

Prognostic Performance of SOFA Score in Conjunction with Inflammatory Markers & Lymphocytes in Critically-Ill Covid-19 Patients

Dhananjay Batwara¹, Arjun Verma², Ashwin Choubey², Manish Gupta³, Iqbal Hasan⁴, Saurabh Puri⁵

ABSTRACT

Background: There are no standardized prognostic markers available for early detection of critically-ill COVID-19 patients. This study aims to evaluate the co-relation of changes in inflammatory markers and lymphocytes with Sequential Organ Failure Assessment (SOFA) score in predicting disease severity and mortality in COVID-19 patients admitted to ICU. **Methods:** This was a single-center, non-randomized, observational study. The study included 80 critically-ill COVID-19 patients admitted to ICU from 3rd August- 2nd October 2020. The core outcome was 28 days mortality in COVID-19 patients admitted to ICU. **Results:** For APACHE II score no significant co-relation was found among survivors (9.68 ± 3.95) and non-survivors (11.62 ± 4.92); $P=0.087$. At 96hrs of admission to ICU, SOFA score was significantly higher in non-survivors than survivors (3.75 ± 2.94 vs 2.16 ± 0.87 ; $P<0.001$). The longitudinal analysis showed no significant co-relation between markers and SOFA score in predicting disease severity. However, multi-variate regression analysis showed significantly increased odds of mortality associated with higher SOFA score (OR- 2.228 [95% CI: 1.220 - 4.068]; $P=0.009$), lymphopenia (OR- 0.839 [95% CI: 0.720 - 0.977]; $P=0.024$) and high PCT levels (OR- 1.983 [95% CI: 1.129 - 3.485]; $P=0.017$) at 96 hours of admission. However, the increased PCT levels might be associated with bacterial co-infection in these patients. **Conclusion:** We conclude that, using SOFA score in conjunction with lymphocytes might serve as an effective prognostic tool to predict mortality in critically-ill COVID-19 patients and help in making clinical decisions and improve patient outcomes.

Keywords: COVID-19, SOFA score, Inflammatory markers, Lymphopenia

Trial Registry: Registered for trial in Clinical Trial Registry India (CTRI): CTRI/2020/07/026800

¹Consultant, ²Associate Consultant, ³Director & Head, ⁴Senior Consultant, Department of Critical Care Medicine, ⁵Junior Resident, Department of Medicine, Max Superspeciality Hospital Vaishali, Ghaziabad Uttar Pradesh - 201012, India

Corresponding Author: Dr. Manish Gupta, Associate Director & Incharge Critical care Medicine, Max Superspeciality Hospital Vaishali, Ghaziabad, Uttar Pradesh - 201012, India

E-Mail: drmanish2004@yahoo.co.in

Received: 11th July 2022

Accepted: 17th December 2022

How to Cite this Article: Batwara D., Verma A., Choubey A., Gupta M., Hasan I., Puri S. Prognostic performance of sofa score in conjunction with inflammatory markers & lymphocytes in critically-ill covid-19 patient. *Int Med Sci Acad* 2023;36(1):30-36.

Access this article online : www.jimsaonline.com



Introduction

The coronavirus disease 2019 (COVID-19) pandemic is still posing great challenge to the global healthcare system. The total coronavirus cases count stands at ~ 560 million, with a death toll of 6.37 million till 10th July 2022 [1]. An increased susceptibility to COVID-19 has been shown by individuals with pre-existing comorbidities such as diabetes, hypertension, cardiovascular disease, lung disease or kidney disorders [2-4]. These risk factors have been associated with high morbidity and increased mortality rate [5]. The mortality rate of critically ill-patients varies from 11-62% in patients admitted to intensive care unit (ICU) [6-9]. Critically-ill COVID-19 patient exhibit shortness of breath, difficulty in breathing and pneumonia-like symptoms. As the pathogenic condition progress there is release of pro-inflammatory cytokines/chemokines which intensifies the systemic inflammatory response against the Severe Acute Respiratory Syndrome Coronavirus -2 (SARS-CoV-2) [9-11]. This cytokine storm is accompanied by pulmonary edema, acute respiratory distress syndrome (ARDS), acute lung injury (ALI) and multiple organ failure, which deteriorates

the clinical outcome of patients. Therefore, an early medical intervention is crucial to reduce the mortality rate in critically-ill COVID-19 patients.

Accumulating evidence from various studies suggest that the serum levels of inflammatory markers have the potential to discriminate between mild and severe disease, and possibly may serve as potential prognostic biomarkers for COVID-19 pathogenesis. Increased levels of inflammatory markers such as Interleukin-6 (IL-6), Procalcitonin (PCT), D-Dimer, C-Reactive Protein (CRP) and Ferritin, are found to be associated with poor clinical outcome in severe patients [6, 15-17]. ICU patients had increased levels of PCT and D-Dimer as compared to non-ICU patients [6]. Dynamic changes in hematological markers such as lymphocytes and Neutrophil-Lymphocyte Count Ratio (NLR) were significantly altered in severe COVID-19 patients and were identified as an independent risk factors to indicate COVID-19 severity [15-17].

Application of scoring system for critically-ill COVID-19 patients would facilitate critical care physicians for prognostication and predicting mortality. However, no such scoring system is yet

available for COVID-19. Therefore, the existing scoring systems, Acute Physiology and Chronic Health Evaluation II (APACHE - II) score and Sequential Organ Failure Assessment (SOFA) score, [18,19] which were used routinely to assess disease severity and estimate mortality in hospitals, was adopted for COVID-19 [19,20]. The use of SOFA score in identification of severe or critically-ill COVID-19 patients as well as prediction of mortality has been observed [19] and further validation is proposed in the clinical trial NCT04713852.

Since laboratory-derived data plays a critical role in decision making, the inflammatory biomarkers and blood counts could facilitate risk stratification of COVID-19 patients. This will aid clinicians to decide effective treatment strategy for patients.

The goal of the present study was to determine the potential role of ICU scoring system and serial changes in inflammatory markers along with lymphocytes as prognostic factors in predicting poor clinical outcome and mortality in critically-ill COVID-19 patients.

Methods

Study Design

This prospective, non-randomized, observational study was conducted on critically-ill COVID-19 patients admitted to a tertiary level ICU from 3rd August- 2nd October 2020, after taking approval from the institutional ethics committee. Based on the defined inclusion and exclusion criteria, patients were recruited after obtaining informed consent.

Patients

Adult patients aged >18 years with moderate to severe symptoms, with/without pre-existing co-morbidities who were admitted to ICU after a confirmed positive result of SARS-CoV-2 with Reverse-Transcriptase – Polymerase Chain Reaction (RT-PCR) or COVID-19 Antigen Test. Patients with chronic multi-organ disease, severely compromised immune system (HIV and a CD4 count <200 cells/mm³, neutropenic patients <500 neutrophils/mm³) and pregnant females were excluded from the study.

Data Collection

Demographic data, medical history, laboratory values and treatment outcome of each patient was extracted from electronic medical records of the hospital to calculate APACHE II and SOFA score. Two physicians independently reviewed the data collection forms to double check the data collected. The physicians directly communicated with patients or their families to learn the epidemiological and symptom data, which were not available in the electronic medical records.

Outcome

The main outcome variable was 28 days mortality in critically-ill COVID-19 patients admitted to ICU. APACHE II and SOFA scores were calculated within 24 hours of admission and SOFA score was assessed thereafter for 4 days. The patients were clinically assessed and monitored continuously for vital parameters (respiratory rate, heart rate, blood pressure, etc.) as long as they stayed in the ICU. Routine blood test of all the patients was performed as part of usual clinical care, which included complete blood profile, arterial blood gas analysis, kidney and liver function test, serum levels of IL-6, D-dimer, PCT, CRP and ferritin at admission and 96hrs.

Sample Size

Sample size was calculated based on the retrospective study by Zhou F. et al [24] to understand the clinical course and risk factors in COVID-19 patients in Wuhan, with 95% confidence interval (95% CI) and margin of error 10%, a sample size of 72 patients was estimated.

Statistical Analysis

Descriptive data for continuous variables are reported as mean \pm standard deviation (SD) and for categorical data median [interquartile range (IQR)] or percentage (n%), as appropriate, is used. We divided the study sample into survivors and non-survivors and carried out intergroup comparisons of demographic variables, clinical parameters, laboratory findings, and both SOFA and APACHE II scores. Continuous data was compared by the student *t*-test or the Mann–Whitney *U* test; categorical variables was tested by using either the chi-square test or Fisher exact test (when the expected value was <5 in one cell), as appropriate.

To explore the risk factors associated with in-hospital death, univariate and multivariate logistic regression models were used. A stepwise approach was used to enter new terms into the model, with a limit of $P < 0.05$ to enter the terms. We chose lymphocytes, D-dimer, ferritin, IL-6, PCT, CRP, SOFA and APACHE II at 0 hrs and 96 hrs for our multivariable logistic regression model.

The receiver operating characteristic (ROC) curve analysis was applied for a discriminatory evaluation of the performance of the SOFA scores and various inflammatory markers like CRP, ferritin, D-Dimer, PCT, IL-6 and lymphocytes. The classification performance of scoring system and inflammatory markers to discriminate between survivors and non-survivor was evaluated by calculating the area under the curve (AUC) of the ROC and its 95% CI.

For each rapid scoring system, the score with the largest Youden Index was defined as the optimal cut-off value for predicting COVID-19 mortality. A two-sided α of less than 0.05 was considered statistically significant. A *p*-value < 0.05 was accepted as statistically significant. The statistical analysis was performed using IBM Statistical Product and Service Solutions (SPSS) version 17.0.

Results

Data was collected from 80 patients aged 18 years or older, admitted to the ICU, who were tested positive for SARS-CoV-2 virus on RT-PCR or COVID-19 Antigen Test. Baseline demographics and clinical characteristics of the study population divided into two groups (survivors and non-survivors) is summarized in (Table 1).

The mean age of the study cohort was 59.58 ± 11.26 years, among which 54 (67.5%) were male and 26 (32.5%) were females. During the hospitalization, 24 patients died and 56 survived. Among the non-survivor, 19 (79.2%) were male and 5 (20.8%) were females, whereas among survivors, 35 (62.5%) were male and 21 (37.5%) were females.

Comorbidities were present in both the survivors and non-survivors, the most common being diabetes, followed by hypertension. Compared with survivors, mean APACHE II score (9.68 ± 3.95 vs 11.62 ± 4.92) and SOFA score (2.43 ± 0.95 vs 3.12 ± 1.70) were higher in non-survivors at the time of ICU admission. No significant co-relation was found for mean APACHE II score among survivors (9.68 ± 3.95) and non-survivors (11.62 ± 4.92); $P = 0.087$. At 96hrs, a statistically significant co-relation was found

Table 1: Demographic Data and Baseline Characteristics of Survivors and Non-Survivors

| Variable | All Patients | Survivors | Non-survivors | P value |
|--|---------------|---------------|-------------------|---------|
| | (n=80) | (n=56) | (n=24) | |
| Age (years), Mean ±SD | 59.58 ± 11.26 | 57.34 ± 11.97 | 64.79 ± 7.24 | 0.001* |
| Gender, No./Total (%) | | | | |
| Female | 26/80 (32.5%) | 21/56 (37.5%) | 5/24 (20.8%) | 0.145 |
| Male | 54/80 (67.5%) | 35/56 (62.5%) | 19/24 (79.2%) | |
| BMI, Mean ±SD | 24.37 ± 4.17 | 23.87 ± 3.96 | 25.54 ± 4.49 | 0.101 |
| Comorbidity, No./Total (%) | | | | |
| Diabetes | 35/80 (43.8%) | 27/56 (48.2%) | 8/24 (33.3%) | 0.219 |
| Hypertension | 32/80 (40%) | 23/56 (41.1%) | 9/24 (37.5%) | 0.765 |
| COPD/Asthma | 4/80(5%) | 2/56 (3.6%) | 2/24 (8.3%) | 0.579 |
| Kidney Disease | 9/80 (11.3%) | 5/56 (8.9%) | 4/24 (16.7%) | 0.441 |
| Hypothyroid | 8/80 (10%) | 7/56 (12.5%) | 1/24 (4.2%) | 0.424 |
| Others | 31/80 (38.8%) | 21/56 (37.5%) | 10 (41.7%) | 0.726 |
| No comorbidities | 20/80 (25%) | 13/56 (23.2%) | 7/24 (29.2%) | 0.573 |
| APACHE II Score at ICU admission, | | 9.68 ± 3.95; | 11.62 ± 4.92; | 0.087 |
| Mean ±SD or Median (IQR) | 10.26 ± 4.33 | 9 (7 - 12) | 10 (8.25 - 14) | |
| SOFA Score at ICU admission, Mean ±SD | 2.64 ± 1.26 | 2.43 ± 0.95; | 3.12 ± 1.70; | 0.070 |
| or Median (IQR) | | 2 (2 - 3) | 3 (2 - 3) | |
| SOFA Score at 96 Hours, | 2.64 ± 1.89 | 2.16 ± 0.87; | 3.75 ± 2.94; | <0.001* |
| Mean ±SD or Median (IQR) | | 2 (2 - 3) | 3 (2 - 4) | |
| Length of ICU stay (days), | 12.65 ± 7.93 | 10.91 ± 7.26; | 16.58 ± 8.09; | <0.001* |
| Mean ±SD or Median (IQR) | | 9 (7 - 12) | 15 (11.25 - 22.5) | |

BMI – Body Mass Index, COPD- Chronic Obstructive Pulmonary Disease, APACHE II - Acute Physiology and Chronic Health Evaluation II, SOFA- Sequential Organ Failure Assessment, ICU- Intensive Care Unit, SD- Standard Deviation, IQR- Interquartile range. *p<0.05

between survivors and non-survivors for SOFA score (2.16 ± 0.87 vs 3.75 ± 2.94 ; $P < 0.001$) and length of ICU stay (median [IQR]: 9 days [7 – 12] vs 15 days [11.25 - 22.5]; $P < 0.001$).

The serial changes in inflammatory markers with respect to SOFA score, to assess mortality and disease severity was analysed using Spearman's correlation coefficient (ρ). Levels of inflammatory markers (IL-6, CRP, D-dimer, ferritin and PCT) were collected at 2 time points - 0hrs (at admission) and 96hrs. No statistically significant co-relation coefficient was found in longitudinal changes of these inflammatory markers to indicate disease severity (Table 2).

To verify the importance of longitudinal changes in inflammatory markers and ICU scoring system as prognostic indicator in COVID-19, we conducted univariate and multivariate logistic regression analysis. (Table 3)

In univariate analysis, SOFA score (at 0hr, 96hrs), PCT (at 96hrs), IL-6 (at 96hrs), D-dimer (96hrs), ferritin (at 96hrs), CRP (at 0hr, 96hrs) and lymphocytes (at 0hr, 96hrs) were prognostic predictors of severe COVID-19 ($P < 0.05$); while in multivariate logistic regression analysis, only SOFA score at 96hrs [odds ratio (OR)- 2.228 (95% CI: 1.220 - 4.068); $P = 0.009$], PCT levels at 96hrs (OR- 1.983 [95% CI: 1.129 - 3.485]; $P = 0.017$) and lymphocyte at

Table 2: Spearman's Co-relation to assess the Relationship between Serial Changes in Serum Inflammatory Biomarkers Levels and Disease Severity

| Change in Inflammatory Markers levels (from admission to 96hrs) | Spearman's Correlation | |
|--|------------------------------------|---------|
| | Delta SOFA score | |
| | Correlation Coefficient (ρ) | P value |
| Delta PCT | 0.101 | 0.372 |
| Delta CRP | 0.07 | 0.537 |
| Delta Ferritin | 0.185 | 0.100 |
| Delta D-dimer | 0.055 | 0.628 |
| Delta IL-6 | 0.159 | 0.158 |

PCT- Procalcitonin, CRP- C-Reactive Protein, IL-6 – Interleukin 6, SOFA- Sequential Organ Failure Assessment *P<0.05 – Significant

Table 3: Univariate and Multivariate Regression Analysis for Mortality Risk in Critically-ill COVID-19 patients

| Variable | Univariate (unadjusted) | | Multivariate (Adjusted) | |
|-----------------------|-------------------------|---------|-------------------------|---------|
| | OR (95%CI) | P value | OR (95%CI) | P value |
| SOFA Score 0 hours | 1.548 (1.021 - 2.346) | 0.040* | | |
| APACHE II Score | 1.108 (0.991 - 1.239) | 0.073 | | |
| SOFA Score 96 hours | 2.201 (1.285 - 3.772) | 0.004* | 2.228 (1.220 - 4.068) | 0.009* |
| PCT-0 hours | 1.421 (0.836 - 2.416) | 0.195 | | |
| PCT-96 hours | 2.426 (1.104 - 5.330) | 0.027* | 1.983 (1.129 - 3.485) | 0.017* |
| IL6-0 hours | 1.000 (0.999 - 1.001) | 0.701 | | |
| IL6-96 hours | 1.001 (1.000 - 1.002) | 0.046* | | |
| D-dimer-0 hours | 1.000 (1.000 - 1.001) | 0.180 | | |
| D-dimer-96 hours | 1.000 (1.000 - 1.001) | 0.007* | | |
| Ferritin-0 hours | 1.000 (1.000 - 1.001) | 0.266 | | |
| Ferritin-96 hours | 1.001 (1.000 - 1.002) | 0.022* | | |
| CRP- 0 hours | 1.005 (1.001 - 1.010) | 0.029* | | |
| CRP-96 hours | 1.013 (1.003 - 1.024) | 0.009* | | |
| Lymphocytes- 0 hours | 0.932 (0.857 - 1.012) | 0.095 | | |
| Lymphocytes- 96 hours | 0.845 (0.745 - 0.957) | 0.008* | 0.839 (0.720 - 0.977) | 0.024* |

PCT- Procalcitonin, CRP- C-Reactive Protein, IL-6 – Interleukin 6, SOFA- Sequential Organ Failure Assessment, APACHE II - Acute Physiology and Chronic Health Evaluation II, OR-Odds Ratio, 95% CI- 95% Confidence Interval

96hrs (OR-0.839 [95% CI: 0.720 - 0.977]; P=0.024) were significant predictors of mortality and morbidity. (Fig 1)

The ROC analysis was done to determine the cut-off values of SOFA Score, lymphocytes and PCT at 96 hrs of admission to ICU (Fig 2).

The AUC was 0.728 [95% CI: 0.599- 0.858], 0.689 [95% CI: 0.548-0.83] and 0.745 [95% CI: 0.62-0.87], respectively.

At a cut-off value of ≥ 4 , SOFA score had sensitivity of 41.70%, specificity of 96.40%, positive predictive value (PPV) of 83.33% and negative predictive value (NPV) of 79.41%. For PCT at cut-off value ≥ 0.6 and for lymphocytes $\leq 5.15\%$, sensitivity, specificity, PPV and NPV were 45.80% vs 70.80%; 89.30% vs 76.80%; 64.72% vs 56.67% and 79.37% vs 86.0%; respectively. (Table 4).

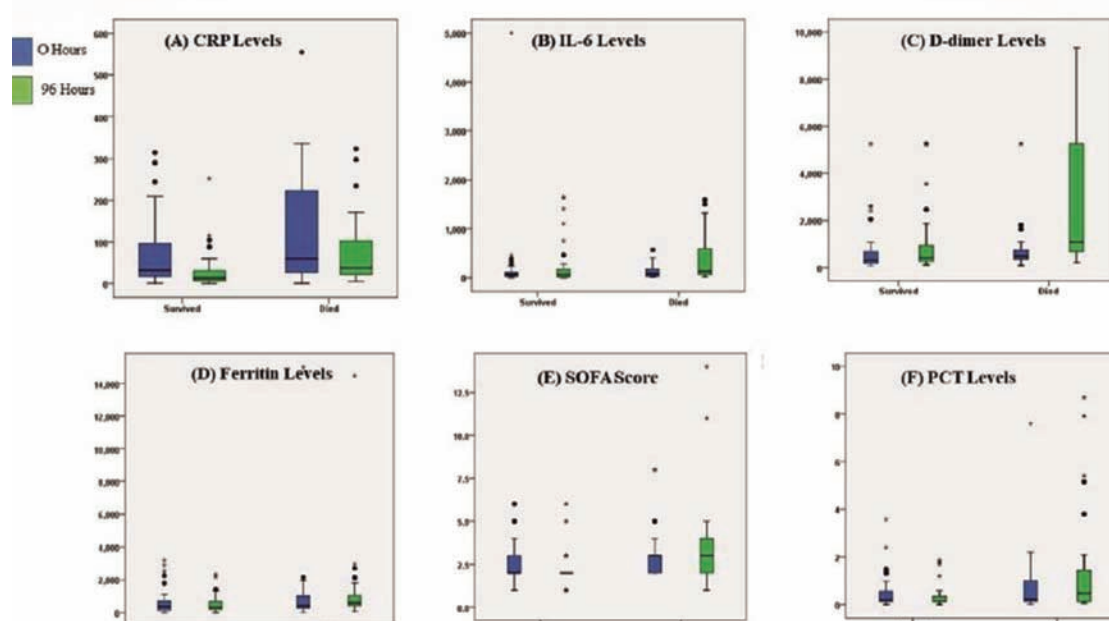


Fig 1: Change in levels of SOFA score and Inflammatory Biomarkers at the time of admission (0 hours) and at 96 hours.

Figure shows box plot graphs depicting change in (A) C-Reactive Protein (CRP) levels, (B) Interleukin-6 (IL-6) levels, (C) D-dimer Levels, (D) Ferritin Levels, (E) Sequential Organ Failure Assessment (SOFA) Score, and (F) Procalcitonin (PCT) levels from the time of admission to 96 hours. The blue box represent levels at 0 hours and green box represents levels at 96 hours.

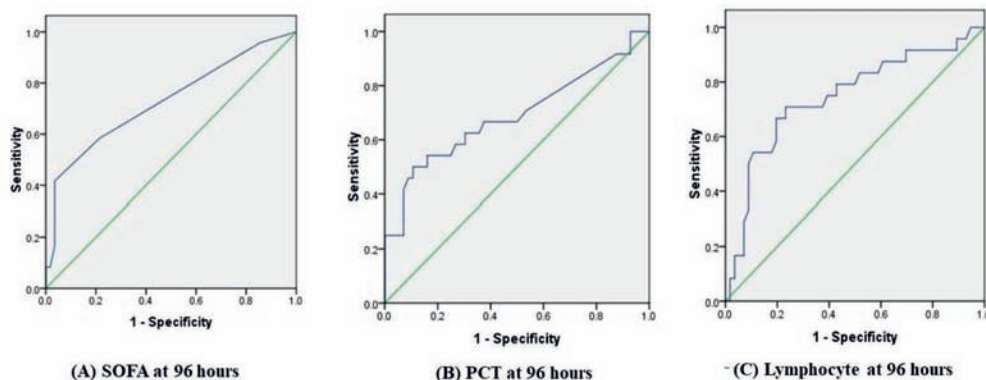


Fig 2: ROC curves predicting mortality in critically-ill COVID-19 patients

The figure shows ROC plots depicting performance of (A) SOFA score at a cut-off value of ≥ 4 , (B) PCT at a cut-off value ≥ 0.6 and (C) Lymphocyte at a cut-off value of ≤ 5.15 ; which co-related significant with mortality ($P < 0.001$)

Table 4: Sensitivities, Specificities, Positive Predictive Values, Negative Predictive Values and Accuracy for predicting Mortality Risk in Critically-ill COVID-19 Patients

| Test variables (at 96 hours) | Cut off value | Sensitivity (n%) | Specificity (n%) | PPV (n%) | NPV (n%) | Accuracy (n%) | P value |
|------------------------------|---------------|------------------|------------------|----------|----------|---------------|-------------|
| SOFA | ≥ 4 | 41.70% | 96.40% | 83.33% | 79.41% | 80.00% | $< 0.001^*$ |
| PCT | ≥ 0.6 | 45.80% | 89.30% | 64.71% | 79.37% | 76.25% | $< 0.001^*$ |
| Lymphocyte | ≥ 5.15 | 70.80% | 76.80% | 56.67% | 86.00% | 75.00% | $< 0.001^*$ |

PPV- Positive Predictive Value, NPV- Negative Predictive Values, PCT- Procalcitonin, SOFA- Sequential Organ Failure Assessment

* $P < 0.05$ - Significant

All these variables significantly co-related mortality ($P < 0.01$), however, among them SOFA score had the best accuracy (80%) as compared to PCT and lymphocytes (76.25%, 75%, respectively).

Discussion

This prospective observational study evaluated the prognostic markers associated with poor clinical outcome among critically-ill COVID-19 patients admitted to ICU of a tertiary care centre in northern India. The SARS-CoV-2 infection fatality rate increases with advanced age (> 50 years) and noticeable more in men than women [22]. The higher mortality rate among older individuals is attributed to the presence of co-morbid factors (diabetes, hypertension, cardiovascular disease, lung and kidney disorders) [23,24] and immunosenescence, [25] which affects the severity of virus infection. A seroprevalence survey to determine age-specific fatality rate across 45 countries, found that the relative infection fatality risk is more in older individuals [26]. In the present study we found that patients with advanced age had higher mortality rate which was statistically significant. Among the non-survivors, mortality was higher in men than women. Further, deceased patients had comparatively higher BMI than survivors, but no significant co-relation was found.

Early evaluation of critically-ill patient is of paramount importance, in order to decide specific treatment approach. In such patients, organ functions rapidly deteriorate as the disease progress, which might lead to multiple organ failure and even death in some patients. APACHE II and SOFA score are commonly used to evaluate organ functions and assess disease severity and mortality in critically-ill patients [18,19]. In COVID-19, APACHE II score at cut-off value of ≥ 17 served as an indicator of mortality. High APACHE II score and SOFA scores increased risk of hospital mortality in SARS-CoV-2 infected patients [20]. In our study we found SOFA score to be more significant than APACHE II score in identifying risk of mortality.

SOFA score is used to assess the severity of organ dysfunction and it includes 6 variables ($\text{PaO}_2/\text{FiO}_2$, mean arterial pressure, platelets count, bilirubin, creatinine and GCS) which helps to predict morbidity and mortality [27,28]. SOFA score at the time of admission has been found to be effective in predicting mortality risk in severe/critically-ill COVID-19 patients [21,29,30] and discriminant accuracy to be used for ventilator triage in patients [31]. Similar results were found in our study, wherein increase in SOFA score over a period of 96hrs of ICU admission had positive co-relation with poor clinical outcome. Non-survivors had higher SOFA score as compared to survivors at 96hrs. At an optimal cut-off of ≥ 3 , SOFA had shown high sensitivity and specificity, [29] on the contrary we found a cut-off of ≥ 4 to be highly specific in predicting mortality in critically-ill patients.

Immune system disturbance in COVID-19 patients, results in exuberant release of inflammatory cytokines/chemokines [9-11]. Evaluating the levels of inflammatory biomarkers, were found to co-relate with disease severity and prediction of COVID-19 progression [6,32,33]. Increased circulating levels of IL-6 and CRP were closely related to disease severity in COVID-19 and highly predicts the need for mechanical ventilation [34]. The increased value of D-dimer (> 1 mcg/ml) at admission, could help clinicians to identify patients with poor prognosis [21]. In deceased patients, the initial and peak D-dimer value was statistically higher compared to survivors [16]. Although in our study also, D-dimer levels were increased in patients admitted to ICU but there was no significant difference between survivors and non survivors. Ferritin is a key mediator of immune dysregulation. Increased ferritin levels have been associated with pro inflammatory effects, contributing to cytokine storm in COVID-19 [35]. A systemic review and meta-analysis showed that increased levels of PCT are associated with higher risk (~ 5 folds) of SARS-CoV-2 infection [36]. In present study we observed that increased PCT level at 96 hrs was associated with increased mortality, however, this poor clinical outcome could be due to bacterial co-infection [37]. Hence, additional studies are

required to verify the validity of PCT in critically-ill COVID-19 patients.

Measuring serial changes in inflammatory markers during the course of hospitalization predicted worse clinical outcome in moderate or severe COVID-19 patients, however no significant co-relation was found in critically-ill or deceased patients [38,39]. The results of our study corroborate with the above studies. We found no statistically significant co-relation coefficient between inflammatory markers and SOFA score, measured serially from the time of admission (0 hrs) and up to 96 hrs of ICU stay. Therefore, analysis of longitudinal changes of inflammatory biomarkers is not sufficient to predict morbidity or mortality in critically-ill COVID-19 patients admitted to ICU. However, multivariate analysis in our study revealed that at 96hrs, SOFA score, PCT levels and lymphocytes were associated with 28 days mortality in critically-ill patients with COVID-19.

Lymphopenia was reported in mild -severe COVID-19 as a haematological marker for disease severity [7,8]. Dysregulation of immune response during SARS-CoV-2 infection tends to decrease lymphocytes which co-relates with disease severity [6,40]. The current study observed a similar trend, wherein, lymphocytes decreased significantly at 96 hrs and were found to be associated with poor outcomes in COVID-19 patients.

Our study validates the importance of SOFA score, lymphopenia and PCT levels at 96 hrs, in predicting poor clinical outcome and 28 days mortality in critically-ill COVID-19 patients admitted to ICU. However, the increased PCT levels might be associated with bacterial co-infection in patients. These findings support the concept that SOFA score could be used as an adjunctive prognostic tool along with simple laboratory marker (lymphocytes) to estimate disease severity and early intervention to reduce mortality risk in critically-ill patients with COVID-19.

Limitations

There were some limitations in our study. First, the present study was a single centre study conducted at a tertiary care hospital with relatively small sample size, therefore the results may not be generalized for the entire population. Second, patient outcomes could have been influenced by treatment. Therefore, additional studies in larger cohorts are needed to estimate the efficacy of SOFA score in conjunction with lymphocyte count, in predicting the risk of mortality in critically-ill COVID-19 patients.

Conclusion

Among critically-ill patients with COVID-19, we found that higher SOFA score, lymphopenia and increased PCT levels in first 96 hours after admission to ICU were significantly associated with 28 days mortality. The present study also indicate that serial evaluation of inflammatory markers does not co-relate with disease severity in critically-ill COVID-19 patients. Thus, suggesting that for longitudinal analysis of patients, instead of using comparatively expensive inflammatory markers, which are often not easily available in many hospitals especially in developing countries, like India, using a simpler ICU based scoring system (SOFA score) in combination with simple laboratory marker (lymphocytes), is a competent approach to predict mortality in critically-ill patients with COVID-19.

| | |
|------------------------------|---|
| Conflict of Interest: | All authors declare no COI |
| Ethics: | There is no ethical violation as it is based on voluntary anonymous interviews |
| Funding: | No external funding |
| Guarantor: | Dr. Manish Gupta will act as guarantor of this article on behalf of all co-authors. |

References

- 1.) *Coronavirus Update (Live): 560,539,378 cases and 6,372,770 deaths from COVID-19 Virus Pandemic – Worldometer.* <https://www.worldometers.info/coronavirus/> Accessed: 2022-07-11
- 2.) Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med.* 2020;180(7):934-943.
- 3.) Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using Open SAFELY. *Nature.* 2020;584(7821):430-436.
- 4.) Deng G, Yin M, Chen X, Zeng F. Clinical determinants for fatality of 44,672 patients with COVID-19. *Crit Care.* 2020;24(1):179.
- 5.) Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* 2020; 8(5):475-481.
- 6.) Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020;395(10223):507-513.
- 7.) Arentz M, Yin E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *JAMA.* 2020;;323(16):1612—1614.
- 8.) Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA.* 2020; 323(16):1574-1581.
- 9.) Cao X. COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol.* 2020 May;20(5):269-270
- 10.) Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. *Cytokine Growth Factor Rev.* 2020; 53:25-32.
- 11.) Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med.* 2020;8(6): e46-e47.
- 12.) Malik P, Patel U, Mehta D, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. *BMJ Evid Based Med.* 2020; bmjebm-2020-111536.
- 13.) Zeng M, Shen S, Zhang Y, Liu S. Combinatorial assessment of serum inflammation reactants in patients with acute urticaria accompanied by systemic symptoms. *Indian J Dermatol.* 2020;65(1):67–68
- 14.) Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol.* 2020;146(1):128-136.
- 15.) Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. *J Med Virol.* 2020; 92(10):1733-1734
- 16.) Ye W, Chen G, Li X, et al. Dynamic changes of D-dimer and neutrophil-lymphocyte count ratio as prognostic biomarkers in COVID-19. *Respir Res.* 2020;21(1):169.
- 17.) Henry BM. COVID-19, ECMO, and lymphopenia: a word of caution. *Lancet Respir Med.* 2020.
- 18.) Richards G, Levy H, Laterre PF, et al. CURB-65, PSI, and APACHE II to assess mortality risk in patients with severe sepsis and community acquired pneumonia in PROWESS. *J Intensive Care Med.* 2011;26(1):34-40.
- 19.) Sun D, Ding H, Zhao C, et al. Value of SOFA, APACHE IV and SAPS II scoring systems in predicting short-term mortality in patients with acute myocarditis. *Oncotarget.* 2017;8(38):63073-63083.
- 20.) Zou X, Li S, Fang M, et al. Acute Physiology and Chronic Health Evaluation II Score as a Predictor of Hospital Mortality in Patients of Coronavirus Disease 2019. *Crit Care Med.* 2020;48(8):e657-e665.
- 21.) Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054-1062.
- 22.) Pastor-Barrüso R, Pérez-Gómez B, Hernán MA, et al. Infection fatality risk for SARS-CoV-2 in community dwelling population of Spain: nationwide seroepidemiological study. *BMJ.* 2020;371:m4509.
- 23.) CDC. Coronavirus (COVID-19): symptoms of coronavirus. Centers for Disease Control and Prevention. 2020. [Accessed February 19, 2021, <https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>].
- 24.) 16 BCCDC. COVID-19 vulnerable populations. British Columbia Centre for Disease Control. 2020. [Accessed February 19, 2021, <http://www.bccdc.ca/health-info/diseases-conditions/covid-19/vulnerable-populations>].
- 25.) Nikolich-Zigich J. The twilight of immunity: emerging concepts in aging of the immune system. *Nat Immunol.* 2018;19(1):10-19.
- 26.) Pastor-Barrüso R, Pérez-Gómez B, Hernán MA, et al. Infection fatality risk for SARS-CoV-2 in community dwelling population of Spain: nationwide seroepidemiological study. *BMJ.* 2020;371:m4509.
- 27.) Schoe A, Bakhshi-Raiez F, de Keizer N, van Dissel JT, de Jonge E. Mortality prediction by SOFA score in ICU-patients after cardiac surgery; comparison with traditional prognostic-models. *BMC Anesthesiol.* 2020;20(1):65
- 28.) Trancá S, Petri H^Å or C, Hagãu N, Ciuce C. Can APACHE II, SOFA, ISS, and RTS

- Severity Scores be used to Predict Septic Complications in Multiple Trauma Patients? *J Crit Care Med.* 2016;2(3):124-130.
- 29.) Liu S, Yao N, Qiu Y, He C. Predictive performance of SOFA and qSOFA for in-hospital mortality in severe novel coronavirus disease. *Am J Emerg Med.* 2020;38(10):2074-2080.
- 30.) Martínez AC, Dewaswala N, Tuarez FR, et al. Validation of SOFA score in critically ill patients with COVID-19. *Chest.* 2020;158(4):A613.
- 31.) Raschke RA, Agarwal S, Rangan P, Heise CW, Curry SC. Discriminant Accuracy of the SOFA Score for Determining the Probable Mortality of Patients With COVID-19 Pneumonia Requiring Mechanical Ventilation. *JAMA.* 2021. doi: 10.1001/jama.2021.1545. Epub ahead of print. PMID: 33595630
- 32.) Liu F., Li L., Xu M., Wu J., Luo D., Zhu Y. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *J. Clin. Virol.* 2020 Apr 14;127
- 33.) Qin C, Zhou L, Hu Z, et al. Dysregulation of Immune Response in Patients with Coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis.* 2020;71(15):762-768. doi:10.1093/cid/ciaa248
- 34.) Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol.* 2020;146(1):128-136.e4.
- 35.) Vargas-Vargas M, Cortés-Rojo C. Ferritin levels and COVID-19. *Rev Panam Salud Publica.* 2020;44:e72.
- 36.) Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. *Clin Chim Acta.* 2020; 505:190-191.
- 37.) Kotula J.J., 3rd, Moore W.S., 2nd, Chopra A., Cies J.J. Association of procalcitonin value and bacterial coinfections in pediatric patients with viral lower respiratory tract infections admitted to the pediatric intensive care unit. *J. Pediatr. Pharmacol. Ther.* 2018; 23:466-472.
- 38.) Lucas C, Wong P, Klein J, et al. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature.* 2020; 584(7821):463-469.
- 39.) Zeng Z, Yu H, Chen H. et al. Longitudinal changes of inflammatory parameters and their correlation with disease severity and outcomes in patients with COVID-19 from Wuhan, China. *Crit Care* 2020; 24(525).
- 40.) Guan WJ, Ni ZY, Hu Y, Liang WH., Ou CQ, He JX. Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med.* 2020;382(18):1708-1720

