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CORRELATION OF PATIENT PROFILES AND BIOMARKERS WITH OUTCOMES IN COVID-19 ICU PATIENTS: A RETROSPECTIVE ANALYSIS

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Abstract

Background: *COVID-19 is a novel disease with a highly variable and unpredictable clinical course. Various clinico-demographic factors and numerous biomarkers have been identified in studies from the West and marked as possible predictors of severe illness and mortality which may be used to triage patients for early aggressive care. This triaging becomes even more significant in resource-limited critical care settings of the Indian subcontinent.*

Methods: *This retrospective observational study recruited 99 cases of COVID-19 admitted to intensive care from 1 May to 1 August 2020. Demographic, clinical and baseline laboratory data were collected and analysed for association with clinical outcomes, including survival and need for mechanical ventilatory support.*

Results: *Male gender (p=0.044) and diabetes mellitus (p=0.042) were associated with increased mortality. Binomial logistic regression analysis revealed Interleukin-6 (IL6) (p=0.024), D-dimer (p=0.025) and CRP (p<0.001) as significant predictors of need of ventilatory support and IL6 (p=0.036), CRP (p=0.041), D-dimer (p=0.006) and $P_aO_2F_IO_2$ ratio (p=0.019) as significant predictors of mortality. CRP >40 mg/L predicted mortality with sensitivity of 93.3% and specificity of 88.9% (AUC 0.933) and IL6> 32.5 pg/ml with a sensitivity of 82.2% and specificity of 70.4% (AUC 0.821).*

Conclusion: *Our results suggest that a baseline CRP >40 mg/L, IL6 >32.5 pg/ml or D-dimer >810 ng/ml are early accurate predictors of severe illness and adverse outcomes and may be used to triage patients for early intensive care.*

Keywords

COVID-19 • intensive care units • demographic profile • ferritin • LDH, CRP • IL-6 • NLR • mechanical ventilation • mortality

Introduction

The COVID-19 pandemic is placing an acute strain on resource-limited intensive care setups in many developing Asian nations, including India. This disease is characterised by protean manifestations ranging from asymptomatic illness to acute respiratory distress syndrome, which may be further complicated by pulmonary and systemic thrombosis, disseminated intravascular coagulation, direct myocardial injury, and multi-organ dysfunction. Experiences of the past few months suggest that the disease course is highly unpredictable with rapid clinical deterioration often seen in patients presenting with moderate to severe illness. There is a pressing need to effectively triage patients for intensive care. Prediction of disease severity and institution of early aggressive care for at-risk patients may promote judicious use of limited resources and improve outcomes.

Observations primarily from Western populations have identified numerous clinical and demographic factors associated with severe illness and poor prognosis, including advanced age, male sex, and co-morbid illnesses such as diabetes, hypertension and end-stage renal disease. [1,2] Significant racial and ethnic variations in susceptibility to severe illness and mortality have been seen in reports from around the world. [3]

Numerous biomarkers expected to represent the underlying pathogenetic mechanisms of severe COVID-19 illness have been advanced as potential diagnostic and prognostic indicators. They include lymphopenia (increased neutrophil-lymphocyte ratio [NLR]), serum ferritin, serum lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimers, serum procalcitonin, cardiac

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troponins, and IL6 levels. [4] Alterations in these markers potentially represent the combination of direct pulmonary injury and dysregulation of inflammation and coagulation that is considered pathognomonic of severe illness. However, utility of these various biomarkers as predictors of disease severity, progression, recovery, and mortality is still being evaluated.

There is paucity of data of clinical and demographic profiles of Indian COVID-19 patients requiring intensive care, especially with regard to biomarker profiles and derangements. The aim of this observational study was to describe the demographic, clinical and biomarker profiles of patients with moderate to severe COVID-19 admitted to intensive care in northern India and to correlate these with clinical outcomes. The study results may help us in triaging critical patients needing aggressive management in the first 24 to 48 hours after admission.

Materials and Methods

Study design and population

This retrospective observational study was conducted in the dedicated COVID ICUs of a tertiary care multi-speciality teaching hospital in New Delhi, India from 1 May 2020 to 1 August 2020. The trial was prospectively registered with the clinical trials registry of India (No. CTRI/2020/12/030049). After institutional ethical approval (80/8/2020/No. 215) the study was carried out on patients with laboratory-confirmed SARS-CoV-2 with moderate to severe illness (as per national COVID treatment guidelines) admitted to intensive care units. These ICUs did not admit paediatric patients, so a total of 99 adult patients with complete clinical and laboratory data were enrolled in this study. In view of the retrospective and observational nature of the study, an ethics waiver for informed consent was granted by the institutional ethics committee. All patients received a standard treatment including steroids, convalescent plasma, broad-spectrum antibiotics, and Remdesivir in addition to supportive management as per institutional policy.

Data collection

Data was collected from medical records. Demographic and clinical details recorded at the time of admission to the ICU including age, sex, and co-morbid medical conditions (hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease and anaemia) were noted. Baseline (first blood sample taken within 6 hours of admission to the ICU) arterial blood gas P_aO_2:F_iO_2 ratio (PFR), serum ferritin, serum lactate dehydrogenase (LDH), serum high-sensitive C-reactive protein (hsCRP), IL6, D-dimer, and neutrophil-lymphocyte ratio (NLR) were noted. Note was made of need for non-invasive (NIV-BiPAP) or invasive mechanical ventilatory support. Patients only requiring oxygen therapy including high flow nasal oxygen were classified as not requiring mechanical ventilation. Patients who required either non-invasive (NIV) or invasive mechanical ventilation (IV) were classified as requiring mechanical ventilatory support (MVS). The final outcomes of the patients (either they improved or expired) was noted.

Statistical analysis

Statistical analysis of collected data was done with MS-Excel, SPSS v22.0 software (Armonk, NY, USA: IBM Corp). Quantitative variables such as age of the patients, value of biomarkers and PF ratio were expressed as median and interquartile range. Qualitative variables such as gender of the patients, prevalence of comorbidities and clinical outcome were expressed as frequencies and percentages. Categorical variables were compared between the outcome groups with the chi-squared (χ^2) test or Fisher exact test whereas continuous variables were compared using the Mann Whitney U test. Comparison of continuous variables between multiple outcome groups was done with one-way analysis of variance (ANOVA). Binomial logistic regression analysis was performed to ascertain the effects of biomarkers and PFR on the likelihood of the need of ventilatory support and mortality of participants. Correlation between continuous variables and biomarkers was assessed with Pearson's product moment coefficient. Receiver operating characteristic (ROC) curves were constructed for biomarkers and PFR to calculate the optimal cut-offs for predicting mortality and need of mechanical ventilatory support. A p-value of <0.05 was taken as significant.

Results

Clinico-demographic and biomarker comparisons with respect to patient survival and need for ventilatory support are summarized in Tables 1 and 2, respectively. Ninety-nine patients with laboratory-confirmed COVID-19 who were admitted to intensive care with moderate to severe illness were recruited for this study. The median age was 57 years (IQR, 45–65) and 62 (62.6%) were men. 77 (77.7%) had one or more comorbidities including diabetes (44.4%), hypertension (48.5%), chronic kidney disease (15.2%), coronary heart disease (13.1%) and anaemia (24.2%). The overall mortality in ICU was 45.4%. 23 (23.2 %) patients required non-invasive ventilatory support with BiPAP and 37 (37.3%) patients required invasive mechanical ventilation. 39 (39.3%) patients were managed with oxygen therapy, including high-flow nasal oxygenation. Values of biomarkers of inflammation (serum ferritin, LDH, CRP, NLR, and IL6) and coagulation

(D-dimers) were comparable across age groups. D-dimers were significantly lower in females (p=0.046) when compared to males, who showed higher mortality. Patients with diabetes, who also showed higher mortality, showed significantly higher NLR (0.023) and lower PFR (p=0.011). Correlation analysis revealed significant inverse correlation between all biomarkers and the baseline PFR. The strongest correlations observed were between CRP and PFR (Pearson's R=0.421, p<0.01) and between CRP and IL-6 (Pearson's R=0.313, <0.01). Male gender and diabetes mellitus showed significant association with mortality (p=0.044 and p=0.042 respectively) as well as with the need of non-invasive or invasive mechanical ventilatory support (p=0.021 and p=0.027, respectively). Coronary artery disease was significantly associated with invasive mechanical ventilation (p=0.015). Prevalence of other comorbidities was not significantly different across outcome groups. Elevations of all biomarkers showed significant association with mortality and the need of ventilatory support (Figure 1). Subgroup analysis (post-hoc Bonferroni correction) revealed that elevations in all biomarkers were significantly associated with incidence of invasive ventilation.

CRP levels of patients requiring either non-invasive or invasive ventilatory support were significantly higher than that of patients not requiring any ventilatory support (p<0.001).

Table 1: Clinico-demographics and laboratory parameters compared across survival groups.

Clinical & Demographic Characteristics	Total (N=99)	Expired (N=45)	Recovered (N=54)	p-value
AGE (yrs)	57 (45.0-65.0)	57 (45.0-65.0)	54 (45.0-65.5)	0.898
≥60 YEARS, (N,%)	46, 46.5	22, 48.9	24, 44.4	0.659
MALES, (N,%)	62, 62.6	33, 73.3	29, 53.7	0.044
FEMALES, (N,%)	37, 37.4	12, 26.7	25, 46.7	
HYPERTENSION, (N,%)	48, 48.5	22, 48.9	26, 48.1	0.941
TYPE II DIABETES MELLITUS, (N,%)	44, 44.4	25, 55.6	19, 35.2	0.042
CHRONIC KIDNEY DISEASE, (N,%)	15, 15.2	8, 17.8	7, 13	0.506
CORONARY HEART DISEASE, (N,%)	13, 13.1	9, 20	4, 7.4	0.065
ANEMIA, (N,%)	24, 24.2	10, 22.2	14, 25.9	0.669
Arterial oxygenation and biomarkers				
SERUM FERRITIN, ng/ml	352 (184-674)	449 (225-852)	277.5 (123.7-484.7)	0.004
SERUM LDH, U/L	544 (340-724)	679 (458-865)	418 (275.7-591.7)	0.001
Serum CRP, mg/L	37 (12-88)	88 (68-106)	12.5 (8-23.2)	<0.001
IL6, pg/ml	38 (11-121)	88 (42-245.5)	14 (2-43.2)	<0.001
NLR	8 (5-15)	14 (8.5-17)	5.5 (4-8.2)	<0.001
D-DIMER, ng/ml	845 (340-2100)	1447 (937-4609)	426.5 (254.5-817.7)	<0.001
PFR	118 (80-220)	80 (70-102.5)	192 (122.5-281.5)	<0.001

Parameters are shown as medians with interquartile ranges. p-values calculated by Chi-square test, Fisher's exact test, or Mann–Whitney *U* test.
LDH = Lactate dehydrogenase, CRP = C-reactive protein, IL6 = Interleukin-6, NLR = Neutrophil-lymphocyte ratio, PFR = PaO2/FiO2

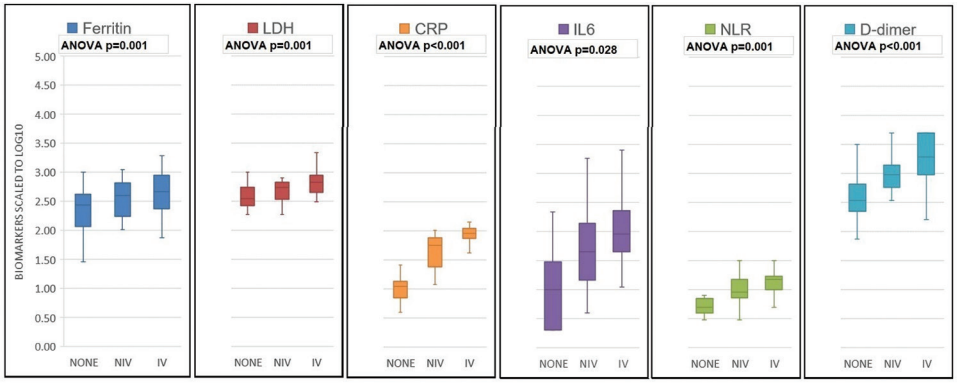

Figure 1. Serum ferritin, LDH, CRP, IL6, NLR, and D-dimer across 3 categories of ventilatory support i.e. none, non-invasive ventilation (NIV) or invasive ventilation (IV). One way ANOVA showed the medians of all biomarkers to significantly different across the three categories.

D-dimers of patients requiring invasive ventilation were significantly higher than that of patients requiring non-invasive ventilatory support (p=0.013) or no ventilatory support (p<0.001).

A binominal logistic regression was performed separately to ascertain the effects of biomarkers (Ferritin, LDH, CRP, IL6, NL ratio, D-dimer) and PF ratio on the likelihood of need of ventilatory support and mortality of participants. The model explained 77% (Nagelkerke R^2) of the variance in incidence of patients needing ventilation support and 64% (Nagelkerke R^2) of the variance in mortality of patients. Similarly, the model correctly classified 87.9% of participants who received ventilatory support and 85.9% of participants who died from COVID. IL6 (p=0.024), D-dimer (p=0.025) and CRP (p<0.001) were significant predictors for the need of ventilatory support. Similarly, IL6 (p=0.036), CRP (p=0.041), D-dimer (p=0.006), and PFR (p=0.019) remained significant predictors for mortality.

Receiver operating characteristic curves of CRP, IL6, NLR, D-dimer and PFR were analysed to ascertain optimal cut-offs for predicting mortality or need of mechanical ventilatory support (Table 3). All the variables were significant (p<0.05) predictors, with AUC>0.7. CRP >40 mg/L predicted mortality with a sensitivity of 93.3% and a specificity of 88.9% (AUC 0.933, 95%CI 0.879-0.987). The same cut-off of 40 mg/L had a sensitivity of 76.7% and specificity of 94.9% for predicting need for mechanical ventilatory support (AUC 0.956, 95%CI 0.915-0.996) (Figure 2).

Discussion

Worldwide, with over 94 million cases and over 2 million deaths, the pandemic is showing a worrisome resurgence in the West, putatively associated with emergence of newer, more infectious viral variants sowing apprehension of fresh waves of infections as the race to immunize populations and achieve herd immunity is underway. The unpredictability of COVID illness has fuelled searches for clinical and laboratory scoring systems for patient triage so that intensivists can predict which subset of patients are likely to deteriorate faster and need immediate attention, even at the time of admission. This present study aims to fill knowledge gaps regarding clinico-demographic and biomarker profiles of COVID-19 patients to improve accuracy of triage algorithms.

Table 2: Clinico-demographics and laboratory parameters compared across groups of escalating ventilatory support.

Parameters	NO MVS (N=39)	MVS (NIV + IV) (N=60)		p-value
		NIV (N=23)	IV (N=37)	
AGE (yrs)	59 (43-67)	57 (50-65)	54 (44-65)	0.895
MALES, (N,%)	19, 48.7	16, 69.6	27, 73	0.068
		43, 71.6		**0.021**
HYPERTENSION, (N,%)	17, 43.6	15, 65.2	16, 43.2	0.186
TYPE II DIABETES MELLITUS, (N,%)	12, 30.8	14, 60.9	18, 48.6	0.057
		32, 53.3		**0.027**
CHRONIC KIDNEY DISEASE, (N,%)	5, 12.8	5, 21.7	5, 13.5	0.601
CORONARY ARTERY DISEASE, (N,%)	3, 7.7	1, 4.3	9, 24.3	0.051
	4, 6.4			0.015
ANEMIA, (N,%)	13, 33.3	3, 13	8, 21.6	0.177
SERUM FERRITIN, ng/ml	273 (112-421)	394 (165-663)	464 (233-940)	0.001
SERUM LDH, U/L	356 (254-551)	550 (330-689)	679 (446-893)	0.001
Serum CRP, mg/L	11 (7-14)	56 (23-77)	92 (71.5-114)	<0.001
IL6, pg/ml	10 (2-32)	45 (14-152)	90 (44.5-245.5)	0.028
NLR	5 (4-7)	9 (6.5-16)	15 (9.5-17.5)	0.001
D-DIMER, ng/ml	339 (224-670)	946 (524-1560)	1953 (937-5000)	<0.001
PFR	214 (146-298)	110 (72-160)	82 (72-102.5)	<0.001

Parameters are shown as medians with interquartile ranges. p-values calculated by chi-square test, Fisher's exact test, or analysis of variance (ANOVA).
MVS = Mechanical ventilatory support, No MVS = Oxygen therapy including high flow nasal oxygen, NIV = Non-invasive ventilation with BiPAP, IV = Invasive ventilation, LDH = Lactate dehydrogenase, CRP = C-reactive protein, IL6 = Interleukin-6, NLR = Neutrophil-lymphocyte ratio.

Table 3: Outcome tabulation of receiver operating characteristic curve analysis of biomarkers.

Parameters, cut-off	AUC (95% CI)	Sensitivity, %	Specificity, %
Prediction of Survival			
Serum CRP, 40mg/L	**0.933 (0.879-0.987)**	**93.3**	**88.9**
IL6, 32.5 pg/ml	0.821 (0.739-0.902)	82.2	70.4
NLR, 8.5	0.749 (0.648-0.851)	75.6	75.9
D-DIMER, 810 ng/ml	0.8 (0.711-0.889)	82.2	75.9
PFR, 106	0.886 (0.790-0.942)	88.9	80
Prediction of need for mechanical ventilatory support (NIV or IV)			
Serum CRP, 40mg/L	**0.956 (0.915-0.996)**	76.7	**94.9**
IL6, 32.5 pg/ml	0.843 (0.765-0.921)	73.3	76.9
NLR, 8.5	0.797 (0.695-0.899)	70	87.2
D-DIMER, 810 ng/ml	0.816 (0.726-0.905)	71.7	82.1
PFR, 106	0.840 (0.758-0.922)	94.9	66.7
Prediction of need for invasive mechanical ventilation			
Serum CRP, 40mg/L	**0.895 (0.832-0.958)**	**91.9**	77.4
IL6, 32.5 pg/ml	0.797 (0.709-0.884)	83.8	64.5
NLR, 8.5	0.768 (0.672-0.863)	78.4	71
D-DIMER, 810 ng/ml	0.773 (0.676-0.870)	81.1	67.7
PFR, 106	0.790 (0.696-0.885)	80.6	81.1

CRP = C-reactive protein, IL6 = Interleukin-6, NLR = Neutrophil-lymphocyte ratio, NIV = Non-invasive ventilation with BiPAP, IV = Invasive ventilation.

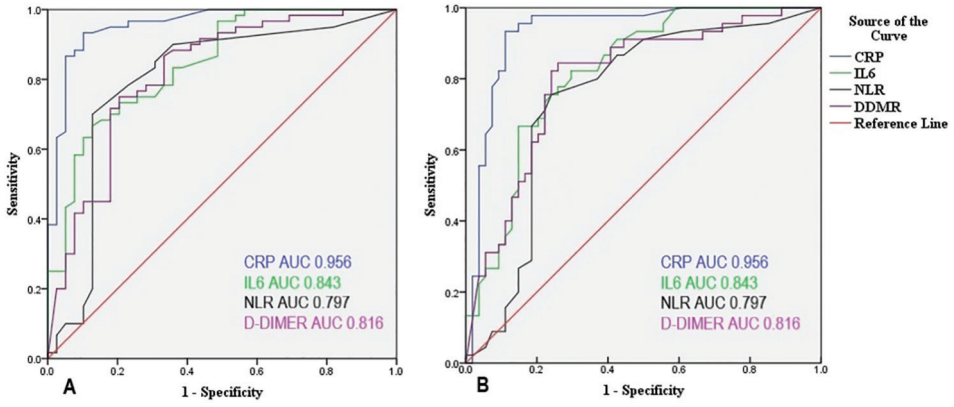

Figure 2. Receiver operating characteristic (ROC) curves for CRP, IL6, NLR, and D-dimers. A) ROC curves to predict need for mechanical ventilatory support (NIV or invasive ventilation). B) ROC curves to predict mortality.

Available epidemiological profiles of COVID-19 patients from the Indian subcontinent have mostly evaluated cohorts with mild to moderate illness and biomarker profiles have not been studied. [5,6]

The principal findings of this study are that male gender and diabetes mellitus are associated with severe illness and poorer outcomes in terms of need for mechanical ventilation and mortality. Derangements of almost all study biomarkers (CRP, IL6, D-dimers, NLR, ferritin and LDH) were associated with ventilatory support and mortality. Analysis of cohorts of COVID-19 patients from across the globe have yielded similar observations, including a meta-analysis of 32 studies from around the world by Malik et al. [1,7-9] On a lookout for a combination of biomarkers which accurately predicts patient outcomes, further data analysis was performed, and an interesting observation emerged, which may be helpful in resource-limited nations. In our study, CRP, IL6 and D-dimers emerged as independent predictors of mortality and need of

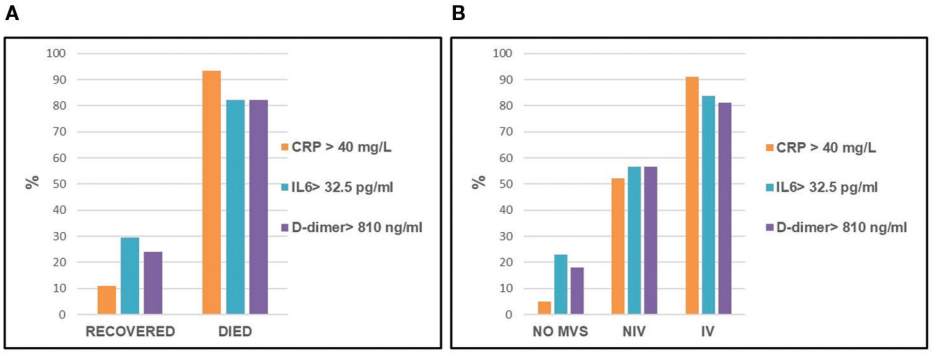

Figure 3. A) Comparison of the proportion of patients with levels of CRP, IL6, and D-dimers above the suggested cut-offs amongst recovered and expired patients. B) Comparison of the proportion of patients with levels of CRP, IL6, and D-dimers above the suggested cut-offs amongst patients who required invasive ventilation (IV), non-invasive ventilatory support (NIV), and those who did not require any mechanical ventilatory support (NO MVS).

mechanical ventilation, with a combined model predicting the outcomes correctly in over 85% of cases.

Contrary to hypothesis no association was found between age of patients and survival. This may be indicative of selection bias arising from inclusion of only moderate to severe cases under intensive care. Also, institutional triage policy during acute surge conditions kept a lower threshold for early referral of older patients or patients with comorbidities for intensive care in expectation of rapid clinical deterioration. Consequently, younger patients without comorbidities were likely to be referred to intensive care later in the course of their illness when their clinical condition had already worsened. This might have led to equivocal mortality figures. Complementing clinical criteria with biomarker data for triage decisions will aid more judicious allocation of intensive care resources.

Higher prevalence of comorbid illnesses among COVID-19 patients with moderate to severe illness requiring hospitalisation has been noted across the world, especially diabetes, cardiovascular disease including hypertension, chronic pulmonary disease, and chronic kidney disease. Individual comorbidities have been associated with adverse outcomes with varying significance across studies. [1,10,11] 77% of our intensive care patients had one or more co-morbidities.

In our study, coronary artery disease was seen to be associated with need of invasive ventilatory support. This likely reflects the role of direct myocardial injury and increased systemic thromboembolic events seen in moderate-severe COVID-19 which are particularly deleterious for this patient group. Similar observations have been reported in studies by Cummings MJ and Park BE. [10,12]

Diabetes mellitus is known to induce immunodeficiency and immune dysregulation with increased susceptibility to infections. Guo et al. found diabetics in Wuhan to be predisposed to more severe COVID pneumonia with increased derangements in IL6, CRP, ferritin, and D-dimers but not increased mortality. [13] Our study findings were suggestive of increased mortality and need for mechanical ventilation in diabetics with severe COVID illness who also had significantly higher NLR. Asirvatham et al. in their study had also suggested that prevalence of diabetes was associated with higher adjusted case fatality in Indian patients. [14] Thus, diabetes should be factored in triaging Indian COVID-19 patients and it may be a factor in higher mortality in younger age groups of urban populations. It is notable that systemic steroids for moderate to severe COVID pneumonia precipitate further derangement of blood sugars in diabetics.

Dysregulated systemic inflammation and coagulation remain the enduring challenge in severe COVID-19. We have evaluated a full spectrum of inflammatory biomarkers previously associated with adverse outcomes: serum ferritin, LDH, IL6, hsCRP, and NLR. IL6 is one of the cytokines which has received intense interest as the possible driving agent of COVID-19 cytokine storm syndrome and is being evaluated as a therapeutic target. IL6 elevations have significant association with mechanical ventilation and mortality in COVID-19. [15] Herold et al. validated a IL6 cut-off of >80 pg/ml at any point in the course of illness, accurately predicting respiratory failure requiring invasive ventilation in 80% of cases. [16] Their study also suggested a cut-off of 35 pg/ml to be optimal for IL6 at initial assessment though with lower specificity. This correlates with our findings with respect to baseline IL6 values that suggested an optimal cut-off of 32.5 pg/ml to predict invasive mechanical ventilation and mortality. IL6 estimation has the additional value of guiding therapeutics. Studies evaluating monoclonal antibody therapies targeting IL6 have shown inconsistent benefits so far, though recent work has shown promising results with timely therapy in select critically ill patients. [17] Elevated IL6 with critical illness at presentation should prompt consideration of targeted therapies.

C-reactive protein elevations have been widely associated with severe COVID-19 [9]. It has special value in being an early predictor of deterioration. CRP production in the liver is driven by IL6, thus explaining the close correlation of these two markers. We found baseline hsCRP to be an independent predictor of mortality with a cut-off of 40 mg/L strongly predictive (AUC>0.9) of mechanical ventilation and mortality with 93% sensitivity and 88% specificity. Herold et al. have validated a cut-off of 32.5 mg/L for CRP at presentation to predict invasive ventilation, though they have suggested a cut-off of >97 mg/L at any point during the course of illness to predict impending respiratory failure with greater specificity. Thus, a baseline CRP is a valuable and relatively widely available biomarker which can be utilised independently for patient triage.

D-dimer monitoring has become standard of care in COVID-19 due to high risk of venous thromboembolic events in moderate to severe illness and derangements have been widely associated with mortality risk. [10,18] Systemic dysregulated coagulation associated with the inflammatory reaction results in hypercoagulability and may evolve into disseminated intravascular coagulation in critically ill patients. [19, 20] Zhang et al. described a cut-off of 2000ng/ml of D-dimers at admission to predict in-hospital mortality with 92% sensitivity and 83% specificity. [21] Our findings suggest a lower cut-off of 810ng/ml can accurately predict all adverse outcomes, including non-invasive or invasive ventilation, apart from mortality, which would be valuable while triaging patients. We found progressive elevations of D-dimer to be associated with escalating need for ventilatory support, with significantly higher elevations in patients requiring invasive ventilation compared to those requiring non-invasive ventilation. Gao et al. further showed increased predictive value for severe illness when D-dimer evaluation was combined with IL6 measurement in tandem. [22] Also, D-dimers can vary significantly during the course of the illness and serial measurements to note the trend can be valuable in predicting outcomes, as noted by Naymagon et al. [23]

Profound lymphopenia is a nearly universal finding in severe COVID-19 infection. [9] The role of ACE-II receptor–mediated infection of subsets of lymphocytes by the SARS-CoV-2 virus is being evaluated. [24] Similarly, we found elevated NLR to be significantly associated with adverse outcomes and a cut-off of >8.5 was found to be a moderately good predictor of survival. However, baseline NLR was not found to be an independent predictor of outcomes. Considering the multiple factors likely to influence it during the course of the illness, we suggest that dynamic trends are likely to have better predictive value, much as observed by Ye et al. in their study. [25]

LDH is an established marker of lung injury in acute respiratory distress syndrome (ARDS) and predicts the extent of respiratory compromise. Thus, it is unsurprising to find significant inverse correlation with PFR in COVID ARDS. LDH elevations have thus been associated with severe COVID ARDS, invasive mechanical ventilation and poor outcomes [16,26]. Our study results reflect the same, but regression analysis failed to show significant predictive value in predicting mechanical ventilation or mortality. Since it indicates ongoing lung inflammation and injury its efficacy as an early predictor of deterioration is limited. However, by the same principle a decreasing trend of LDH may be evaluated as an indicator of resolution of lung inflammation signalling recovery in times to come.

Serum ferritin is a known acute phase reactant and levels rise in various systemic inflammatory states and infections. Derangements in ferritin levels have been uniformly reported in COVID-19. [4] An association with possible hemophagocytic lymphohistiocytosis (HLH, macrophage activation syndrome) leading to clinical deterioration was explored. However, though a significant association with poor outcomes has been seen in several studies, ferritin has been seen to be a poor predictor of mechanical ventilation or mortality. The levels commonly encountered in COVID-19 are several orders of magnitude lower than that seen in HLH, refuting that theory of pathogenesis. [27] The elevations are likely representative of the ongoing systemic inflammatory response. Our data suggest a similar conclusion. Serum ferritin elevations were not predictive of outcomes though they showed significant association. Thus, ferritin has poor utility as a predictor of severe COVID-19. Elevations may persist for prolonged periods in spite of clinical recovery. [28]

Our study had some limitations. Selection bias would have been introduced since we were limited to recruiting patients with moderate to severe illness admitted to intensive care. Baseline biomarkers and PFR at the time of admission to the hospital could not be included in the analysis due to data not being available for all cases. Baseline laboratory assessment was done at the time of ICU admission which would have occurred at varied times in the course of illness in different patients. Also, analysis of serial measurements of biomarkers and PFR to understand trends could have improved the predictive value of some biomarkers and helped identify markers of recovery.

Conclusion

Among COVID-19 patients, male gender and diabetes mellitus are associated with need of ventilatory support and mortality. Baseline CRP >40 mg/L, IL6>32.5 pg/ml, and D-dimer >810 ng/ml are sensitive and specific independent predictors of need for ventilatory support and risk of mortality. hsCRP and IL6 elevations are highly correlated and represent the same pathogenetic mechanism and are early predictors of impending adverse outcomes when used

in isolation or in conjunction. A baseline NLR >8.5 is sensitive and specific to predict adverse outcomes though its predictive value is likely to be greater if used as a dynamic measure. Ferritin and LDH are not accurate predictors of outcomes, though LDH may be a surrogate marker for the extent of lung injury. Further studies incorporating dynamic changes in biomarkers could identify algorithms to improve assessment of disease course, therapy, and prognosis.

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Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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References

[1] Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed ML, et al. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. JAMA Intern Med [Internet]. 2020 Jul 15 [cited 2020 Jul 27]; Available from: https://doi.org/10.1001/jamainternmed.2020.3596

[2] Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med. 2020 Oct 1;180(10):1345–55.

[3] Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020 Aug;584(7821):430–6.

[4] Velavan TP, Meyer CG. Mild versus severe COVID-19: Laboratory markers. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2020 Jun;95:304–7.

[5] Dosi R, Jain G, Mehta A. Clinical characteristics, comorbidities,and outcome among 365 patients of coronavirus disease 2019 at a tertiary care centre in Central India. J Assoc Physicians India. 2020 Sep;68(9):20–3.

[6] Soni SL, Kajal K, Yaddanapudi LN, Malhotra P, Puri GD, Bhalla A, et al. Demographic & clinical profile of patients with COVID-19 at a tertiary care hospital in north India. Indian J Med Res. 2020 Nov 19; doi: 10.4103/ijmr.IJMR_2311_20. Epub ahead of print. PMID: 33208558.

[7] Ayaz A, Arshad A, Malik H, Ali H, Hussain E, Jamil B. Risk factors for intensive care unit admission and mortality in hospitalized COVID-19 patients. Acute Crit Care. 2020 Nov;35(4):249–54.

[8] Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020 Jun 25;58(7):1021–8.

[9] Malik P, Patel U, Mehta D, Patel N, Kelkar R, Akrmah M, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. BMJ Evid-Based Med. 2020 Sep 15; bmjebm-2020-111536. doi: 10.1136/bmjebm-2020-111536. Epub ahead of print.

[10] Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet Lond Engl. 2020 Jun 6;395(10239):1763–70.

[11] Li W, Lin F, Dai M, Chen L, Han D, Cui Y, et al. Early predictors for mechanical ventilation in COVID-19 patients. Ther Adv Respir Dis. 2020 Dec;14:1753466620963017. PMID: 33054630; PMCID: PMC7570781

[12] Park BE, Lee JH, Park HK, Kim HN, Jang SY, Bae MH, et al. Impact of cardiovascular risk factors and cardiovascular diseases on outcomes in patients hospitalized with COVID-19 in Daegu Metropolitan City. J Korean Med Sci. 2021 Jan 11;36(2):e15.

[13] Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020;36(7):e3319.

[14] Asirvatham ES, Lakshmanan J, Sarman CJ, Joy M. Demystifying the varying case fatality rates (CFR) of COVID-19 in India: Lessons learned and future directions. J Infect Dev Ctries. 2020 Oct 31;14(10):1128–35.

[15] Guirao JJ, Cabrera CM, Jiménez N, Rincón L, Urra JM. High serum IL-6 values increase the risk of mortality and the severity of pneumonia in patients diagnosed with COVID-19. Mol Immunol. 2020 Dec;128:64–8.

[16] Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M, et al. Elevated levels of IL-6 and

CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol. 2020 Jul;146(1):128-136.e4.

[17] Huang E, Jordan SC. Tocilizumab for Covid-19 — The ongoing search for effective therapies. N Engl J Med. 2020 Dec 10;383(24):2387–8.

[18] Shah S, Shah K, Patel SB, Patel FS, Osman M, Velagapudi P, et al. Elevated D-dimer levels are associated with increased risk of mortality in coronavirus disease 2019: A systematic review and meta-analysis. Cardiol Rev. 2020 Dec;28(6):295–302.

[19] Görlinger K, Dirkmann D, Gandhi A, Simioni P. COVID-19 associated coagulopathy and inflammatory response: What do we know already and what are the knowledge gaps? Anesth Analg [Internet]. 2020 Jul 28 [cited 2021 Jan 22]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7389937/

[20] Asakura H, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. Int J Hematol. 2020 Nov 7;1–13.

[21] Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost JTH. 2020 Jun;18(6):1324–9.

[22] Gao Y, Li T, Han M, Li X, Wu D, Xu Y, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol. 2020 Jul;92(7): 791–6.

[23] Naymagon L, Zubizarreta N, Feld J, van Gerwen M, Alsen M, Thibaud S, et al. Admission D-dimer levels, D-dimer trends, and outcomes in COVID-19. Thromb Res. 2020 Dec;196:99–105.

[24] Candia P de, Prattichizzo F, Garavelli S, Matarese G. T Cells: Warriors of SARS-CoV-2 infection. Trends Immunol. 2021 Jan 1;42(1):18–30.

[25] Ye W, Chen G, Li X, Lan X, Ji C, Hou M, et al. Dynamic changes of D-dimer and neutrophil-lymphocyte count ratio as prognostic biomarkers in COVID-19. Respir Res. 2020 Jul 3;21(1):169.

[26] Poggiali E, Zaino D, Immovilli P, Rovero L, Losi G, Dacrema A, et al. Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in CoVID-19 patients. Clin Chim Acta Int J Clin Chem. 2020 Jun 9;509:135–8.

[27] Feld J, Tremblay D, Thibaud S, Kessler A, Naymagon L. Ferritin levels in patients with COVID-19: A poor predictor of mortality and hemophagocytic lymphohistiocytosis. Int J Lab Hematol [Internet]. 2020 Aug 13 [cited 2020 Nov 17]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7436675/

[28] Sonnweber T, Boehm A, Sahanic S, Pizzini A, Aichner M, Sonnweber B, et al. Persisting alterations of iron homeostasis in COVID-19 are associated with non-resolving lung pathologies and poor patients' performance: a prospective observational cohort study. Respir Res [Internet]. 2020 [cited 2020 Nov 16];21. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7575703/