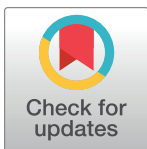


## RESEARCH ARTICLE

# A hyperinflammation clinical risk tool, HI5-NEWS2, stratifies hospitalised COVID-19 patients to associate risk of death and effect of early dexamethasone in an observational cohort

Michael R. Ardern-Jones<sup>1,2\*</sup>, Hang T. T. Phan<sup>3,4</sup>, Florina Borca<sup>3,4</sup>, Matt Stammers<sup>2,4</sup>, James Batchelor<sup>3,4</sup>, Isabel C. Reading<sup>5</sup>, Sophie V. Fletcher<sup>3,6</sup>, Trevor Smith<sup>2</sup>, Andrew S. Duncombe<sup>7</sup>



**1** Clinical Experimental Sciences, University of Southampton Faculty of Medicine, Sir Henry Wellcome Laboratories, Southampton General Hospital, Southampton, United Kingdom, **2** Division of Medicine, University Hospitals Southampton NHS Foundation Trust, Southampton General Hospital, Southampton, United Kingdom, **3** NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, **4** Clinical Informatics Research Unit Faculty of Medicine, University of Southampton, Southampton, United Kingdom, **5** Department of Primary Care, Population Sciences and Medical Education, University of Southampton, Southampton, United Kingdom, **6** Department of Respiratory Medicine, University Hospitals Southampton NHS Foundation Trust, Southampton, United Kingdom, **7** Department of Haematology, University Hospitals Southampton NHS Foundation Trust, Southampton, United Kingdom

\* [m.aj@soton.ac.uk](mailto:m.aj@soton.ac.uk)

## OPEN ACCESS

**Citation:** Ardern-Jones MR, Phan HTT, Borca F, Stammers M, Batchelor J, Reading IC, et al. (2023) A hyperinflammation clinical risk tool, HI5-NEWS2, stratifies hospitalised COVID-19 patients to associate risk of death and effect of early dexamethasone in an observational cohort. PLoS ONE 18(1): e0280079. <https://doi.org/10.1371/journal.pone.0280079>

**Editor:** Robert Jeenchen Chen, Stanford University School of Medicine, UNITED STATES

**Received:** June 25, 2021

**Accepted:** December 20, 2022

**Published:** January 17, 2023

**Copyright:** © 2023 Ardern-Jones et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** Raw patient level data cannot be shared publicly because of Institutional Review Board regulations. Aggregated data are available from the University of Southampton for researchers who meet the criteria for access to confidential data. Contact Dr. Mikayla King, assurance manager, University Hospital Southampton, NHS Foundation Trust R&D Quality via [Mikayala.King@uhs.nhs.uk](mailto:Mikayala.King@uhs.nhs.uk).

## Abstract

### Background

The success of early dexamethasone therapy for hospitalised COVID-19 cases in treatment of Sars-CoV-2 infection may predominantly reflect its anti-inflammatory action against a hyperinflammation (HI) response. It is likely that there is substantial heterogeneity in HI responses in COVID-19.

### Methods

Blood CRP, ferritin, neutrophil, lymphocyte and platelet counts were scored to assess HI (HI5) and combined with a validated measure of generalised medical deterioration (NEWS2) before day 2. Our primary outcome was 28 day mortality from early treatment with dexamethasone stratified by HI5-NEWS2 status.

### Findings

Of 1265 patients, high risk of HI (high HI5-NEWS2) ( $n = 367$ , 29.0%) conferred a strikingly increased mortality (36.0% vs 7.8%; Age adjusted hazard ratio (aHR) 5.9; 95% CI 3.6–9.8,  $p < 0.001$ ) compared to the low risk group ( $n = 455$ , 36.0%). An intermediate risk group ( $n = 443$ , 35.0%) also showed significantly higher mortality than the low risk group (17.6% vs 7.8%), aHR 2.2,  $p = 0.005$ ). Early dexamethasone treatment conferred a 50.0% reduction

**Funding:** The author(s) received no specific funding for this work.

**Competing interests:** The authors have declared that no competing interests exist.

in mortality in the high risk group (36.0% to 18.0%, aHR 0.56,  $p = 0.007$ ). The intermediate risk group showed a trend to reduction in mortality (17.8% to 10.3%, aHR 0.82,  $p = 0.46$ ) which was not observed in the low risk group (7.8% to 9.2%, aHR 1.4,  $p = 0.31$ ).

## Interpretation

Higher HI5-NEWS2 scores measured at COVID-19 diagnosis, strongly associate with increased mortality at 28 days. Significant reduction in mortality with early dexamethasone treatment was only observed in the high risk group. Therefore, the HI5-NEWS2 score could be utilised to stratify randomised clinical trials to test whether intensified anti-inflammatory therapy would further benefit high risk patients and whether alternative approaches would benefit low risk groups. Considering its recognised morbidity, we suggest that early dexamethasone should not be routinely prescribed for HI5-NEWS2 low risk individuals with COVID-19 and clinicians should cautiously assess the risk benefit of this intervention in all cases.

## Introduction

Dexamethasone therapy for COVID-19 is the most significant therapeutic intervention in treatment of severe Sars-CoV-2 infection to date and is supported by clinical trial evidence demonstrating a reduction in mortality as reported by the RECOVERY trial [1] and subsequently confirmed in other studies [2–4]. This is in contrast to the use of glucocorticoids in other severe viral respiratory infections which have a long history, but to date remain controversial and lack evidence from prospective clinical studies. Hyperinflammation (HI), characterised by a rapid increase in systemic release of cytokines such as IL-1 and IL-6, has been reported to explain the association of high fever, high C-reactive protein (CRP), hyperferritinaemia and coagulopathy that are more prevalent in COVID-19 than influenza [5, 6] translating into increased morbidity and mortality. The UK COVID-19 Therapeutics Advice & Support Group (CTAG) on use of immunomodulatory agents in COVID-19 identifies COVID-HI as a specific subgroup of HI syndromes (S1 Fig) [7, 8]. There is consensus that HI syndromes have a better outlook if identified and treated early [9, 10] and the most effective initial intervention is steroid therapy [10, 11].

Whilst current guidance recommends dexamethasone only for severe COVID-19 who are oxygen dependent and hospitalised, it remains unclear whether HI exists in all severe cases of COVID-19 or whether there may be a spectrum of HI within this group. It is possible that responsiveness to dexamethasone may be variable where better responses are seen in patients showing greater degrees of HI ranging to very poor or even adverse responses seen in patients with minimal evidence of HI. Indeed, some well known immediate adverse effects from dexamethasone especially impaired antiviral responses, glucose control, and severe fungal infections [12], have been reported in COVID-19 [13]. Indeed, in non-HI cases, other factors are central to mortality such as direct viral invasion of pulmonary tissue [14], existence of significant cardiac [15] and pulmonary [16] co-morbidities and renal failure [17] and require alternative therapeutic strategies. Therefore, targeting the HI group for steroid treatment would seem critically important.

Many algorithms already exist for overall mortality estimation in severe COVID-19 such as ISARIC4 in which the strongest predictor by far is increasing age [18]. The National Early Warning Score-2 (NEWS2) [19] is an aggregate score derived from thresholds of six routinely

measured physiological parameters including respiration rate, oxygen saturation, blood pressure, pulse rate, consciousness level, and temperature. NEWS2 was developed as a marker of sepsis to predict increased risk of poor outcomes and is recommended internationally [20, 21]. NEWS2 has recently been recommended for assessment of COVID-19 [22, 23]. However, no algorithms predict response to steroid therapy.

Therefore, here we set out to assess COVID-19 induced HI, as measured by a novel score (HI5), combined with a validated measure of generalised medical deterioration (NEWS2) to compare treatment response to dexamethasone in HI subgroups. Our primary outcome was 28 day mortality with and without early treatment with dexamethasone stratified by HI5-NEWS2 status.

## Methods

### Ethical considerations

The study followed the principles of the Declaration of Helsinki and was approved by the National Research Ethics Service (Identification of Novel Factors Leading to Activated Macrophage Expansion in COVID19 and related conditions to guide targeted intervention, INFLAME COVID-19 Study, NRES 286016). The study is reported here in accordance with STROBE guidelines [24] and ClinicalTrials.gov ID: NCT04903834.

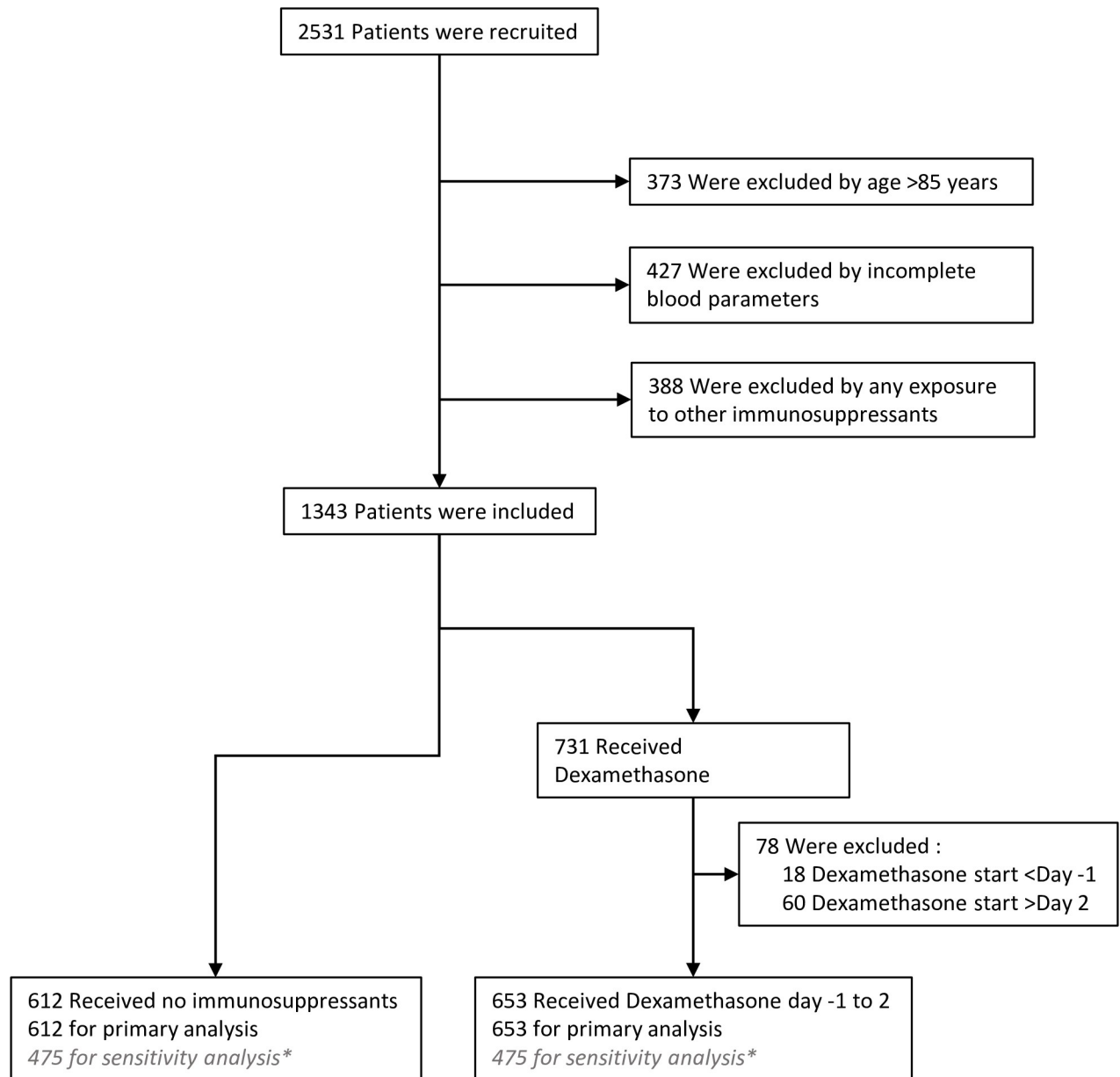
### Study population

Patients from University Hospitals Southampton NHS Foundation Trust (UHS) were the population for this study. All hospitalised cases of COVID-19 infection that tested positive for SARS-CoV-2 viral RNA in our laboratory between 07/03/2020 and 14/03/2021,  $n = 2531$  were included. We standardised the data with respect to the day of first diagnosis of SARS-CoV2 PCR positivity in our laboratory which we designated as Day 0. Comorbidities were identified from ICD-10 coding extracted from the complete clinical records held by our institution. The purpose of this study was to develop an early warning system for HI relevant to routine clinical practice. In our cohort rapid access to SARS-CoV-2 PCR testing was available throughout the study, and clinical teams sent samples for PCR as soon as they considered the diagnosis of COVID-19, or routinely on admission. Whilst we acknowledge that symptom duration may better reflect the precise course of the disease, however these data were not available. Therefore, to compare patients, we chose to pragmatically normalise all parameters to the date of virus confirmation by SARS-CoV-2 PCR test confirmation which we expect may make any misclassification non-differential between groups.

'Early' in the hospitalised disease course was designated Day -1 to 2. In our institution, in the first wave of the pandemic, the proportion of individuals  $>85$  years offered active treatment escalation including respiratory support with non-invasive or invasive ventilation was low. Therefore, because our primary outcome measure was mortality, we included only patients in both cohorts who would have been offered full interventional treatment to avoid bias. Thus 373 individuals  $>85$  years were excluded from the primary analysis (Fig 1).

HI5 and NEWS2 scores were calculated as below based on the most abnormal result over this initial 4 day period (Day-1 to 2). We did not undertake imputation of missing results, we only included patients with a full dataset of all HI5 parameters (thus excluding a further 427 individuals).

In response to data released by the UK Chief Medical Officer (16 June 2020) UHS COVID-19 management guidelines were updated immediately to recommend dexamethasone therapy for all hospitalised COVID-19 cases requiring respiratory support with supplemental oxygen to maintain oxygen saturation  $>94\%$ , Based on data from the Recovery group [1]. In order to



**Fig 1. Enrolment, and inclusion in the primary analysis.** Electronic records were available for 2531 of 2531 patients (100%) of hospitalised COVID-19 cases. 373 cases were excluded due to age (>85 years), and 427 through incomplete blood parameter measurements. 388 cases received other immunosuppressants as well as or instead of dexamethasone and were excluded. 78 dexamethasone treated cases were excluded because the treatment was started before or after the window of interest.

<https://doi.org/10.1371/journal.pone.0280079.g001>

focus specifically on the intervention of early dexamethasone in these COVID-19 patients, we then excluded patients who were on other immunosuppressive therapy ( $n = 388$ ) and a further group who had received prior dexamethasone at Day<-1 or had received late dexamethasone at >Day2 ( $n = 78$ , Fig 1). The timeline of data capture represented a period where Tocilizumab was not yet approved. Some patients did receive Tocilizumab off protocol, but not in a systematic way and were small numbers ( $n = 45/388$ ). Therefore, Tocilizumab treated cases were excluded from the analysis.

Similar to recent COVID-19 studies, the primary outcome utilised in this study was risk of mortality by Day 28 versus survival to Day 28 in patients treated with early dexamethasone (initiated day -1 to 2) compared with those not treated with dexamethasone or any other immunosuppressant.

## Development of score for HI

There is no consensus definition of HI although recognition that COVID-19 induced HI may be considered a subgroup of the overarching term [7, 8]. We therefore chose a priori routine laboratory markers of HI known to indicate severity in other clinical contexts. A key driver in our choice of parameters was the common availability of such indicators in routine laboratory practice with rapid result turnaround times to facilitate urgent clinical decision making. HI5 parameter selection excluded parameters necessitating cytokine assays such as IL-6 [25], TNF [26] and GM-CSF [11] that are currently not routinely available in many hospitals. CRP is recognised universally as a key indicator of infection-induced inflammation but confounders such as underlying disease infection make it unreliable as a single indicator [27]. Serum ferritin is the most sensitive single indicator for the most severe form of HI, secondary Haemophagocytic Lymphohistiocytosis (sHLH) [28]. While complete sHLH criteria are rarely fulfilled in COVID-19 [29, 30] and the degree of elevation in COVID-19 is less than in sHLH, ferritin is still likely to be an important indicator for COVID-HI [31, 32]. Unlike most viral infections, COVID-19 induces a neutrophilia [33], a key component of HI in both infective and inflammatory diseases, and therefore this was included as absolute neutrophil count. Absolute lymphocyte count is relevant to HI responses as this may represent virus induced immunosuppression, co-existing disease or concurrent immunosuppressive therapy [7]. Platelet count reduction correlates with risk of COVID-19 induced microangiopathic coagulopathy known to associate with HI [34]. 5 key parameters were selected: C-reactive protein (CRP), serum ferritin, neutrophil, lymphocyte and platelet absolute counts. While these 5 parameters will not encompass all possible measures of COVID-HI, together they form a coherent and rapidly and universally assessable group of measurements. This novel algorithm was developed from a data cut of UHS COVID-19 cases up to 24-Jun-2020 ( $n = 539$ ) to develop the HI5 algorithm before the widespread use of dexamethasone or other anti-inflammatory agents.

Each parameter was then assessed individually to define thresholds to score 0–4 and weighting added based upon analysis of correlation with the key outcome measure of mortality. The weighting was undertaken using a supervised approach based on linear regression models with weights rounded to integers. This produced a total HI5 score out of 44 (presented furthermore as a percentage of maximum score, Table 1). HI5 was made binary to make it easily clinically applicable, and a 'high' threshold was set pragmatically by splitting the data in two (approximately 50% of the dataset each) according to the median score and a score of  $\geq 28\%$  selected to classify as high HI5 ( $n = 634$ ) vs low HI5 ( $n = 621$ ).

The National Early Warning Score 2 (NEWS2) for hospitalised patients combines scores for each of 7 routine bedside measurements of physiological parameters to provide an overall NEWS2 score. The following parameters are included: respiratory rate, oxygen saturation, supplemental oxygen, systolic blood pressure, pulse rate, consciousness and temperature. The combination of these values provides a score between 0 and 20 [19]. The purpose of the NEWS2 score is to assess acutely ill patients and a score of  $\geq 5$  is validated as a threshold to identify deterioration in patients who require intervention [19]. Therefore, to identify acutely ill patients, NEWS2 was also examined and a score  $\geq 5$  was designated as high risk and NEWS2  $< 5$  designated as low risk.

**Table 1. The HI5 score algorithm.**

HI5 score	0	1	2	3	4	weight	Total score
CRP (mg/L)	≤50	>50	>100	>150	>250	3	12
Ferritin (μg/L)	≤500	>500	>1000	>2000	>4000	2	8
ANC (x10 <sup>9</sup> /L)	≤4	>4	>8	>12	>20	3	12
ALC (x10 <sup>9</sup> /L)	≥1.5	<1.5	<0.9	<0.6	<0.3	2	8
Platelets (x10 <sup>9</sup> /L)	≥250	<250	<150	<100	<50	1	4
						Max score	44

5 routinely available blood test parameters are scored based on their value, and weighted. The sum of each parameter score results in the HI5 score. Percentage values are presented.

<https://doi.org/10.1371/journal.pone.0280079.t001>

### Data handling and statistical analysis

Structured and semi-structured data was accrued from the trust integration engine using SQL Developer 4.2 queries and then cleaned/transformed using python 3.7 and associated libraries: *numpy* and *pandas*. Analysis was performed using *matplotlib*, *seaborn* and *scipy*. Using this approach to retrospectively retrieve data from the electronic hospital record system we collected all blood parameters, bedside observations, and prescribing. In addition, clinical coding information was used to retrieve comorbidity data. Mortality outcome was retrieved from a central NHS Spine database. For the 8/1265 analysed patients where 28 day censoring was not possible (within 28 days of data cut), these cases were censored early with the censor time status, and were indicated on Kaplan-Meier survival curves as indicated. Importantly, all patients had to have all HI5 parameters to be included in the analysis. Those with missing data were excluded. In UHS, NEWS2 is calculated at the bedside by the clinical team and data input to the electronic patient care record. Complete NEWS2 data was available for 73.8% of cases. However, separately, the dataset contained key data elements of the NEWS2 algorithm including respiratory rate, Oxygen saturations, and temperature (97.1%, 97.1%, and 96.9% of cases respectively). To address the missing NEWS2 data, imputation of NEWS2 from these parameters was undertaken using the K-nearest neighbour method and sensitivity analyses without imputed data reported.

Statistical analysis was undertaken in python 3.7, R (RStudio Version 1.4.1106) and Graph-Pad, Prism (8.4.3). All data was censored at Day 28, for Kaplan-Meier survival analysis. For the primary outcome of 28-day mortality, the hazard ratio from Cox regression was used to estimate the mortality hazard ratio. To select the covariate model, we started with four a priori variables, and then tested them one-by-one and gradually built up our multivariable model using forward selection, testing that the addition of extra variables truly added to the model via likelihood ratio tests. Using this approach, for age, ethnicity, sex and comorbidity, we found that age was the most important covariate for use in the model. Age as a covariate met the test for Cox proportionality assessment (Schoenfeld residuals  $p = 0.2$ ; survival package, R). All hazard ratios quoted are adjusted using Cox proportional hazards analysis. Unadjusted hazard ratios were estimated using the Log-Rank method. Results without age adjustment are provided. For t-test comparison of demographic measurements between dexamethasone treated and those not treated with dexamethasone, statistical significance was determined using the Holm-Sidak method, with  $\alpha = 0.05$ . Each characteristic was analysed individually, without assuming a consistent SD. The full anonymised database is held by the research team in the University of Southampton and data linkage is strictly controlled by the data informatics team, University Hospitals Southampton NHS Foundation Trust as per ethical approval.

## Results

A total of 653 patients received dexamethasone between Day -1 and Day 2 (dexamethasone group) and a total of 612 patients did not (untreated group) and there was no statistically significant difference between the groups with respect to age, sex, ethnicity, or comorbidities. Patient age, which is known to be the dominant prognostic factor, showed no overall statistically significant difference between the treated and untreated cohorts (mean age 59.08 versus 61.42 respectively,  $p = 0.08$ , Table 2). However, to exclude the influence of possible age differences in subgroups, age adjusted analyses are reported throughout (with unadjusted results supplementary). Ethnicity status has been shown to adversely affect outcome in COVID-19 and non-white patients were well represented in both cohorts (26.19% in the dexamethasone treated group versus 25.82% in the untreated group,  $p = 0.99$ ). Key co-morbid drivers of adverse outcome were also not significantly different between the groups. In the treated and untreated groups respectively, chronic lung disease was present in 19.14% versus 21.41%,  $p = 0.90$ , cardiac co-morbidity was present in 24.04% vs 30.39%,  $p = 0.10$ , severe renal impairment was seen in 0.77% vs 1.31%,  $p = 0.90$ , severe liver disease in 1.68% vs 1.80%,  $p = 0.99$  and diabetes was present in 16.69% vs 17.81%,  $p = 0.97$  (Table 2).

As expected, the group treated with dexamethasone predominantly comprised the second wave of COVID-19 infection (S2 Fig). Dexamethasone 6mg daily by mouth or intravenously, for 10 days or until discharge was prescribed in accordance with recommendations from the Recovery trial [1]. The average daily dose of dexamethasone in our hospital was 6.15mg (standard deviation 2.32).

Mortality at 28 days in hospitalised COVID-19 patients not treated with dexamethasone (started day -1 to 2) was significantly higher in cases with HI5 high risk score measured early

**Table 2. Characteristics of the patients with confirmed SARS-CoV-2 severe acute respiratory syndrome coronavirus 2 according to treatment.**

Characteristic		Treatment		Adjusted p-Value
		No dexamethasone	Dexamethasone	
Number		612	653	
Age (years)				
	Mean ( $\pm$ SD)	61.42 $\pm$ 16.80	59.08 $\pm$ 14.72	0.08
	Distribution			
Sex—no. (%)				0.52
	Male	345 (56.37)	398 (60.95)	
	Female	267 (43.63)	255 (39.05)	
Ethnicity—no. (%)				0.99
	White	422 (68.95)	448 (68.61)	
	Black, Asian, or minority ethnic group	158 (25.82)	171 (26.19)	
	Unknown	32 (5.23)	34 (5.21)	
Previous co-existing disease—no. (%)				
	Diabetes	109 (17.81)	109 (16.69)	0.97
	Heart disease	186 (30.39)	157 (24.04)	0.10
	Chronic lung disease	131 (21.41)	125 (19.14)	0.90
	Severe liver disease	11 (1.80)	11 (1.68)	0.99
	Severe kidney impairment	8 (1.31)	5 (0.77)	0.90
	Tuberculosis	5 (0.82)	1 (0.15)	0.52
	HIV infection	2 (0.33)	3 (0.46)	0.98

Plus-minus values are means  $\pm$ SD. HIV denotes human immunodeficiency virus, NA not applicable, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

<https://doi.org/10.1371/journal.pone.0280079.t002>

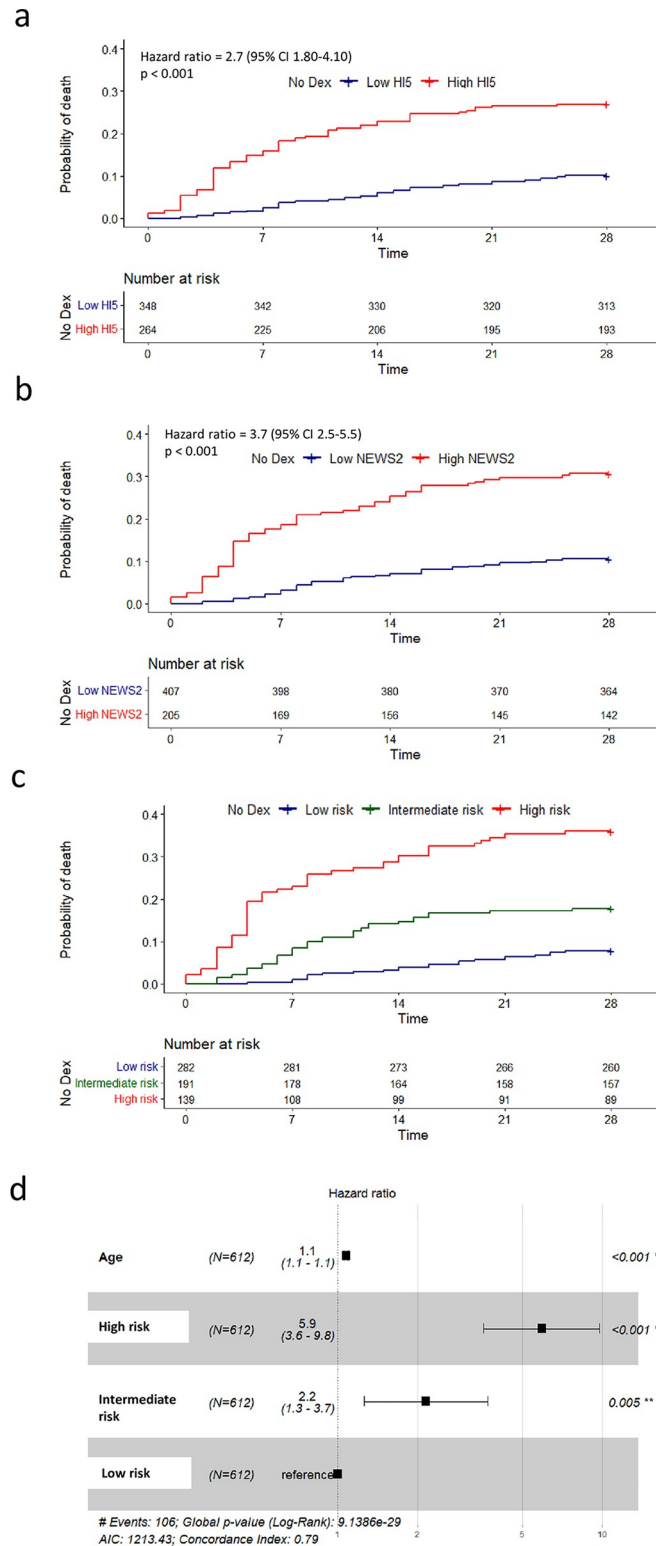
in the disease course with deaths in 71 out of 264 patients (26.9%) compared to 35 out of 348 (10.1%) with low HI5 scores (age adjusted hazard ratio (aHR) 2.7, 95% Confidence interval (CI) 1.80–4.10,  $p < 0.001$ , Fig 2A). For High NEWS2 (score  $\geq 5$ ) mortality in dexamethasone untreated cases was also significantly higher with deaths in 63 out of 205 patients (31.7%) versus 43 out of 407 (10.6%) in those with low NEWS2 scores (aHR 3.7, CI 2.5–5.50,  $p < 0.001$ , Fig 2B). To confirm that imputation of NEWS2 did not affect the overall results, sensitivity analysis with non-imputed NEWS2 in the dexamethasone untreated group was undertaken and showed similar results (S4 Fig). NEWS2 and HI5 were developed to characterise acute risk of medical deterioration and HI respectively. Although some overlap may exist in some patients, to examine their interrelationship, linear regression analysis of NEWS2 and HI5 showed that their correlation was low ( $r^2 = 0.171$ , S3 Fig), suggesting that high HI5 or NEWS2 scores independently confer an excess mortality risk over low scores. Therefore, we postulated that combining the two scores may offer a superior tool as compared to either alone. Indeed, high risk individuals (with both high HI5 and high NEWS2 scores) showed a greater mortality 36.0% (50/139) than observed 7.8% (22/282) in low risk cases (low HI5 and low NEWS2) (aHR 5.9, 95% CI 3.66–9.8,  $p < 0.001$ , Fig 2C and 2D). The groups with high HI5 or high NEWS2 (not both), showed intermediate mortality (16.8%, 21/125; and 19.7%, 13/66 respectively) and Cox regression analysis showed no statistical difference between these two groups ( $p = 0.64$ ). These two groups were therefore subsequently classified as intermediate risk. As compared to low risk groups, intermediate risk groups showed a higher mortality (aHR 2.2, CI 1.3–3.7,  $p = 0.005$ , Fig 2D). Sensitivity analyses without adjustment for age, resulted in similar findings (S1 Table).

To examine the effect of dexamethasone in COVID-19 in a real-world population we compared survival in the early dexamethasone treated versus untreated patients. Treatment of COVID-19 with early dexamethasone conferred a modest but non-significant reduction in mortality (12.7% vs 17.3%, aHR 0.93, CI 0.7–1.2,  $p = 0.62$ , Fig 3A) in our entire cohort. Since a major component of the action of dexamethasone is anti-inflammatory, and is likely to reduce HI in COVID-19, we examined whether the benefit from dexamethasone was stratified by low, intermediate or high HI5-NEWS2 risk status as measured at day -1 to 2. Strikingly, in the HI5-NEWS2 high risk group, treatment with dexamethasone significantly reduced day 28 mortality from 36.0% to 18.0% (aHR 0.56, CI 0.37–0.85,  $p = 0.007$ , Fig 3B). In the intermediate risk group, a non-significant reduction in mortality was observed: 17.8% to 10.3% (aHR 0.82, CI 0.49 to 1.4,  $p = 0.46$ , Fig 3C). In the low risk group, treatment with dexamethasone associated with a non-significant increase in mortality (7.8% to 9.2%) (aHR 1.4, CI 0.73 to 2.6,  $p = 0.32$ , Fig 3D). Sensitivity analyses without imputation for missing NEWS2 data in dexamethasone treated individuals, resulted in similar findings (S5 Fig).

## Discussion

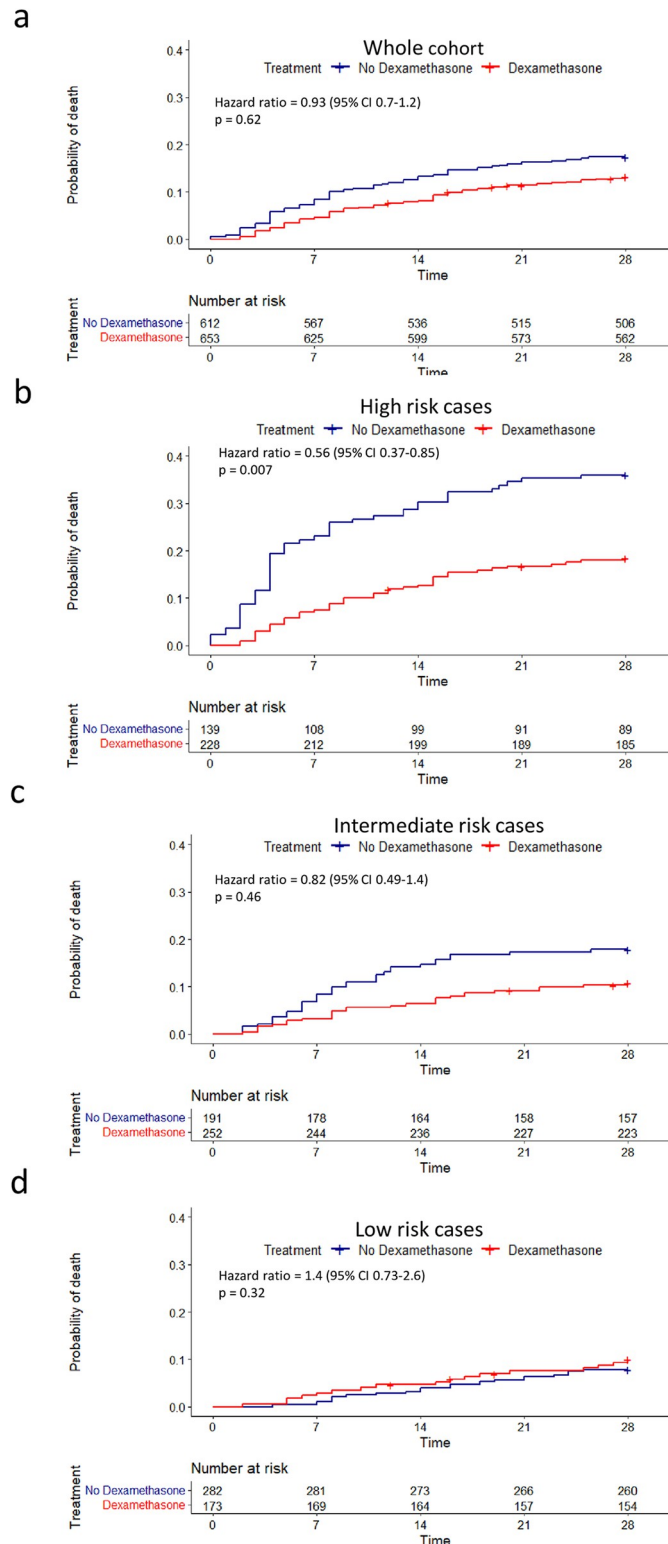
We demonstrate that it is possible to classify COVID-19 patients on admission into high, intermediate, and low risk groups for HI, and that high HI risk status associates with the benefit from early dexamethasone therapy on mortality. The use of our combined HI5-NEWS2 algorithm demonstrates that patients who have evidence of HI and are acutely ill have the best response to dexamethasone whereas those who lack evidence of HI and are relatively well have no response and may risk steroid related morbidity. As has been described in the published literature of COVID, most patients die of respiratory complications. Although we didn't set out to analyse complications and did not collect the data for all individuals, previously reported data has shown that approximately 25% of hospitalised patients with COVID-19 develop ARDS/pneumonia [35].





**Fig 2. Mortality at day 28 in cases not treated with dexamethasone.** Kaplan–Meier survival curves for 28-day mortality among patients who were not treated with dexamethasone with high (red line) or low (blue line) HI5 scores (a) or NEWS2 scores (b). Panel C, Kaplan–Meier survival curves for cases classified as high risk (High HI5 and High NEWS2, red line), intermediate risk (High HI5 or High NEWS2, green line), and low risk (Low HI5 and Low NEWS2, blue line). (d) Cox regression analysis for Age (per year of life), and HI5-NEWS2 risk status. All quoted hazard ratios are adjusted for age (aHR). At risk data are listed beneath plots. Time measured in days.

<https://doi.org/10.1371/journal.pone.0280079.g002>



**Fig 3. Effect of dexamethasone on mortality at day 28.** (a) Kaplan–Meier survival curves for 28-day mortality among the whole cohort in those who were treated with dexamethasone (red line) vs untreated cases (blue line). (b–d) Kaplan–Meier survival curves for those treated with dexamethasone (red lines) vs untreated (blue lines) in HI5-NEWS2 high risk (b), intermediate risk (c) or low risk (d) groups. All quoted hazard ratios are adjusted for age. At risk data are listed beneath plots. Time measured in days. Cases censored before 28 days indicated by +.

<https://doi.org/10.1371/journal.pone.0280079.g003>

Whilst there are published tools for COVID-19 outcome prediction [18], multiparameter models do not distinguish between the pathophysiological pathways leading to the adverse outcome. In addition, advancing age is such a dominant predictor of survival in COVID-19 [18], that important subgroups may be missed if mortality is used as a primary outcome measure in a non-hypothesis driven approach. Therefore, we used a pre-defined measure specifically designed to measure hyperinflammation and adjusted for the influence of age throughout. The attractiveness of identifying patients showing HI features is the relevance to therapies targeting HI which provides the opportunity to validate a proposed HI algorithm as we have shown. While dexamethasone may have other therapeutic actions in COVID-19 such as ACE receptor targeting, its efficacy as initial therapy in other HI syndromes not involving a viral aetiology suggests that its anti-inflammatory action is a crucial component of efficacy. Our data show that this is likely to be true for patients with severe COVID-19, as we have demonstrated the significant benefit of dexamethasone is predominantly in patients demonstrating high risk of HI which will include patients requiring mechanical ventilation or organ support. These findings concur with clinical trial data showing benefit from corticosteroid therapy in severe COVID-19 disease [2–4], systematic reviews which suggest that the greatest benefit from dexamethasone occurs in the high risk hospitalised COVID-19 cases [36, 37] and studies that have shown that early use of dexamethasone is effective in severe disease such as those on intensive care [38]. A recent systematic review reported measurement of hyperinflammation but did not validate for early risk detection or against an anti-inflammatory intervention as we show here [39]. We believe early assessment following admission is crucial for rapid clinical decision making so our score was developed for assessment within 2 days of virus confirmation.

The nature of the rapid reporting during COVID-19 imbues various limitations which are relevant to retrospective analyses such as ours. However, whilst potential pitfalls of bias exist, we have minimised the most important forms of bias as follows: assessment was made of 100% of sequential patients admitted to our institution and the management of COVID-19 remained stable throughout the pandemic. By sampling a single institution, clinical teams and the facilities at the institution were the same for both groups. Furthermore, no differences between dexamethasone and untreated groups were identified including all key potential confounding parameters of ethnicity, sex, diabetes, heart disease, and respiratory disease. Indeed, in our whole cohort analysis the benefit from dexamethasone was small, suggesting that any bias in dexamethasone selection would be unlikely to explain the large subgroup differences associated with high or low risk HI5-NEWS2 status.

The original randomised clinical trial from the RECOVERY Collaborative Group [1] showed mortality across all ages for those who received usual care of 25.7% versus 22.9% in those treated with dexamethasone. Our cohort excluded patients  $\geq 85$  years and so showed lower overall mortality: usual care was 18.4% (number at risk 612) versus 16.3% in dexamethasone treated groups (number at risk 653) although the trend was similar. Importantly, our results suggest that the benefit first identified by the Recovery trial for dexamethasone treatment in COVID-19 is principally restricted to individuals with HI and not the whole cohort. We show that a simple algorithm that can be used rapidly at the bedside in routine clinical practice can identify early in the admission which patients are most likely to benefit from intervention with early dexamethasone. Furthermore, although our data demonstrate that with dexamethasone treatment of HI5-NEWS2 high risk groups mortality is reduced from 36.0% to 18.0%, this is still twice as high as those with low risk scores. This finding raises the important question of whether targeting the high risk HI5-NEWS2 group with more intensive anti-inflammatory therapies such as with tocilizumab or other early interventional immunosuppressive treatments could reduce their mortality still further. We suggest that a randomised clinical trial of intensified immunosuppression specifically in this HI5-NEWS2 high risk subgroup is warranted to further improve outcomes.

We did not set out to look at morbidity from dexamethasone. Nevertheless, it is concerning that no survival advantage was identified from early dexamethasone treatment in HI5-NEWS2 low risk and intermediate risk groups of hospitalised COVID-19 patients who make up 68.8% of our cases. Indeed, in the low risk group (36% of total) the trend is towards harm in the dexamethasone treated group (Fig 3D). This could be due to the action of dexamethasone reducing host immune inhibition of viral replication overcoming any benefit from an anti-inflammatory effect in individuals with little evidence of inflammation. This concern has certainly been a factor in the poor overall results of steroid therapy in other viral conditions unless effective anti-viral therapy is given in conjunction. In addition, there is a valid concern supported by anecdotal experience that these individuals may suffer the well-established adverse effects of high dose steroid therapy, including a significant increased risk of loss of glycaemic control and even new-onset diabetic ketoacidosis [40–42]. Indeed, such concerns about the dangers of a one-size fits all approach to corticosteroids in COVID-19, and the importance of targeting therapy to those who will benefit most have been raised by others [42–45]. Therefore, new therapies are required in the HI5-NEWS2 low risk group to improve outcomes.

While awaiting these risk stratified trials, we urge caution in prescribing early dexamethasone therapy in COVID-19 in the HI5-NEWS2 low risk group and encourage careful consideration of the potential for harm with respect to steroid induced morbidity.

## Supporting information

**S1 Table. 28-day mortality hazard rates for HI5-NEWS2 subgroups.** Unadjusted hazard rates (log-rank method) for all cases, High HI5, High NEWS2, and HI5-NEWS2 High risk, Intermediate risk and Low risk cases, versus age adjusted analysis (Cox regression).

(TIF)

**S1 Fig. Overview of hyperinflammatory syndromes and their classification.** Hyperinflammation is induced as a consequence of a variety of underlying causes including SARS-CoV-2 [46].

(TIF)

**S2 Fig. The number of new admissions with COVID-19 over time and dexamethasone treatment in our institution.** The admission of COVID-19 cases by laboratory confirmed (Sars-CoV-2) polymerase chain reaction confirmation date (X-axis), vs 7 day rolling average of number of cases (Y-axis). Blue line, all cases admitted to the institution; Orange line, cases not treated with dexamethasone recruited in this study; green line, cases receiving prescription for dexamethasone within day -1 to 2 of virus confirmation.

(TIF)

**S3 Fig. Correlation between HI5 and NEWS2.** Correlation between HI5 (x-axis) and NEWS2 (y-axis). Pearson's correlation  $\rho^2$  reported in the figure.

(TIF)

**S4 Fig. Sensitivity analysis with non-imputed NEWS2 data showing mortality at day 28 in cases not treated with dexamethasone.** Kaplan–Meier survival curves for 28-day mortality among patients who were not treated with dexamethasone with high (red line) or low (blue line) HI5 scores (a) or NEWS2 scores (b). Panel C, Kaplan–Meier survival curves for cases classified as high risk (High HI5 and High NEWS2, red line), intermediate risk (High HI5 or High NEWS2, green line), and low risk (Low HI5 and Low NEWS2, blue line). (d) Cox regression analysis for Age, and HI5-NEWS2 risk status. All quoted hazard ratios are adjusted for age. At risk data are listed beneath plots. Time measured in days. Cases censored before 28 days indicated by +.

(TIF)

**S5 Fig. Sensitivity analysis with non-imputed NEWS2 data showing effect of dexamethasone on mortality at day 28.** (a) Kaplan–Meier survival curves for 28-day mortality among the whole cohort in those who were treated with dexamethasone (red line) vs untreated cases (blue line). (b-d) Kaplan–Meier survival curves for those treated with dexamethasone (red lines) vs untreated (blue lines) in high risk (b), intermediate risk (c) or low risk (d) groups. All quoted hazard ratios are adjusted for age. At risk data are listed beneath plots. Time measured in days. (TIF)

## Acknowledgments

We would like to acknowledge Prof S. Holgate, University of Southampton, for his critical review and advice on manuscript preparation, as well as Dr Anastasia Koutalopoulou and Dr Ying Teo for clinical support.

## Author Contributions

**Conceptualization:** Michael R. Ardern-Jones, Matt Stammers, Andrew S. Duncombe.

**Data curation:** Michael R. Ardern-Jones, Hang T. T. Phan, Florina Borca, Matt Stammers, Isabel C. Reading, Sophie V. Fletcher.

**Formal analysis:** Michael R. Ardern-Jones, Hang T. T. Phan, Florina Borca, Matt Stammers, Isabel C. Reading, Trevor Smith.

**Investigation:** Michael R. Ardern-Jones, Florina Borca, Matt Stammers, Isabel C. Reading, Andrew S. Duncombe.

**Methodology:** Michael R. Ardern-Jones, Matt Stammers, James Batchelor, Sophie V. Fletcher, Andrew S. Duncombe.

**Project administration:** Michael R. Ardern-Jones, Hang T. T. Phan, Florina Borca, Matt Stammers, James Batchelor, Sophie V. Fletcher, Andrew S. Duncombe.

**Resources:** Michael R. Ardern-Jones, James Batchelor.

**Software:** Michael R. Ardern-Jones, James Batchelor.

**Supervision:** Michael R. Ardern-Jones, James Batchelor, Isabel C. Reading, Trevor Smith, Andrew S. Duncombe.

**Validation:** Michael R. Ardern-Jones.

**Visualization:** Michael R. Ardern-Jones, Isabel C. Reading, Trevor Smith, Andrew S. Duncombe.

**Writing – original draft:** Michael R. Ardern-Jones.

**Writing – review & editing:** Michael R. Ardern-Jones, Hang T. T. Phan, Florina Borca, Matt Stammers, James Batchelor, Isabel C. Reading, Sophie V. Fletcher, Trevor Smith, Andrew S. Duncombe.

## References

1. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *New England Journal of Medicine*. 2021; 384(8):693–704.
2. Dequin P-F, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *Jama*. 2020; 324(13):1298–306. <https://doi.org/10.1001/jama.2020.16761> PMID: 32876689

3. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *Jama*. 2020; 324(13):1307–16. <https://doi.org/10.1001/jama.2020.17021> PMID: 32876695
4. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *Jama*. 2020; 324(13):1317–29. <https://doi.org/10.1001/jama.2020.17022> PMID: 32876697
5. Gustine JN, Jones D. Immunopathology of Hyperinflammation in COVID-19. *Am J Pathol*. 2021; 191(1):4–17. Epub 2020/09/14. <https://doi.org/10.1016/j.ajpath.2020.08.009> PMID: 32919977; PubMed Central PMCID: PMC7484812.
6. McGonagle D, Ramanan AV, Bridgewood C. Immune cartography of macrophage activation syndrome in the COVID-19 era. *Nat Rev Rheumatol*. 2021; 17(3):145–57. Epub 2021/02/07. <https://doi.org/10.1038/s41584-020-00571-1> PMID: 33547426; PubMed Central PMCID: PMC7863615.
7. England JT, Abdulla A, Biggs CM, Lee AYY, Hay KA, Hoiland RL, et al. Weathering the COVID-19 storm: Lessons from hematologic cytokine syndromes. *Blood Rev*. 2021; 45:100707. Epub 2020/05/20. <https://doi.org/10.1016/j.blre.2020.100707> PMID: 32425294; PubMed Central PMCID: PMC7227559.
8. Royal College of Physicians. Medical management of hospitalised adults with COVID-19 <https://www.ctag-support.org.uk/2021>.
9. Okabe T, Shah G, Mendoza V, Hirani A, Baram M, Marik P. What intensivists need to know about hemophagocytic syndrome: an underrecognized cause of death in adult intensive care units. *Journal of intensive care medicine*. 2012; 27(1):58–64. <https://doi.org/10.1177/0885066610393462> PMID: 21257627
10. Debaugnies F, Mahadeb B, Ferster A, Meuleman N, Rozen L, Demulder A, et al. Performances of the H-Score for diagnosis of hemophagocytic lymphohistiocytosis in adult and pediatric patients. *American journal of clinical pathology*. 2016; 145(6):862–70. <https://doi.org/10.1093/ajcp/aqw076> PMID: 27298397
11. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet (London, England)*. 2020; 395(10229):1033. [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0) PMID: 32192578
12. Ahmadikia K, Hashemi SJ, Khodavaisy S, Getso MI, Alijani N, Badali H, et al. The double-edged sword of systemic corticosteroid therapy in viral pneumonia: A case report and comparative review of influenza-associated mucormycosis versus COVID-19 associated mucormycosis. *Mycoses*. 2021. <https://doi.org/10.1111/myc.13256> PMID: 33590551
13. Matthay MA, Thompson BT. Dexamethasone in hospitalised patients with COVID-19: addressing uncertainties. *The Lancet Respiratory Medicine*. 2020; 8(12):1170–2. [https://doi.org/10.1016/S2213-2600\(20\)30503-8](https://doi.org/10.1016/S2213-2600(20)30503-8) PMID: 33129421
14. Tsatsakis A, Calina D, Falzone L, Petrakis D, Mitrut R, Siokas V, et al. SARS-CoV-2 pathophysiology and its clinical implications: An integrative overview of the pharmacotherapeutic management of COVID-19. *Food Chem Toxicol*. 2020; 146:111769. Epub 2020/09/27. <https://doi.org/10.1016/j.fct.2020.111769> PMID: 32979398; PubMed Central PMCID: PMC7833750.
15. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol*. 2020; 17(9):543–58. Epub 2020/07/22. <https://doi.org/10.1038/s41569-020-0413-9> PMID: 32690910; PubMed Central PMCID: PMC7370876.
16. Bouazza B, Hadj-Said D, Pescatore KA, Chahed R. Are Patients with Asthma and Chronic Obstructive Pulmonary Disease Preferred Targets of COVID-19? *Tuberc Respir Dis (Seoul)*. 2021; 84(1):22–34. Epub 2020/10/27. <https://doi.org/10.4046/trd.2020.0101> PMID: 33099990; PubMed Central PMCID: PMC7801803.
17. Diao B, Feng Z, Wang C, Wang H, Liu L, Wang C, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. *MedRxiv*. 2020.
18. Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. *BMJ*. 2020; 370:m3339. Epub 2020/09/11. <https://doi.org/10.1136/bmj.m3339> PMID: 32907855; PubMed Central PMCID: PMC7116472.
19. Royal College of Physicians. NHS England approves use of National Early Warning Score (NEWS) 2 to improve detection of acutely ill patients. <https://www.rcplondon.ac.uk/news/nhs-england-approves-use-national-early-warning-score-news-2-improve-detection-acutely-ill2017>.
20. Subbe CP, Bannard-Smith J, Bunch J, Champunot R, DeVita MA, Durham L, et al. Quality metrics for the evaluation of Rapid Response Systems: Proceedings from the third international consensus conference on Rapid Response Systems. *Resuscitation*. 2019; 141:1–12. Epub 2019/05/28. <https://doi.org/10.1016/j.resuscitation.2019.05.012> PMID: 31129229.

21. Martín-Rodríguez F, López-Izquierdo R, Del Pozo Vegas C, Delgado-Benito JF, Del Pozo Pérez C, Carbajosa Rodríguez V, et al. A Multicenter Observational Prospective Cohort Study of Association of the Prehospital National Early Warning Score 2 and Hospital Triage with Early Mortality. *Emerg Med Int.* 2019; 2019:5147808. Epub 2019/07/30. <https://doi.org/10.1155/2019/5147808> PMID: 31355000; PubMed Central PMCID: PMC6633971.
22. Kostakis I, Smith GB, Prytherch D, Meredith P, Price C, Chauhan A. The performance of the National Early Warning Score and National Early Warning Score 2 in hospitalised patients infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Resuscitation.* 2021; 159:150–7. Epub 2020/11/12. <https://doi.org/10.1016/j.resuscitation.2020.10.039> PMID: 33176170; PubMed Central PMCID: PMC7648887.
23. Armitage M, Eddleston J, Stokes T. Recognising and responding to acute illness in adults in hospital: summary of NICE guidance. *Bmj.* 2007; 335(7613):258–9. <https://doi.org/10.1136/bmj.39272.679688.47> PMID: 17673769
24. Field N, Cohen T, Struelens MJ, Palm D, Cookson B, Glynn JR, et al. Strengthening the Reporting of Molecular Epidemiology for Infectious Diseases (STROME-ID): an extension of the STROBE statement. *The Lancet infectious diseases.* 2014; 14(4):341–52.
25. Copaescu A, Smibert O, Gibson A, Phillips EJ, Trubiano JA. The role of IL-6 and other mediators in the cytokine storm associated with SARS-CoV-2 infection. *J Allergy Clin Immunol.* 2020; 146(3):518–34 e1. Epub 2020/09/09. <https://doi.org/10.1016/j.jaci.2020.07.001> PMID: 32896310; PubMed Central PMCID: PMC7471766.
26. Karki R, Sharma BR, Tuladhar S, Williams EP, Zalduondo L, Samir P, et al. Synergism of TNF-alpha and IFN-gamma Triggers Inflammatory Cell Death, Tissue Damage, and Mortality in SARS-CoV-2 Infection and Cytokine Shock Syndromes. *Cell.* 2021; 184(1):149–68 e17. Epub 2020/12/06. <https://doi.org/10.1016/j.cell.2020.11.025> PMID: 33278357; PubMed Central PMCID: PMC7674074.
27. Fajgenbaum DC, June CH. Cytokine Storm. *N Engl J Med.* 2020; 383(23):2255–73. Epub 2020/12/03. <https://doi.org/10.1056/NEJMr2026131> PMID: 33264547; PubMed Central PMCID: PMC7727315.
28. Allen CE, Yu X, Kozinetz CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. *Pediatric blood & cancer.* 2008; 50(6):1227–35. <https://doi.org/10.1002/pbc.21423> PMID: 18085676
29. Wood H, Jones J, Hui K, Mare T, Pirani T, Galloway J, et al. Secondary HLH is uncommon in severe COVID-19. *British journal of haematology.* 2020. <https://doi.org/10.1111/bjh.16934> PMID: 32526046
30. Ardern-Jones MR, Stammers M, Phan HT, Borca F, Koutalopoulou A, Teo Y, et al. Secondary haemophagocytic lymphohistiocytosis in hospitalised COVID-19 patients as indicated by a modified HScore is infrequent and high scores do not associate with increased mortality *Clin Med (Lond).* 2021;in press.
31. Chu R, van Eeden C, Suresh S, Sligl WI, Osman M, Cohen Tervaert JW. Do COVID-19 Infections Result in a Different Form of Secondary Hemophagocytic Lymphohistiocytosis. *Int J Mol Sci.* 2021; 22(6). Epub 2021/04/04. <https://doi.org/10.3390/ijms22062967> PMID: 33803997; PubMed Central PMCID: PMC8001312.
32. Kim YR, Kim DY. Current status of the diagnosis and treatment of hemophagocytic lymphohistiocytosis in adults. *Blood Res.* 2021; 56(S1):S17–S25. Epub 2021/05/04. <https://doi.org/10.5045/br.2021.2020323> PMID: 33935031; PubMed Central PMCID: PMC8094004.
33. Wang J, Jiang M, Chen X, Montaner LJ. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. *J Leukoc Biol.* 2020; 108(1):17–41. Epub 2020/06/14. <https://doi.org/10.1002/JLB.3COVR0520-272R> PMID: 32534467; PubMed Central PMCID: PMC7323250.
34. Gu SX, Tyagi T, Jain K, Gu VW, Lee SH, Hwa JM, et al. Thrombocytopeny and endotheliopathy: crucial contributors to COVID-19 thromboinflammation. *Nat Rev Cardiol.* 2021; 18(3):194–209. Epub 2020/11/21. <https://doi.org/10.1038/s41569-020-00469-1> PMID: 33214651; PubMed Central PMCID: PMC7675396.
35. Morales D, Ostropolets A, Lai L, Sena A, Duvall S, Suchard M, et al. Characteristics and outcomes of COVID-19 patients with and without asthma from the United States, South Korea, and Europe. *J Asthma.* 2022;(just-accepted):1–14. <https://doi.org/10.1080/02770903.2021.2025392> PMID: 35012410
36. Wagner C, Griesel M, Mikolajewska A, Metzendorf MI, Fischer AL, Stegemann M, et al. Systemic corticosteroids for the treatment of COVID-19: Equity-related analyses and update on evidence. *Cochrane Database Syst Rev.* 2022; 11(11):Cd014963. <https://doi.org/10.1002/14651858.CD014963.pub2> PMID: 36385229
37. Wagner C, Griesel M, Mikolajewska A, Mueller A, Nothacker M, Kley K, et al. Systemic corticosteroids for the treatment of COVID-19. *Cochrane Database Syst Rev.* 2021; 8(8):Cd014963. <https://doi.org/10.1002/14651858.CD014963> PMID: 34396514

38. Monedero P, Gea A, Castro P, Candela-Toha AM, Hernández-Sanz ML, Arruti E, et al. Early corticosteroids are associated with lower mortality in critically ill patients with COVID-19: a cohort study. *Crit Care*. 2021; 25(1):2. Epub 2021/01/06. <https://doi.org/10.1186/s13054-020-03422-3> PMID: 33397463; PubMed Central PMCID: PMC7780210.
39. Webb BJ, Peltan ID, Jensen P, Hoda D, Hunter B, Silver A, et al. Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study. *Lancet Rheumatol*. 2020; 2(12):e754–e63. Epub 2020/10/06. [https://doi.org/10.1016/S2665-9913\(20\)30343-X](https://doi.org/10.1016/S2665-9913(20)30343-X) PMID: 33015645; PubMed Central PMCID: PMC7524533.
40. Mondal S, DasGupta R, Lodh M, Gorai R, Choudhury B, Hazra AK, et al. Predictors of new-onset diabetic ketoacidosis in patients with moderate to severe COVID-19 receiving parenteral glucocorticoids: A prospective single-centre study among Indian type 2 diabetes patients. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2021. <https://doi.org/10.1016/j.dsx.2021.03.022> PMID: 33839639
41. Alessi J, de Oliveira GB, Schaan BD, Telo GH. Dexamethasone in the era of COVID-19: friend or foe? An essay on the effects of dexamethasone and the potential risks of its inadvertent use in patients with diabetes. *Diabetol Metab Syndr*. 2020; 12:80. Epub 2020/09/15. <https://doi.org/10.1186/s13098-020-00583-7> PMID: 32922517; PubMed Central PMCID: PMC7476640.
42. FakhriRavari A, Jin S, Kachouei FH, Le D, Lopez M. Systemic corticosteroids for management of COVID-19: Saving lives or causing harm? *Int J Immunopathol Pharmacol*. 2021; 35:20587384211063976. Epub 2021/12/21. <https://doi.org/10.1177/20587384211063976> PMID: 34923856; PubMed Central PMCID: PMC8725047.
43. Kelleni MT. Tocilizumab, Remdesivir, Favipiravir, and Dexamethasone Repurposed for COVID-19: a Comprehensive Clinical and Pharmacovigilant Reassessment. *SN Compr Clin Med*. 2021; 3(4):919–23. Epub 2021/03/02. <https://doi.org/10.1007/s42399-021-00824-4> PMID: 33644693; PubMed Central PMCID: PMC7894610.
44. Waterer GW, Rello J. Steroids and COVID-19: We Need a Precision Approach, Not One Size Fits All. *Infect Dis Ther*. 2020:1–5. Epub 2020/09/22. <https://doi.org/10.1007/s40121-020-00338-x> PMID: 32953385.
45. Noreen S, Maqbool I, Madni A. Dexamethasone: Therapeutic potential, risks, and future projection during COVID-19 pandemic. *Eur J Pharmacol*. 2021; 894:173854. Epub 2021/01/12. <https://doi.org/10.1016/j.ejphar.2021.173854> PMID: 33428898; PubMed Central PMCID: PMC7836247.
46. COVID-19 Therapeutics Advice & Support Group. Hyperinflammatory syndromes and their classification. 2020.