, 2020), however we do not know if any of the patients used to generate the Manson score were participating in the dexamethasone arm of the RECOVERY Trial (March 19th—June 20th 2020). In general, we are unable to identify which patients (if any) were in the RECOVERY Trial in any of the cohorts (post 19th March 2020).

Lastly, O2 saturation is known to be strongly associated with mortality and respiratory rate. Therefore, HI4O2 was more likely to outperform other COV-HI criteria. Despite this, these results demonstrate the importance of combining routinely measured markers to identify COV-HI and predict outcomes in COVID-19 patients, as previous focus in the literature has been on using laboratory markers alone or unweighted tools (where all laboratory markers are treated with equal importance). Respiratory rate and temperature were not significantly different between COV-HI-YES survivors and nonsurvivors across COV-HI definitions, suggesting their direct contribution to mortality risk (in the context of hyperinflammation) is weak in isolation. However, in the multivariable Cox models their hazard ratios varied depending on which definition was included: with the Manson definition, temperature had HR>1 and respiratory rate HR<1, whereas with HI5-NEWS2 and HI4O2 the pattern was reversed. This apparent reversal is unlikely to reflect a true biological effect but highlights that the observed associations for temperature and respiratory rate are unstable and influenced by the covariates and COV-HI definition incorporated into the model. This indicates that these two vital signs are not consistent independent predictors of mortality in the context of COV-HI.

In summary, the COVID-19 pandemic has provided a unique opportunity to study a large population of patients experiencing a hyperinflammatory state in contrast to other hyperinflammatory syndromes (e.g., HLH and cytokine release syndrome), where research has been hampered due to their rarity. As a result, this study has shown that published definitions of COVID-19-associated hyperinflammation could predict patient risk of mortality with high performance and dexamethasone treatment was shown to be associated with better outcome in patients with COV-HI, and potentially worse outcome in those without. We would therefore advocate for trials of better targeting of dexamethasone use in patients with COVID-19 and suggest applying stratification by hyperinflammatory response to other trials of immune suppression in the context of infection.

Ethical approval

Ethical approval was obtained from the Yorkshire & The Humber–Leeds West Research Ethics Committee (reference 20/YH/0138), as well as approval from the Health Research Authority (IRAS ID 282,626) and Health and Care Research Wales on April 15, 2020. The study was registered with the Clinical Trials Gateway (NCT04385069), the National Institute for Health Research portfolio (ID45542), and the Health Research Authority website.

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Author contributions

Study design: JJM, ECJ, ASD, MA-J, RST, MH, MFC; Study supervision: JJM, ECJ, GAR, LC; Acquired study data: MC, EH, TL, JJM, RT, SV, MA-J, ASD, MC: Analyzed the data: AEO, LC, MH; Wrote the manuscript: AEO, ECJ, JJM; Reviewed the manuscript: CC, GAR, BC, MA-J, ASD, RST, MFC, MC, MH, LC, SV, EH; All authors approved the final version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108119.

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