ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

A cross-sectional study on the role of hematological and inflammatory biomarkers as predictor of mortality at the time of admission among COVID-19 patients

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Submission: 18-11-2022 Revision: 29-01-2023 Publication: 01-03-2023

ABSTRACT

Background: Whole world experienced COVID-19 pandemic with more than 155 million cases and >3.4 million deaths. Vasculitis and immune system activation plays a critical role in pathogenesis, especially in severely ill and non-survivors COVID-19 patients. **Aims and Objectives:** The aim of the study was to establish the role of hematological indices and inflammatory biomarker as predictors of mortality among non-survivor and survivor COVID-19 cases at the time of admission. **Materials and Methods:** The cross-sectional study was conducted at a dedicated COVID-19 referral hospital from July 2020 to August 2020, among 300 real time-polymerase chain reaction confirmed COVID-19 cases. Demographic, clinical, comorbidity, laboratory investigation, and outcome data were collected from patient's medical record. Outcome variables – discharged (survived) or death (non-survived) were considered for comparison of various hematological indices and inflammatory biomarkers. Data are represented as median, IQR $_{(Q1\text{-}Q3)}$ and difference between median and proportions were calculated by Mann–Whitney U-test and χ^2 test. A predictive power of laboratory parameters between survivors and non-survivors was evaluated using receiver operant curve (ROC) analysis and area under the ROC curve (AUC). **Results:** The median age of non-survivors was significantly higher than survivors. Hypertension was significantly associated with non-survivors. Hematological parameters such as total leukocyte count, absolute neutrophil count, Neutrophil: Lymphocyte ratio were significantly increased with lymphocytopenia (P = 0.001), and Inflammatory biomarkers such as C-reactive protein (CRP), lactate dehydrogenase, D-dimer, ferritin, procalcitonin, and NT-Pro BNP, all were significantly increased in non-survivors patients (P = 0.001). CRP and neutrophil lymphocyte ratio (NLR) showed "Good" predictive value for mortality with cutoff value of 74.0 mg/l (AUC = 0.841, Sensitivity = 80.4%, Specificity = 73.0%) and 5.65 (AUC = 0.805, Sensitivity = 76.1%, Specificity = 73.0%), respectively. Pro-BNP showed "Fair" predictive value for mortality with cutoff value of 330.5 pg/ml (AUC = 0.726, Sensitivity = 73.9%, Specificity = 58.2%). **Conclusion:** We suggest that CRP, NLR, and Pro-BNP can be used as a screening tool to predict mortality in COVID-19 patients for timely intervention to save valuable life, especially when sensitivity toward severity of COVID-19 among medical health professionals and general public is on decline.

Key words: Hematology; Inflammatory biomarker; Non-survivors; Adverse outcome; C-reactive protein; Neutrophil lymphocyte ratio

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v14i3.49923

E-ISSN: 2091-0576

P-ISSN: 2467-9100

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INTRODUCTION

COVID-19 pandemic threatened the humanity and rendered whole world struggling to save humanity from its effect on human life and economy. Pathogen responsible for this outbreak was Severe Acute Respiratory Syndrome- Coronavirus 2.[1] The whole world including India experienced the second wave of COVID-19 which was highly contagious and had high fatality rate than the previous wave. The WHO reported 155,743,839 confirmed cases of COVID-19 globally with 3,406,839 deaths. India stood second after the USA in the world with 21,491,598 confirmed cases and 2,34,083 deaths where more than four lakhs (4,14,188) of new confirmed cases were being reported daily as on May 7, 2021. In spite of administration of more than 1.9 billion vaccine doses, India is facing forth wave with 13,313 COVID-19 cases as on June 23, 2022.[2]

The clinical spectrum of COVID-19 infection appears to be wide, encompassing asymptomatic infection, mild influenza like illness, and severe viral pneumonia with respiratory failure and even death.[3] Review of several studies shows that the overall mortality rate of COVID-19 was 3.77–5.4%; however, it increased significantly up to 41.1–61.5% among severe or critically ill patients.[4]

As evident, COVID-19 affects multiple systems such as respiratory, hematopoietic, immune, cardiovascular, gastrointestinal, and neurological system.[1] Vasculitis plays a critical role in pathogenesis of underlying organ damage in seriously ill COVID-19 patients. It is induced by the activation of inflammatory cascades, compliment activation, and pro-inflammatory cytokines. Vasculitis may lead to lung edema and acute respiratory distress syndrome (ARDS), cardiovascular damage which include ischemia (increase cardiac enzyme), deep venous thrombosis, and pulmonary thromboembolism.[5] High mortality rate associated with COVID-19 can be attributed to hyper activation of the adaptive and innate immune system which lead to cytokine storm and cytokines release syndrome.[3]

Aims and objectives

The aim of this study is to find out utility of Hematological and bioinflammatory parameters in prediction of mortality in Covid 19 patients.

The objectives of the study were

1. To study the demographic, clinical and laboratory variables which include haematological profile, coagulation profile and inflammatory biomarkers in admitted RT-PCR confirmed Covid 19 cases.
2. To compare these parameters among survived and non-survived RT-PCR confirmed Covid-19 patients.
3. To study Potential risk factors for death on admission in Covid 19 patients. We tried to provide some useful information to predict the mortality in Covid-19 patients to assist in early identification of patients at higher mortality risk for guiding timely and appropriate intervention to improve the outcome and save valuable life.

MATERIALS AND METHODS

Study oversight

This record-based cross-sectional study was conducted from July 2020 to August 2020 at dedicated COVID-19 referral hospital of the central India. The study was approved by the Institutional Ethical Committee on August 20, 2020. In this study, patient's identity was deidentified as nature of disease is highly contagious so requirement to take consent was waived off by the Institutional Ethical Committee. Only COVID-19-positive cases whose status was confirmed by RT-PCR test admitted in hospital were included in this study.

Inclusion criteria

The following criteria were included in the study:

1. RT-PCR confirmed COVID-19 patients admitted in hospital during study period
2. COVID-19 cases who underwent hematology and bioinflammatory markers testing.

Exclusion criteria

The following criteria were excluded from the study:

1. Clinically suspected COVID patients that came negative by RT-PCR
2. COVID-19 patients who were brought dead or died before the investigations were performed.

At the time of admission, three whole blood samples were collected and were tested at institutional laboratory, one in ethylene diamine tetra-acetic acid (EDTA) vial for hemogram, second in citrate vial for coagulation profile, and last one in plane tube for biomarkers. All the EDTA samples were run on fully automated hematology analyser (Mindray BC3600) for hemogram. Total leukocyte count (TLC), platelet count, absolute neutrophil counts (ANC), and other parameters were noted in all cases. Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio were calculated. Prothrombin time and D-dimer tests were done by coagulometer (STAGO-SATELLITE) on all samples collected in Na-citrate vial. Serum was separated from all the plane vial samples and was used to estimate C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, procalcitonin and NT- Pro BNP on (Randox imola) clinical chemistry analyser.

Data collection

Data related to demography, clinical findings, comorbidity, laboratory investigation, and outcome was collected

from patient's medical records. Outcome variable was discharged (survived) or death (non-survived) considered for comparison of various hematological and inflammatory biomarkers.

Statistical analysis

Collected data were entered into Microsoft office 2007 Excel spread sheet and analyzed by IBM SPSS version-26 statistical software (IBM, Armonk, New York). Data are represented as median with interquartile Range ($IQR_{(Q1-Q3)}$). Difference between median and means was calculated by Mann–Whitney U-test while difference between proportions was calculated by χ^2 test or Fisher's exact test, where $P<0.05$ considered being significant. A predictive power of laboratory parameters and indices between survivors and non-survivors was evaluated using receiver operant curve (ROC) analysis and area under the ROC curve (AUC). The parameters with AUC >0.8 and $P<0.05$ were considered to have good discriminative precision. The diagnostic cutoff was selected with values corresponding to best possible sensitivity and specificity combination.

RESULTS

In this study, data of clinical and laboratory investigation of 300 patients were collected when patient was either discharged or declared dead. Out of all patients included in study, 93 (32.7%) died during hospitalization and 208 (69.3%) were discharged. We observed that COVID-19 infection showed male predominance with 206 (68.7%) patients as compared to female patients who were 94 (31.3%).

Patient's demographic and clinical characteristics as shown in Table 1 compared between survivors and non-survivors. The median age of sample selected was 58 ($IQR_{(Q1-Q3}$ 45–65) ranging from 19 to 90 years of age. The median age of 62 years ($IQR_{(Q1-Q3)}$ 54.50–70.50) for non-survivors was significantly higher than the median age of 55 years ($IQR_{(Q1-Q3}$ 44–63) among survivors. Although most patients were males in both survivors and non-survivors group, this difference was not statistically significant.

Among clinical presentation, patients who presented with dyspnea showed a higher risk of mortality as proportion of dyspneic patients was significantly higher among non-survivors with 82.61% as compared to 49.04% among survivors. The differences of the other symptoms such as fever, cough, headache, and sore throat between survivors and non-survivors were not significant Table 1.

Most common comorbidities were hypertension (45.33%) and diabetes mellitus (36%). Among these comorbidities, hypertension was significantly higher among non-survivors compared to survivor group. The difference of other comorbidities was not significant between two groups Table 1.

Among hematological parameters, median TLC was 8.7 (IQR 7–11.6) versus 12.2(IQR 7.8–16) $10^3/\mu l$, median ANC was 6 (IQR 4.3–8) versus 9.3 (IQR 5.95–13.35) $10^3/\mu l$, median Absolut lymphocyte count (ALC) was 1.8 (IQR 1.2–2.5) versus 1.2 (IQR 0.8–1.55) $10^3/\mu l$, N/L ratio was 3.48 (IQR 2–5.24) versus 7.86 (IQR 4.535–15.39) and median platelet count was 252 (186.8–326.5) 198 (128–323.5) $10^3/\mu l$ for survivor versus non-survivor groups. Among coagulation parameters, median serum D-dimer level was 252 (IQR 186.8–326.5) versus 198 (IQR 128–323.5) ng/ml for survivor versus non-survivor groups. Among inflammatory parameters, median serum LDH was 380 (IQR 288–570) versus 567 (IQR 423.5–762.5) IU/l, median procalcitonin was 0.1 (IQR 0.07–0.2425) versus 0.4

Table 1: Demographic and clinical characteristics of study groups

Patient characteristics	Survivors (n=208) (%)	Non-survivors (n=92) (%)	P-value
Age	55.00 (44.00–63.00)	62.00 (54.50–70.50)	0.000*
Sex			
Male	139 (66.83)	67 (72.83)	0.3456
Female	69 (33.17)	25 (27.17)	
Symptoms			
Fever	184 (88.46)	86 (93.48)	0.2148
Cough	126 (60.58)	54 (58.7)	0.7988
Headache	3 (1.44)	1 (1.09)	>0.9999
Sore throat	27 (12.98)	9 (9.78)	0.6977
Dyspnea	102 (49.04)	76 (82.61)	<0.0001
Comorbidities			
Diabetes	68 (32.69)	40 (43.48)	0.0898
Hypertension	85 (40.87)	51 (55.43)	0.0235
Cardiovascular disease	4 (1.92)	6 (6.52)	0.0734
Chronic kidney disease	8 (3.85)	5 (5.43)	0.5465
Respiratory disease	10 (4.81)	7 (7.61)	0.4164

Data are represented as median (interquartile Range) $IQR_{(Q1-Q3)}$. P values were calculated by *Mann–Whitney U-test, χ^2 test or Fisher's exact test

(IQR 0.16–1.2) ng/ml, median CRP was 21.5 (IQR 5.9–79) versus 143 (IQR 79–186.5) mg/l, median S. Ferritin was 313 (IQR 113–650) versus. 854 (IQR 407–1470) ng/ml, and median Pro-BNP was 173 (IQR 65.4–927) versus 1353 (IQR 373–4973) pg/ml for survivor versus non-survivor groups. The differences between all laboratory parameter for survivor and non-survivor are statistically significant Table 2.

Moreover, the predictive power of these indices was evaluated using ROC analysis only CRP, NLR, and Pro-BNP were "Good to Fair" in classifying survivors and non-survivors with statistical significance. CRP and NLR showed "Good" predictive value for mortality with cutoff value of 74.0mg/l (AUC=0.841, Sensitivity=80.4%, Specificity=73.0%) and 5.65 (AUC=0.805, Sensitivity=76.1%, Specificity=73.0%), respectively. Pro-BNP showed "Fair" predictive value for mortality with cutoff value of 330.5 pg/ml (AUC=0.726, Sensitivity=73.9%, Specificity=58.2%). While LDH showed "Poor" predictive value for mortality with cutoff value of 403.5 IU/l (AUC=0.670, Sensitivity=73.97%, Specificity=51.6%) Table 3.

DISCUSSION

This cross-sectional study was conducted at referral hospital in the central India during COVID-19 first wave among 300 RT-PCR-positive COVID-19 patients. Although presentation of COVID-19 ranges from mild influenza like symptoms to ARDS, even death, with recurring COVID-19 waves, sensitivity of public and even treating physician is blunting towards the importance of identification of risk factors and laboratory markers to help selecting high risk patient at the time of admission, who may develop severe complications or untoward outcome. Based on outcome of COVID-19, patients were categorized in survivors and non-survivors. In our study, 93 (32.7%) patients were non-survivors while 208 (69.3%) were survivors.

We observed that all the laboratory parameters; hematological (TLC, ANC, NLR, and Platelet count), D-dimer and immunological parameters (LDH, Procalcitonin, CRP, S.Ferritin, and Pro-BNP) were increased significantly in non-survivors as compared to survivors. Among these CRP, NLR, LDH, and Pro-BNP have good to fair discriminative power to predict non-survivor at the time of admission itself.

We found that older age was significantly associated with adverse outcomes similar to the previous studies. The median age of 62 years (IQR $_{(Q1\text{-}Q3}$ 54.50–70.50) among non-survivors was significantly higher than the median age of 55 (IQR $_{(Q1\text{-}Q3)}$ 44–63) years among survivors. Older patients are more likely to have a weak immune system and age associated comorbidities. They also show an increased expression of ACE-2(Angiotensin Converting Enzyme -2), ACE receptor (an entry receptor for COVID-19 virus) in the lung alveoli and also had low level of lung progenitor cell for repairing of damaged lungs, potential to contribute to severe form of disease.[6]

Similar to observation of Huang et al., we found significant association of dyspnea in severely ill COVID patients. Most probable reason is that the COVID-19 virus primary affects alveoli.[7]

Among comorbidities, hypertension was the most common disease that was significantly associated with mortality. Through the mechanism behind this is not clear, the most probable reason could be increased expression of ACE-2 receptor due to Antihypertensive drug therapy and polymorphism of ACE-2 gene Table 1.[8,9]

Among non-survivors TLC, ANC, NLR significantly increased and ALC and platelet counts decreased compared to survivors. Neutrophilia was found in both peripheral blood and lung parenchyma of patients with ARDS. The degree of lung damage correlated with extensive

Table 2: Comparison of laboratory parameters between survivors and non-survivors

Lab parameters	Survivors (n=208)	Non-survivors (n=92)	Total	Mann–Whitney U
TLC (10^3/µl)	8.7 (7–11.6)	12.2 (7.8–16)	9.52 (7.1–13.225)	0.00
ANC (10^3/µl)	6 (4.3–8)	9.3 (5.95–13.35)	6.5 (4.7–10)	0.00
ALC (10^3/µl)	1.8 (1.2–2.5)	1.2 (0.8–1.55)	1.6 (1–2.2)	0.00
N/L Ratio	3.48 (2–5.24)	7.86 (4.535–15.39)	4.07 (2.2325–7.325)	0.00
Platelet (10^3/µl)	252 (186.8–326.5)	198 (128–323.5)	238 (162–326)	0.02
D-dimer (ng/ml)	480 (247.8–1027)	1597 (458.5–5000)	597 (279–1514.5)	0.00
LDH (IU/l)	380 (288–570)	567 (423.5–762.5)	423 (307–640.5)	0.00
Procalcitonin (ng/ml)	0.1 (0.07–0.2425)	0.4 (0.16–1.2)	0.14 (0.1–0.41)	0.00
CRP (mg/l)	21.5 (5.9–79)	143 (79–186.5)	48 (10.825–135)	0.00
S. Ferritin (ng/ml)	313 (113–650)	854 (407–1470)	423 (162.75–907.25)	0.00
Pro-BNP (pg/ml)	173 (65.4–927)	1353 (373–4973)	376 (92–1568.25)	0.00

Data are represented as median (IQR $_{(Q1\text{-}Q3)}$) for various laboratory parameters and *P* values were calculated by Mann–Whitney U-test. TLC: Total leucocyte count, ANC: Absolut neutrophil count, ALC: Absolut lymphocyte count, LDH: Lactate dehydrogenase, CRP: C-reactive protein, Pro-BNP - N-terminal (NT)-pro hormone BNP

Table 3: ROC analysis (AUC, cutoff, sensitivity, and Specificity) of major predictor among laboratory parameters for non-survival

Investigation	AUC	Cutoff value	Sensitivity (%)	Specificity (%)
CRP (mg/l)	0.841	74.0	80.4	73
NLR (Ratio)	0.805	5.65	76.1	73
LDH (IU/l)	0.670	403.5	73.9	51.6
Pro-BNP (pg/ml)	0.726	330.5	73.9	58.2

LDH: Lactate dehydrogenase, CRP: C-reactive protein, Pro-BNP, N-terminal (NT)-pro hormone BNP, NLR: Absolute neutrophil lymphocyte ratio, ROC: Receiver operant curve, AUC: Area under the ROC curve

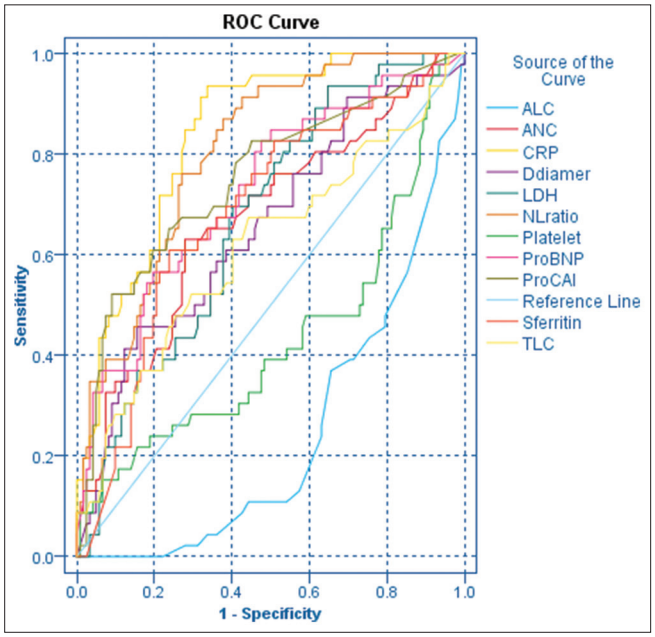

Figure 1: ROC for significant parameters to discriminate between survivors and non-survivors

pulmonary infiltration of neutrophil and macrophage as well higher number of neutrophils in peripheral blood. Neutrophils are the main source of chemokines and cytokine generation that leads to cytokine storm. The cytokine storm was found to be a leading cause of death in SARD of COVID patients.[10]

NLR is the most established marker that reflect the severity of disease among COVID-19 patients. The increased neutrophil counts reflect intensity of systemic inflammation while lymphocytopenia reflects sequestration of lymphocyte at inflammatory site and apoptosis. Similar to our findings, a meta-analysis done by Mahat et al.,[3] also found increased NLR associated with severity and mortality.

Thrombocytopenia has been independently associated with disease severity and mortality in intensive care unit (ICU) patients. The number of platelets significantly reduced in non-survivor COVID-19 patients than survivor.[5] Myocardial injury due to COVID-19 infection associated with increased mortality and these non-survivor patients with myocardial injury had increased leukocyte, neutrophils, and decrease lymphocyte and platelet counts.[11,12]

In our study, we found that the blood was in a hypercoagulable state as indicated by significantly higher D-dimer levels in critically ill patients. The blood hypercoagulable state and vasculitis lead to DIC and multiorgan dysfunction.[13] A similar finding by Dolhnikof et al., on ultrasound based minimal invasive autopsy found that eight out of 10 cases of COVID-19 had small fibrinous thrombi in lung capillary supports our results.[14]

As shown in Table 2, in this study, we found that the inflammatory biomarker such as CRP, S. ferritin, PCT, LDH, and Pro-BNP increased significantly in non-survivors than survivors. CRP is an acute phase inflammatory protein induced by IL-6 in liver and elevated levels are directly correlated with level of inflammation and disease severity.[15,16]

PCT is another crucial biomarker significantly increased in non-survivor than survivor group. Here, it indicates systemic bacterial infection, as it is usually not increased in viral infection.[17] The increased levels of PCT among COVID-19 patients indicate secondary bacterial infection and progression toward more severe complications like covid-19 pneumonia and ARDS.[18] Meta-analysis done by Lippi et al., showed that elevated PCT associated with fivefold increase severe COVID-19 infection.[15]

S. Ferritin is an acute phase protein, its level increases in inflammation and also affected by iron storage status. We found that S. ferritin was significantly higher in non-survivors than survivors. Higher S. ferritin values have been independently associated with a severe disease course and hyperferritinemia is also an independent risk factor for ARDS in COVID-19 cases.[19,20]

LDH is an enzyme that is located in cytoplasm of all cells and participate in glucose anaerobic oxidation and catalyze interconversion between pyruvate and lactate. Serum level of LDH increases in case of hypoxia and/or cell death. Abnormal LDH levels can result from decreased oxygenation; leading to an upregulation of the glycolytic pathway. Some researchers also reported increase LDH associated with a higher risk of ARDS, need of ICU support and death. Similarly, Henry et al., found that elevated LDH value was associated with 16-fold increased mortality in COVID-19 patients.[21] Similar to the previous studies, we also found that serum LDH levels significantly increased in non-survivors than survivors among COVID-19 cases.

NT-Pro-BNP is a marker used for diagnosis of heart failure. Hill et al.,[22] reported that the cutoff value of Pro-BNP to predict the adverse outcome of severe COVID-19 patients was very low than that of threshold for diagnosing heart failure. It suggests that heart failure due to virus or hypoxia is not only cause for increased pro-BNP, but it is secreted in response to increased myocardial stress and it is also controlled by acute renal injury and pro-inflammatory molecules. Gao et al.,[23] found pro-BNP levels were positively correlated to the makers of cardiac injury, renal injury, and systemic inflammation. A meta-analysis conducted by Pranata et al.,[24] concluded higher NT-Pro-BNP level in non-survivor compared to survivor and it is an independent risk factor for in hospital death in severe COVID-19 patients. Similar to aforementioned studies, we also found significantly higher Pro-BNP levels among non-survivor compared to survivor group.

ROC analysis

All values the laboratory indices that were studied showed a significant ($P<0.05$) difference in the median of non-survivor group compared to survivor group Table 2. When predictive power of these indices was evaluated using Receiver Operant Curve (ROC) analysis only CRP, NLR and Pro-BNP were "Good to Fair" in classifying survivors and non-survivors with statistical significance. CRP and NLR showed "Good" predictive value for mortality with AUC (0.7–0.8) Table 3 and Figure 1.

In this study, CRP showed "Good" predictive value for mortality with cutoff value of 74.0 mg/l (AUC=0.841, Sensitivity=80.4%, Specificity=73.0%). Similarly, Parimoo et al., calculated optimal cutoff value of CRP by ROC curve to predict mortality in COVID-19 patients which was 66.7 mg/l with sensitivity 78.43% and specificity 74.12% while Li et al.,[25] reported a higher best cut-off value for CRP being 91.39 mg/l with AUC=0.87, sensitivity of 81.3% and a specificity of 88.2% and concluded that CRP have good prediction power of mortality.

NLR also have good predictive power to predict mortality in COVID-19 cases with best cutoff value for NLR was 5.65 (AUC=0.805, Sensitivity=76.1%, Specificity=73.0%). Prediction analysis (ROC) done by prasantya et al.,[26] found an AUC=0.84 with optimal cutoff point to predict mortality at admission time was 6, with 75.9% sensitivity and 88% specificity. Sayah et al.,[27] in study conducted at Algeria found best cutoff value for NLR to predict mortality (AUC=0.831) slightly higher than our study which was 7 with sensitivity of 75% and specificity of 84%.

In this study, third important inflammatory marker that we found to have fair predictive power for mortality in COVID-19 patients at the time of admission was NT-Pro-BNP (AUC=0.726). Best cutoff value of NT-Pro-BNP was 403.5 pg/ml with 73.9 % sensitivity and 58.2 % specificity. Selçuk et al.,[28] conducted a study on 137 patients of COVID-19 to predict mortality, found that on ROC analysis of NT-Pro-BNP ideal cutoff value was 260ng/l with sensitivity of 82% and specificity of 93% (AUC:0.86).

Limitations of the study

This study was conducted in covid reference hospital patients of single center only. A multicentric study could have a better power.

CONCLUSION

We found that older age, comorbidity (especially hypertension) was significantly associated with mortality among COVID-19 patients. The analysis of derangements in hematological indices and inflammatory biomarkers, such as lymphopenia, thrombocytopenia and elevated level of ANC, NLR, CRP, D-dimer, LDH, S. ferritin, and NT-Pro-BNP, showed that they are significantly associated with non-favorable outcome in COVID-19 patients.

ROC analysis of all these parameters showed that CRP and NLR have "Good" predictive value for mortality with cutoff value of 74.0mg/l (AUC=0.841, Sensitivity=80.4%, Specificity=73.0%) and 5.65 (AUC=0.805, Sensitivity=76.1%, Specificity=73.0%), respectively, and Pro-BNP also showed "Fair" predictive value for mortality with cutoff value of 330.5 pg/ml (AUC=0.726, Sensitivity=73.9%, specificity=58.2%). Thus CRP, NLR, and Pro-BNP can be used as predictors for mortality among COVID-19 patients during time of admission, which will help clinician or medical health professionals to plan timely interventions to save valuable lives. This could play a significant role these days, where incidence of COVID-19 cases been decreased but proportion of mortality has been increased.

ACKNOWLEDGMENT

We acknowledge contribution of our statistician Mr. Jagmohan Singh Dhakad and Dr. Pinki Singh, Assistant Professor (Speech-language pathologists) for their insight in improving this article.

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Authors' Contributions:
SKT- Guidance for the study and prepared first draft of manuscript; **AV and NT-** Interpreted the results; **BSY-** Reviewed the literature and manuscript preparation; **CD and RKM-** Statistical analysis and interpretation, preparation of manuscript, and revision of the manuscript.

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Source of Support: Nil, **Conflicts of Interest:** None declared.