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Using Clinical and Biochemical Parameters for Safer Discharges in COVID-19: A Comparative Study

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Abstract

The objective of this retrospective case control study was to determine clinical and biochemical parameters associated with a poorer prognostic outcome in both COVID-19 and non-COVID-19 pneumonias and use these to create safe discharge guidelines.

This study in a single respiratory ward of a district general hospital compared admission and discharge C-reactive protein (CRP) levels, eosinophil and lymphocyte counts, respiratory rate, oxygen saturations and NEWS2 score from two groups of patients admitted with either confirmed COVID-19 pneumonia (46 patients) or pneumonia of other aetiology (45 patients). Outcome was defined as either 'good' or 'poor'.

Combined values of prognostic markers analysed by binary logistic regression followed by ROC analysis showed a final combined AUC value of 0.955 thus yielding a test that had a better prognostic capability in predicting the outcome of patients with COVID-19. This combined test could be used to guide safe discharge of patients with COVID-19.

Keywords

COVID-19, SARS-CoV-2, Biochemical Parameters, Discharge, Eosinopenia

Introduction

The SARS-CoV-2 is a novel, single stranded RNA virus currently at the centre of a pandemic that has led to significant mortality around the world. Infection with the virus causes a wide range of clinical presentations, the manifesting disease being termed 'COVID-19'.

The underlying pathophysiology of the disease is not yet well understood. Various blood markers are altered significantly in those with COVID-19 and have been shown to play a role in aiding diagnosis as well as identifying a more severe course of disease. Many of these have been examined to aid in identifying patients both likely to have the disease, and those likely to run a more severe disease course [1].

The presence of eosinopenia alongside lymphopenia

has been suggested to be an indicator of the diagnosis of COVID-19 [2], supported by other studies that have concluded that the presence of eosinopenia was observed more frequently in those testing positive for SARS-CoV-2 as compared to those testing negative [3,4]. The presence or absence of eosinopenia has previously been suggested to be associated with worse outcomes though there has recently been debate over this [5].

Multiple studies suggesting that rising C- reactive protein (CRP) levels and falling lymphocyte levels are suggestive of worse outcomes [6-8].

A recent systematic review by Zhao et al also supported the observation that lymphopenia in COVID-19 patient's correlates with disease severity [9]. The primary aim of our study was to explore if various clinical and biochemical features measured during treatment of patients with COVID-19 could help predict outcome. Our hypothesis was that falling lymphocyte and eosinophil counts would be correlated with poor outcome. The secondary aim of the project was to determine safe discharging parameters based on our findings to help guide decision making.

Correlation was made between admission and discharge clinical parameters including respiratory rate, oxygen saturation and National Early Warning Score version two (NEWS2 score). The NEWS2 score is a scoring system originally devised by the Royal College of Physicians of London to help clinical staff recognise a patient that is deteriorating through a standardised scoring system. A second version was implemented in 2019, and is the version used to date [10].

Limited guidelines exist for guiding safe discharge in this group of patients. This data was also used as a means of examining discharge practices at the unit, comparing discharge parameters in both groups to available recommended discharge criteria from other international regulatory bodies [11]. No clear specific guidelines were found from the UK stating when a patient with COVID-19 is deemed clinically safe to be discharged.

Methods

Study Design, Institutional Review, Ethical Approvals, and Participants' Eligibility Criteria:

- Retrospective case control study looking at comparative parameters between COVID-19 & non COVID-19 pneumonias.
- Recruitment: November 2019 to March 2020 into non COVID-19 group and March 2020 to April 2020 into COVID group.
- 100 % specificity for COVID-19 group with positive nasopharyngeal swabs with a total of 46 patients who had positive RT-PCR [12].
- Non COVID-19 group included pneumonia of other aetiology- community acquired, hospital acquired and aspiration (45 patients).
- Non COVID-19 group: excluded exacerbation of obstructive airway disease, heart failure, interstitial lung disease.
- Majority of patients in COVID-19 group needed non-invasive ventilation (NIV) as the ward setting was designated as a respiratory HDU during the pandemic.
- Study registered as an audit-research study with number 1413 & ethics approval deemed not necessary as data collected retrospectively.

Table-1 shows the inclusion and exclusion criteria for recruitment of patients into this study.

Data Collection:

- Clinically relevant information was obtained from electronic medical records including age, sex, CRP, lymphocyte and eosinophil counts.
- Clinical parameters recorded on admission and discharge:
  (1) Respiratory rate; (2) pulse oximeter oxygen saturation (SpO_2), temperature and NEWS2 score.
- Outcome was defined as poor, with either death or prolonged intensive care (ICU) admission. Good outcome was defined as discharge from hospital.

Statistical Analysis:

All statistical analysis was carried out with SPSS ver.25 (IBM Corp), PRISM (Graph Pad), SciPy module (version 1.3) for Python (version 3.7.2) and R (version

3.60) with P<0.05 considered as statistically significant.

To determine the combined effect of all biomarkers and clinical parameters on the final prognostic outcome, a binary logistic regression (BLR) model examining all 5 variables (eosinophil count at discharge, CRP level at discharge, lymphocyte count at discharge, respiratory rate at discharge and NEWS2 score at discharge). These were classed as predictors and the outcome of treatment (good or poor outcome) was classed as the dependent variable. The predicted values from the BLR run over 7 iterations were then used as the new covariates in the final ROC analysis for the combined biomarkers in SPSS.

Table-1: Inclusion and exclusion criteria for recruitment of patients into the study

Inclusion and exclusion criteria for COVID-19 participants	
Inclusion criteria	**Exclusion criteria**
Participants > 17 years old	Participants < 17 years old
Participant tested positive on nasopharyngeal swabs for SARS-CoV-2 RNA	Not receiving treatment on the designated respiratory ward
Receiving treatment on respiratory ward	
Inclusion & exclusion criteria for non-COVID-19 participants	
Inclusion criteria	**Exclusion criteria**
Participants > 17 years old admitted between November 2019 and March 2020 with a clinical diagnosis of pneumonia (either community acquired, hospital acquired or aspiration)	Participants < 17 years old
Receiving treatment on the respiratory ward	Not receiving treatment on respiratory ward or not receiving treatment for pneumonia

A minimum sample size of 34 was required for 90% power, $\alpha = 0.05$ and the ideal anticipated Cohen's "d" effect size of 0.80, calculated using a two-sample T-test with SPSS ver. 25 (IBM Corp) integrated with R version 3.33. Thus, the sample size of 46 participants in the COVID-19 group and 45 participants in the non-COVID-19 group ensured that the study was not underpowered.

Results

Demographics and Participant Characterisation in the Study:

The breakdown of clinical outcomes observed in both groups of patients is summarised schematically in **Fig-1**, and **Table-2**.

Swab Testing of Participants in the Study:

A total of 46 participants in the COVID-19 group tested positive for SARS-CoV-2 on swabs that were collected at the time of admission using the RT- PCR method. Participants recruited prior to March 2020 in the non-COVID-19 pneumonia group (n = 45) were not tested by RT-PCR for the presence of SARS-CoV-2 RNA since facilities for testing were not available prior to the outbreak in the local area and COVID-19 was not believed to be widely in circulation. All patients admitted from March 2020 in the non-COVID-19 group had tested negative for SARS-CoV-2 RNA on nasopharyngeal swabbing with no radiological evidence of the disease.

Comparison of Prognostic Parameters by SARS-Cov-2 RNA Positive or Negative Status:

- The Kruskal-Wallis test carried out to determine the differences between various prognostic factors in patients with COVID-19 compared to patients with non COVID-19 Pneumonia.
- Parameters compared include age, eosinophil count, CRP count, lymphocyte count, respiratory rates, oxygen saturation and NEWS2 score.

Table-2: Demographic and study information of participants ± standard deviation (SD)
Median age : 70.00 ± 14.91 (N=91)
Sex (f/m) : 35/ 11
Swab COVID-19 positive : 46 (50.5%, N =91)
Swab COVID-19 negative: 45 (49.5%, N=91)
Median age of Swab COVID19 positive : 68.00 ± 12.49 (n= 46)
Median age of Swab COVID19 negative : 73.00 ± 16.44 (n=45)
Sex (m/f, %) – COVID19 positive: 76/ 24
Sex (m/f, %) – COVID19 negative: 71/ 29
Outcomes
Good: n=66 (72.5% of total , N=91)
Poor: n=25 (27.5% of total, N=91).
Median age of participants with Good outcome: 69.5 ± 15.25 (n=66)
Median age of participants with Poor outcome: 72.00 ± 13.64 (n=25)
Sex (m/f, %) – good outcome: 77/ 23
Sex (m/f, %) – poor outcome : 75/ 25
Endpoint
Discharged safely home: 66 (72.5%, N=91)
Transferred to ITU: 8 (8.8%, N=91)
Death: 17 (18.7%, N =91)

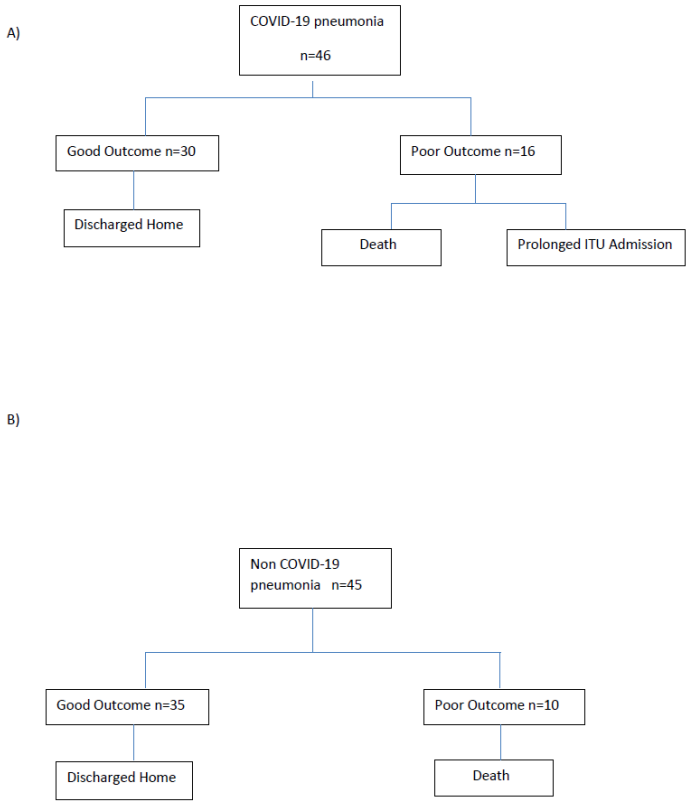

Fig-1:

A schematic diagram depicting the outcomes of patients within (a) the COVID-19 group and (b) the non-COVID-19 group.

Discussion

Six clinical and biochemical features were highlighted in the ROC curve analysis as being helpful in predicting safe and successful discharge from hospital; eosinophil count, CRP levels, lymphocyte count, respiratory rate, oxygen saturation levels and NEWS2 scores (**Fig-2**).

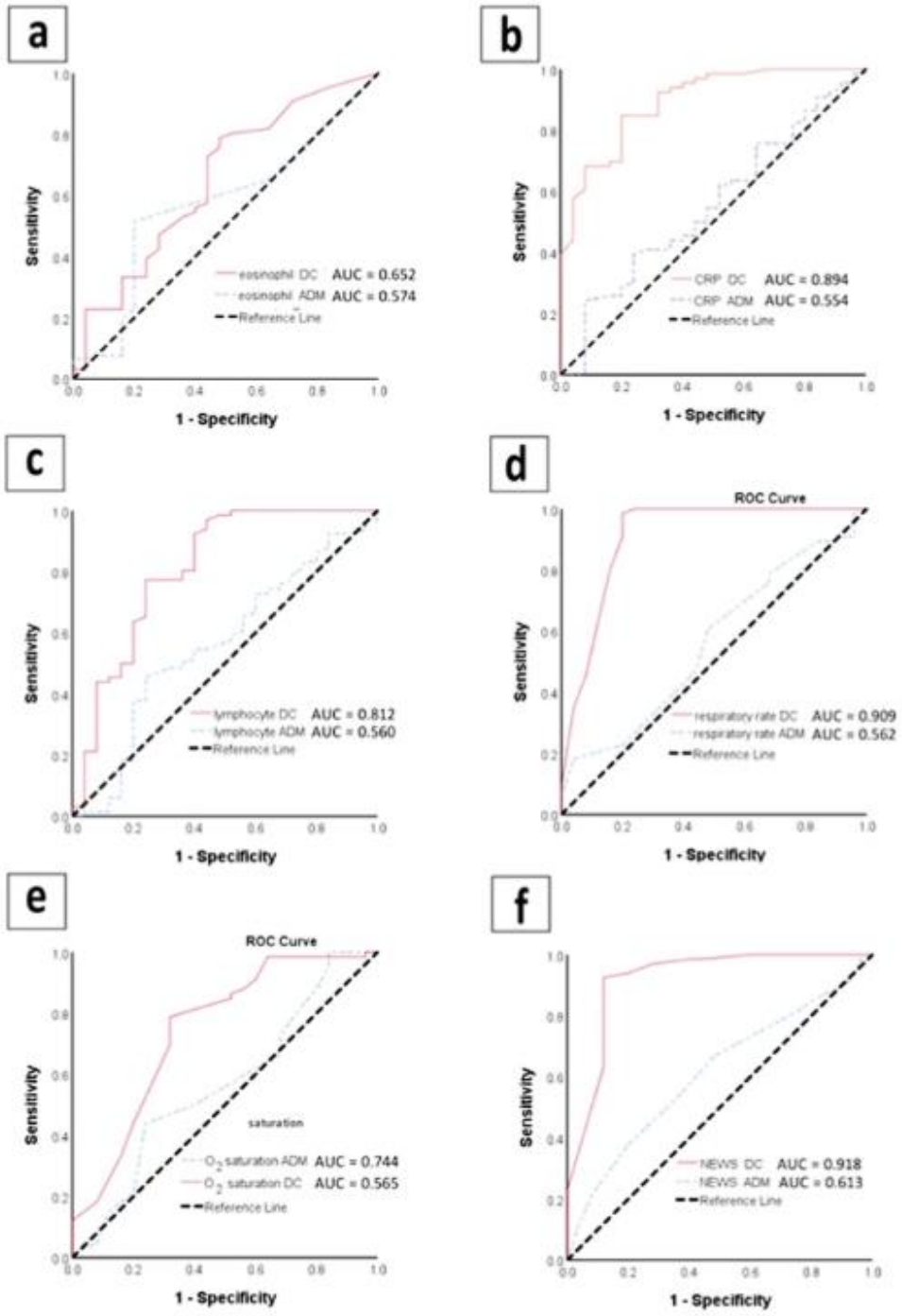

Fig-2:

A Receiver Operating Curve (ROC) characteristic analysis exploring the relationship of various parameters to outcome in patients with COVID-19. The state variable in the ROC analysis was set to the successful discharge and resolution of all symptoms following acute admission to hospital for COVID-19 infection. The dotted reference line indicates the state where sensitivity = 1-specificity, and points that fall on this line represent a non-diagnostic test.

a) *ROC analysis of eosinophil counts in patients with COVID-19 showed an AUC of 0.652 ± 0.067 at the point of discharge, a significant increase from the AUC of 0.574 ± 0.066 admission (p=0.026, C.I. 95%).*
b) *CRP values of inpatients admitted for COVID-19 showed gradual improvement with an AUC of 0.894 ± 0.036 at discharge, thus showing strong prognostic value.*
c) *Lymphocyte counts also showed a significant increase (p< 0.001, C.I. 95%) in COVID-19 patients with a better outcome at the point of discharge, AUC of 0.812 ± 0.058.*
d) *Reduction in respiratory rate was a significant clinical feature (p<0.001, C.I. 95%) in patients with COVID-19 with a good outcome at the point of discharge, AUC = 0.909 ± 0.043.*
e) *The oxygen saturation levels in COVID-19 patients at discharge showed significant improvement (p<0.001, C.I. 95%) compared to levels at admission (AUC 0.565 ± 0.069). Significantly improved oxygen saturation levels at discharge (AUC 0.744 ± 0.063) was indicative of a better prognosis.*
f) *NEWS2 score at discharge was a significant (p<0.001, C.I. 95%) clinical feature predictive of a good outcome in COVID-19 infection, AUC: 0.918 ± 0.039.*

Though infection with SARS CoV-2 was originally purported to be an infection associated with advancing age [13], those admitted to this respiratory unit were younger overall than those with pneumonias of other aetiologies (**Fig-3a**). This was largely reflective of its role as the designated area for patients who could require non-invasive ventilation or escalation to the ICU if appropriate. Many patients who were older in the COVID-19 group were not felt to be appropriate for further escalation to ICU (at a time when NIV was not being recommended routinely) and so were not transferred to the respiratory ward but to other designated wards for patients with the virus where management was conservative. The non-COVID-19 pneumonia group receiving treatment on the respiratory unit prior to the pandemic likely represented the standard group of patients who would be treated for pneumonia on the respiratory ward.

Eosinopenia:

Eosinopenia has been noted and discussed in several studies of patients with COVID-19 [2,3,6] and significant differences are noted in eosinophil counts (cells/ml) between patients testing positive and patients testing negative for the SARS-CoV-2 virus (p< 0.001, 95% C.I.) at the point of admission (**Fig-3b**) and at time of discharge from hospital (**Fig-3c**). It appears that there is a small yet significant level of eosinopenia among patients who have COVID-19 pneumonia and this feature persists throughout their treatment up to the point of their recovery of respiratory symptoms and a successful discharge from hospital. This may help support a diagnosis of COVID-19 prior to confirmation by PCR and is a cheap and accessible test [2-4].

In addition to their well-established role in allergic and parasitic disease, extensive research and discussion has been carried out to consider the role of the eosinophil in other disease processes [14].

The cause for the suppression of eosinophils in COVID-19 is not clearly understood but is well-correlated with acute inflammation or stress [15-17]. Other biological processes such as complement activation is known to cause prompt eosinopenia in humans [16]. The primary eosinopenic response observed in acute inflammation is thought to be due to peripheral sequestration of circulating eosinophils by chemotactic migration into the inflammatory site [15]. Eosinophils are known to mediate allergic disorders; their action is largely mediated via Th2-type cytokines while simultaneously downregulating the effect of Th-1 type pro-inflammatory pathways [18]. The apparent depletion of eosinophils is thought to be due to chemotaxis and targeted sequestration of these cells to the site of infection in the lungs, the disappearance of Th-2 type cytokine secreting cells triggers a Th-1 switch, releasing cytokines which mediate inflammation such as interferon-alpha and interleukin-1 [18]. This could help to explain the "cytokine storm" theory which is felt to explain many of the most severe sequelae of not only COVID-19, but other infectious diseases [19].

This small study supports the previous notion that eosinopenia on admission (**Fig-3b**) helps support a diagnosis of COVID-19 [1,2] and that persistent

eosinopenia is associated with a poorer outcome (**Fig-4a**).

Lymphocyte Count:

Though there was no statistical difference between

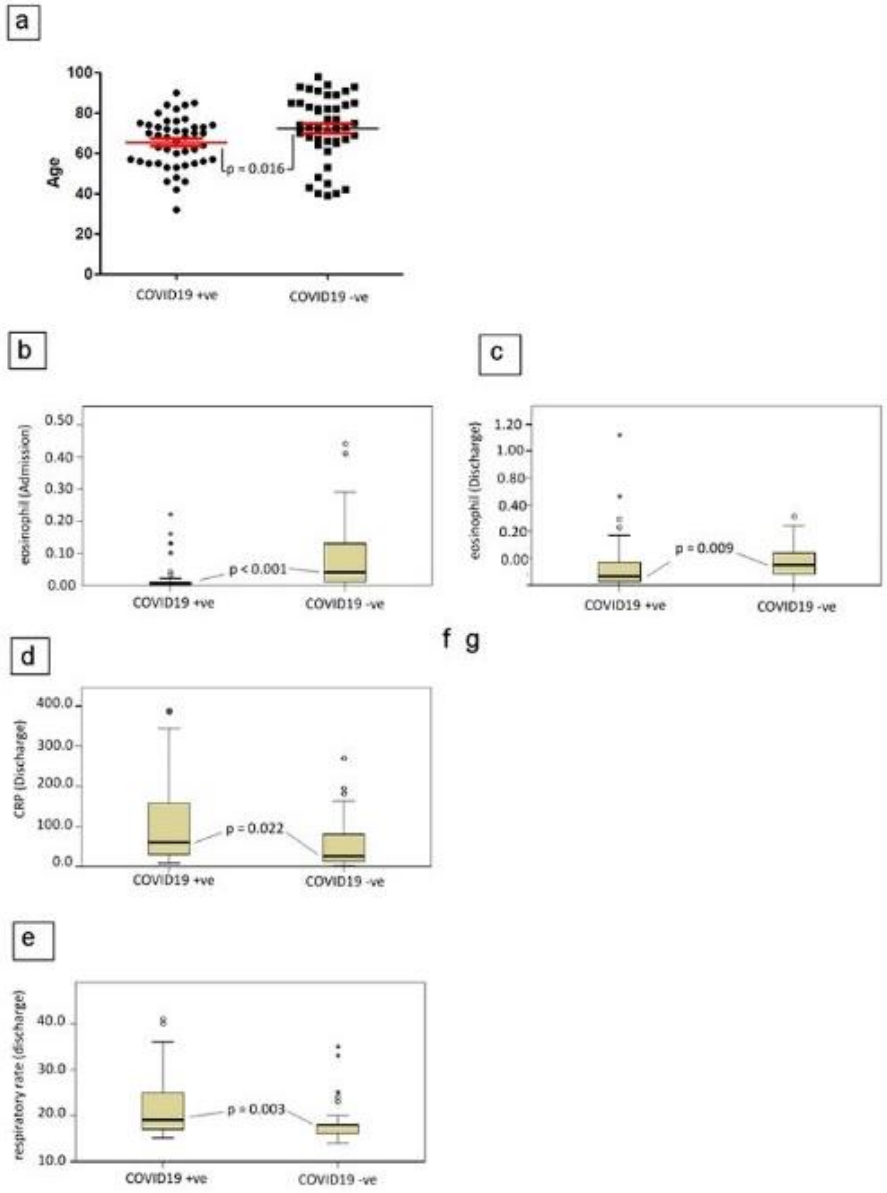

Fig-3:

The difference of prognostic parameters in patients with and without COVID-19.

a) *The difference of age-distribution among patients admitted with COVID-19 and patients negative for COVID-19 yet presenting with severe pneumonia-like symptoms.*
b) *Eosinophil counts (cells/ ml) of participants with COVID-19 were significantly lower at admission and discharge compared to participants testing negative for the virus and with pneumonias of other causes, p<0.001, C.I. 95% (Fig-3b, Fig-3c).*
c) *A significant difference is also seen in eosinophil counts (cells/ml) between patients with COVID-19 and patients with non-COVID-19 pneumonia (p= 0.009, 95% C.I.) at the point of discharge from the hospital.*
d) *CRP levels at discharge were significantly higher in patients with COVID-19 compared to patients with pneumonia from all other aetiology (p= 0.009, 95% C.I.)*
e) *Patients with COVID-19 were significantly more tachypnoeic on discharge, noted by their increased respiratory rate (p=0.003, C.I. 95%) compared to non-COVID pneumonia-19 patients.*

the two groups in admission and discharge lymphocyte counts though there was obvious correlation in the COVID-19 sample with falling lymphocyte count and poor prognosis at discharge (**Fig-4c**). This is supportive of previous research suggesting that falling lymphocyte count is associated with worse outcomes [1].

C - Reactive Protein (CRP):

There was no statistically significant difference in CRP levels between groups on admission (P=0.956). CRP counts in those with COVID-19, however, were generally higher on discharge than in those without the infection (P= 0.022, **Fig-3d**). In addition, those with COVID-19 pneumonia and a poor outcome had a higher discharge CRP (**Fig-4b**), confirming findings of previous studies [1,20]. This finding may be reflective of an overall higher mortality rate and poorer prognosis in those with COVID-19 pneumonia as compared to those with pneumonia of other aetiology. In some patients who were most unwell, the CRP level may not have been repeated many times prior to their transfer to the ICU or death. In such cases the CRP is therefore likely to have been much high reflecting a worsening condition.

In this study, falling CRP levels from admission to discharge was considered a good prognostic marker (**Fig-4b**).

Respiratory Rate:

The respiratory rate was not significantly different between the two groups on admission, though there was a difference detected in the respiratory rate at discharge, with the overall rate and range in respiratory rates observed being smaller in the non-COVID-19 group (**Fig-3e**). We noted that in non-COVID-19 patients, the respiratory rate did not vary as much as they did in the COVID-19 group.

What we can infer from these results is that a higher respiratory rate or tachypnea suggests either clinical deterioration or that the patient is not yet ready to be discharged home and was associated with a poorer prognosis at discharge in the COVID-19 group (**Fig-4d**). This can therefore be used as a helpful surrogate marker to help guide discharge decisions.

Oxygen Saturations:

There was no statistical difference between groups in the oxygen saturations of patients on admission or discharge. Those with lower oxygen saturations at discharge were more likely to have a poor prognosis (**Fig-4e**). A pneumonic process regardless of aetiology would expect to create a hypoxaemia, reflected in reduced oxygen saturation levels measured using pulse oximetry. This is, however, a less accurate way of measuring the partial pressure of oxygen in the blood, and measurement from an arterial blood gas result would have been more accurate. The presence of other undiagnosed comorbid lung conditions could also have affected oxygen saturations though care was taken to exclude these from the control group.

National Early Warning System Score (NEWS2 Score):

No statistical difference was detected between the groups in the NEWS2 Score on admission. On discharge the NEWS2 Score of the non-COVID-19 group was lower, with less variation in the scores (**Fig-4f**). The results may have been distorted by higher NEWS2 Score results prior to death or transfer to ICU in COVID-19 patients. This would create a skew in the data towards higher NEWS2 scores in those with COVID-19.

The individual prognostic markers evaluated for their performance in identifying patients with different clinical outcomes is shown in the assessments via receiver operating characteristic (ROC) curves in **Fig-2**. Previous studies have demonstrated that combining various prognostic markers can dramatically increase diagnostic accuracy [21].

Our sample group with COVID-19 pneumonia was from a single ward, designated as a respiratory HDU during the pandemic, where patients could be treated with non-invasive ventilation (NIV) and with the potential to full escalation to ICU if needed. In addition, the group with COVID-19 associated pneumonia were predominantly white in ethnic background, reflecting relative homogeneity of the local population.

Our study strongly shows that a good clinical outcome and timely discharge of patients with

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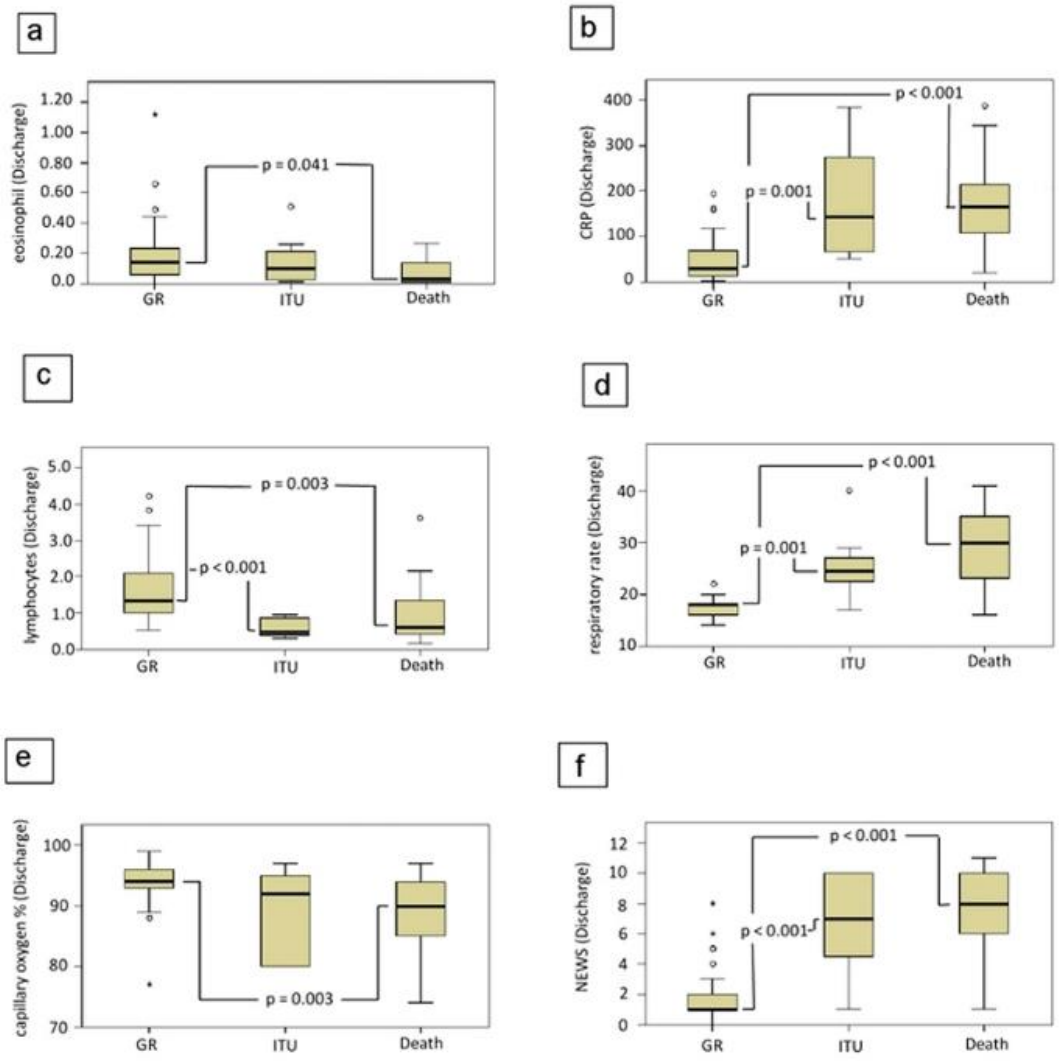

Fig-4:

The effect of different prognostic parameters measured in patients categorised in three groups as having good response (GR, safely discharged home), transferred to intensive-care units (ITU) or succumbed to death (Death). The lines drawn represent the difference (shown as p- values at 95% C.I.) between the measured median levels in each category.

a) *Patients with COVID-19 pneumonia with a good clinical response to in-hospital treatment and whom eventually were fit for discharge showed significantly higher eosinophil counts (p =0.041, C.I. 95%) during their hospital stay compared to patients who responded poorly and succumbed to death.*

b) *Patients who eventually were fit for discharge and showed good response to treatment showed marked reduction of CRP levels (p<0.001, C.I. 95%) compared to patients who either showed a worsening of symptoms and had to be escalated to ICU or whom eventually died.*

c) *The lymphocyte count of patients with COVID-19 who responded well to treatment were significantly higher as treatment progressed until the point of discharge from hospital compared to those who had to be transferred to ITU (p<0.001, C.I. 95%) or those who eventually died (p=0.003, C.I. 95%).*

d) *Patients with COVID-19 with a more positive outcome had a significant reduction in respiratory rate compared to those who worsened in their symptoms and had to be transferred to ICU or those who eventually died (p<0.001, C.I. 95%).*

e) *Patients who responded well to treatment and were eventually fit for discharge showed significant improvement in oxygen saturation levels (p=0.003, C.I. 95%) compared to those who showed deterioration of symptoms.*

f) *Patients with a better prognosis showed gradual but significant improvement in NEWS2 scores compared to those who had to have their treatment escalated to ICU or died (p<0.001, C.I. 95%).*

significantly improved respiratory reserve is seen when (i) lymphocyte and eosinophil counts are higher at discharge as compared to admission and (ii) CRP levels are improving towards baseline.

What this study adds:

A summary of the discharge criteria for patients with COVID-19 for various global organisations is available from the European Centre for Disease Control (ECDC) [11]. A consistent criterion across different countries is clinical improvement, which can be measured in various ways. Values such as CRP, lymphocyte count and NEWS2 score, of which we have analysed, can serve as excellent markers of clinical progress.

Combined statistical analysis of the data strongly suggests that the parameters examined can give close to 100% specificity and sensitivity with an area under the curve (AUC) of 0.955 (**Fig-5**). This would provide a solid basis for guidelines for the safe discharge of patients with COVID-19 (**Fig-6**).

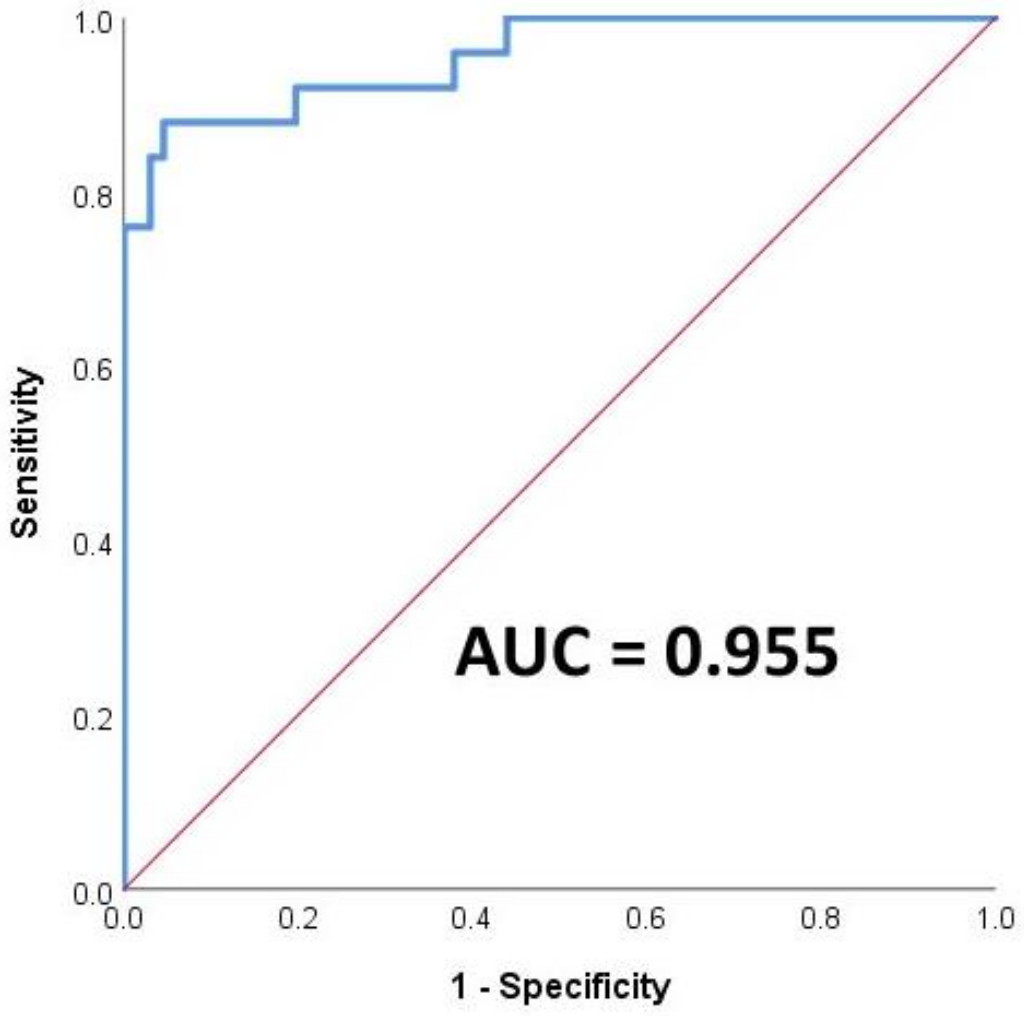

Fig-5:

ROC analysis on combined test probabilities as a model for predicting safe discharge. Individual prognostic markers evaluated and shown to be of value in predicting outcome as shown in Fig-4 (markers determined close to discharge: i) eosinophil counts, CRP levels, lymphocyte counts, respiratory rate and NEWS2 score) were analysed using binary logistic regression (BLR). The resulting predicted probabilities were computed using ROC curve analysis, and the final combined AUC value was 0.955. This value was much higher when compared to the individual AUC values obtained from carrying out each of the prognostic tests in isolation.

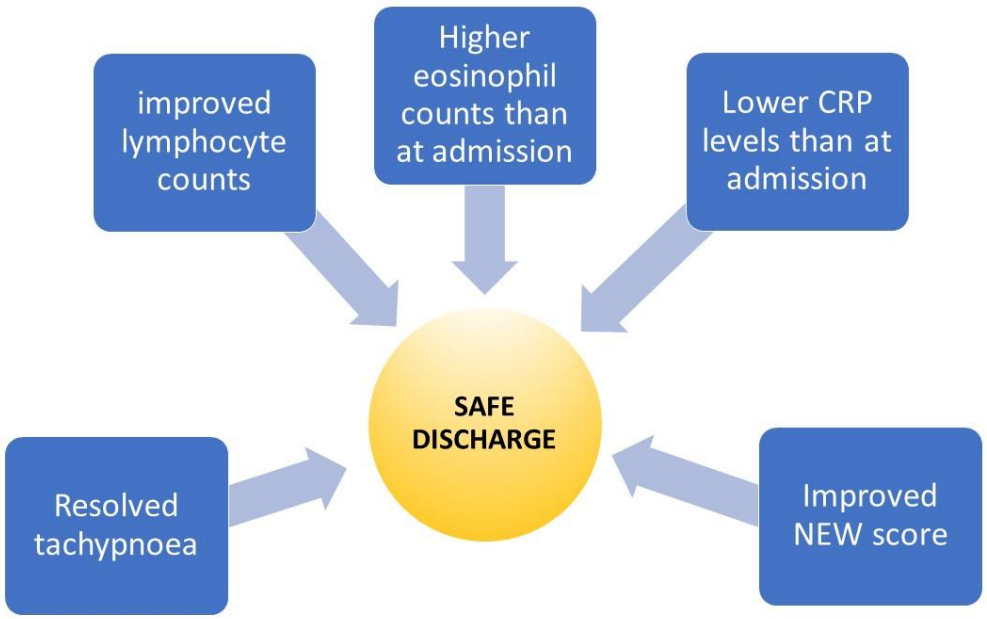

Fig-6:
Guidelines for the safe discharge of patients with COVID-19

Table-3 shows the proposed scoring system based upon the parameters investigated, validated statistically to suggest a good prognosis and support discharge in patients if all five criteria are met.

In those patients where all criteria are not yet met it suggests further optimisation or escalation as an inpatient would be appropriate.

Although we did not use the scoring system initially to guide discharges during the pandemic, modified versions were incorporated which included all of these parameters for those patients with COVID-19 pneumonia. Our study was done as part of an audit-research project during COVID-19 and on analysis we managed to achieve a 98% successful discharge rate using the system and had no re-admissions to the unit due to COVID-19 or its related complications. One patient was discharged with the score due to discharge with supplemental oxygen which was reviewed in the community. The authors acknowledge that this scoring system is by no means exhaustive nor does it give a complete outlook for COVID-19 patients but can be used to aid clinical decisions regarding safe discharge practices and also to support prognostic outlook in patients with COVID-19 pneumonia as evidenced by our statistical analysis and clinical performance.

Table-3: Developed scoring system to identify patients with poorer prognosis I COVID-19: The Maidstone Scoring System

Parameter Score	Eosinophils	Lymphocytes	CRP	Respiratory Rate	NEWS2 Score
1	Normal or Improving	Normal or Improving	Falling CRP	Normal	<2 without supplemental Oxygen
0	Reducing or Persistent Eosinopenia	Reducing or Persistent Lymphopenia	Elevated CRP	Tachypnoea	>3 or on supplemental oxygen therapy

Strengths and Limitations of this Study

Strengths:

1. This was a unique study looking at a holistic approach to patient care, incorporating biochemical and clinical markers.
2. Comparison between COVID-19 and non COVID-19 pneumonia managed by the same team of physicians to avoid bias.
3. Devising a scoring system for safe discharges which could be useful in the event of a second wave or in countries that are still being affected.
4. 100% specific group with positive nasopharyngeal swabs in the COVID-19 cohort.

Limitations:

1. The study was performed retrospectively, subjecting it to possible bias, though with COVID-19 being a novel disease, prospective studies are difficult.
2. Older patients were predominant in the non-COVID-19 group whereas a slightly younger population was admitted in the COVID-19 group.
3. Study conducted with a small sample size in a single institution which may limit generalisability.

The goal of this study was to determine if combinations of various test-variables could result in a good predictor model system. The use of machine-learning algorithms such as binary logistic regression facilitated the calculation of new predicted probabilities using the combined values of test-variables. The resulting predicted probabilities were used for subsequent ROC-analysis, resulting in a higher AUC value (**Fig-5**) than the previously calculated values on the individual test variables (**Fig-2**).

The final model that this study proposes is summarised in **Table-3**, where a score of one is awarded if any of the test-variable criteria is satisfied. For example, if CRP levels recorded at a time following convalescence during in-patient stay are lower than at admission and within normal parameters then a score of 1 is awarded. A cumulative score of five indicates that the criteria for safe discharge have been attained.

Competing Interests

All authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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Author Contributions

SAH designed and advised on the study, and was clinical supervisor to VL, SS, ABK and LGD. VL wrote the primary manuscript. VL, SS, ABK and SAH clinically examined & assessed participants, recruited participants, and applied for audit approval for the study. LGD carried out statistical analysis and contributed to the writing of the manuscript.

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