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BIOCHEMICAL MARKERS OF SEVERE COVID PATIENTS ADMITTED TO ICU IN A TERTIARY CARE HOSPITAL IN KERALA

Medical Microbiology

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ABSTRACT

Background: COVID-19 has presented diverse clinical characteristics in different countries. Studies on the laboratory parameters of severe COVID-19 patients admitted to ICUs in India are limited. This study aims to investigate the laboratory findings of patients with COVID-19 at different stages of the disease, focusing on the differences between survivors and non-survivors among severe COVID-19 patients admitted to the ICU in Kerala, India.**Materials and Methods:** This cross-sectional study analyzed medical records of patients admitted to the ICU of Chazhikattu Memorial Hospital in Thodupuzha, India, from January 2021 to June 2022. The hospital was designated as a COVID Hospital by the Government of Kerala during the early phase of the pandemic. Patients who met the inclusion criteria were selected, and the study was approved by the Hospital Ethics Committee. **Results:** Significant differences were observed between survivors and non-survivors in terms of age, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), neutrophil-to-lymphocyte ratio (NLR), urea, creatinine,D-Dimer and C-reactive protein (CRP) levels. Elevated D-dimer and CRP levels at admission, as well as persistently high ANC, low ALC, increased NLR, and high CRP levels during hospitalization, were significantly associated with a higher risk of mortality. **Conclusion:** The study highlights the importance of certain laboratory parameters in predicting the clinical outcome of patients with severe COVID-19. These findings may help guide the clinical management and risk stratification of patients with COVID-19, ultimately contributing to improved patient care and outcomes.

KEYWORDS

INTRODUCTION

In late 2019, a new coronavirus that caused a viral pneumonia outbreak was reported in China 1. This was dubbed SARS-CoV-2 and led to a severe acute respiratory syndrome known as SARS. The virus quickly spread beyond China, leading to restrictions on global air travel and quarantine measures. In response, the World Health Organization declared a global health emergency on January 31, 2020 and later renamed the outbreak COVID- 19. On March 11, 2020, the WHO declared the COVID-19 outbreak a global pandemic 2. The first case of COVID- 19 in India was reported on January 30, 2020 in a student returning from Wuhan. By January 31, 2021, over 100 million confirmed cases and one million deaths had been reported globally, with India reporting over 10 million confirmed cases and more than 150,000 deaths.

The COVID-19 pandemic has posed a significant global public health challenge, with varying impacts on different regions and populations. In recent times, India has been witnessing a slow increase in daily new COVID-19 cases, particularly due to the Omicron XBB 1.16 sublineage of the virus 3. As of early April 2023, the country recorded the highest number of fresh cases in the last 203 days, with active cases on the rise. In the stateof Kerala, a resurgence of COVID-19 cases is being observed, leading the government to reintroduce restrictions and guidelines to curb the spread of the virus.

In light of the recent surge in COVID-19 cases and the emergence of new variants, it is essential to revisit and assess the relevance of previously conducted studies to inform our understanding and management of the pandemic. Although the data analyzed in our research study consists of patients hospitalized until June 2022, we believe that the findings remain valuable in the current scenario of emerging new cases. By analysing the laboratory findings and identifying significant differences between survivors and non-survivors, we aim to evaluate the potential prognostic value of some of these common laboratory parameters in predicting the clinical outcome of patients with COVID-19.

AIMS & OBJECTIVES

Given that the clinical characteristics of COVID-19 are diverse and variable across different countries, it is essential to investigate the clinical symptoms and co-morbidities associated with severe COVID-19 in the local population. In India, although there have been numerous studies on the symptoms and clinical characteristics of COVID-19 patients in general, there is a limited number of studies with large sample sizes focusing on the clinical characteristics of severe COVID-19 patients admitted to the ICU. The objective of our research study is to examine the variations in laboratory results between survivors and non-survivors of COVID-19 at three different stages of hospitalization, specifically at the time of admission, within the first week, and after the first week. We will focus on parameters such as Age, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), neutrophil-to-lymphocyte ratio (NLR), urea, creatinine, C-reactive protein (CRP), D-dimer levels, Haemoglobin (Hb), random blood sugar (RBS), sodium (Na), and potassium (K) levels.

MATERIALS AND METHODS\

STUDY DESIGN

In this cross-sectional study, we utilized data from the medical records of patients admitted to the intensive care unit (ICU) of Chazhikattu Memorial Hospital in Thodupuzha, India, between January 2021 and June 2022.

Chazhikattu Memorial Hospital was designated as a COVID Hospital by the Government of Kerala during the early phase of the pandemic. The admission of COVID-19 patients to the ICU followed the guidelines set forth by the Indian Council of Medical Research (ICMR).

From the cohort of ICU patients, we selected those who met the inclusion criteria for our study. The study was approved by the Hospital Ethics Committee, ensuring that all ethical considerations were observed in the process of conducting the research. By analyzing the medical records of severe COVID-19 patients in this specific ICU setting, our study aims to provide valuable insights into the clinical characteristics associated with survival outcomes in this population.

STUDY POPULATION

The study involved patients who had been diagnosed with COVID-19, were over the age of 18, and were admitted to the ICU. The criteria for exclusion included pregnant patients, those who left against medical advice, those who were admitted for another disease and later developed COVID-19, those who developed other non-COVID-related diseases during hospital treatment, those who were readmitted to the ICU/hospital for COVID-related diagnosis, and those with incomplete data. The COVID-19 diagnosis and ICU admission criteria were made in accordance with ICMR guidelines, with the majority of cases confirmed using RT-PCR at DDRC Laboratories and the rest through Rapid Antigen Test (RAT) at the Chazhikattu Memorial Hospital's microbiology lab. Other respiratory infections were ruled out. Out of the 381 COVID cases admitted to the ICU in January 2021, 143 were excluded and 238 patients were included in the study. The patients received standard care based on ICMR guidelines andinvasive

procedures were performed when necessary. Before discharge from the ICU, viral clearance was confirmed in all patients using RAT in the hospital's microbiology lab.

DATA COLLECTION/VARIABLES

The demographic information, symptoms reported by patients at admission, comorbidities, and outcome data were retrieved from the electronic medical records retrospectively. No post-discharge follow-up was conducted. The data was collected anonymously and verified by two independent physicians. The information was recorded on a printed form and then transferred to MS Excel for analysis.

STATISTICAL ANALYSIS

In this study, all categorical variables are presented as count (%). All continuous variables which were normally distributed are represented using mean (SD) and all continuous variables without normal distribution are represented using median (IQR). Based on the normal distribution, the continuous data was analysed using the Independent Samples T-test and Mann–Whitney U tests. A two-tailed P-value less than 0.05 was considered statistically significant. All statistical analysis was performed using SPSS (version 29, IBM Corp.) software.

RESULTS

	Count(N)	Percentage(%)
Sex		
Male	158	66.4
Female	80	33.6
Overall Survival	143	60.1
14Day Survival	165	69.3

Characteristics	All Patients	Survivors	Non-Survivors	P Value
Age, Median(IQR)	67(26)	65(25)	73(22)	<0.001
At admission				
Hb, Mean(SD)	12.5(2.4)	12.7(2.5)	12.3(2.2)	0.188
ANC, Median(IQR)	6100(6389)	5051(5795)	7113(6836)	<0.001
ALC, Median(IQR)	1063(770)	1096(683)	964(793)	0.015
NRL, Median(IQR)	5.5(8)	4.4(5.7)	8.5(10.7)	<0.001
Platelets, Median(IQR)	2.2(1)	2.2(0.9)	2.2(1.1)	0.868
RBS, Median(IQR)	188(150)	188(161)	184(142)	0.579
Urea, Median(IQR)	49(56)	41(37)	62(64)	<0.001
Creatinine, Median(IQR)	1.2(1.2)	1.1(0.9)	1.4(1.9)	0.038
Na, Median(IQR)	134(5.4)	134.3(5.3)	133.5(7.4)	0.358
K, Median(IQR)	4.2(1)	4.1(1)	4.2(1)	0.699
D-Dimer, Median(IQR)	1269(2189)	927(1230)	1930(3008)	<0.001
CRP, Median(IQR)	53.1(81.15)	26.1(71.2)	86(81.8)	<0.001
Within 1st week				0.037
Hb, Mean(SD)	12.5(2.3)	12.5(2.3)	12.4(2.3)	0.743
ANC, Median(IQR)	9058(6374)	7249(5783)	11357(7372)	<0.001
ALC, Median(IQR)	909(800)	1147(747)	693(646)	<0.001
NRL, Median(IQR)	10.6(14.5)	5.7(8)	19(15.7)	<0.001
Platelets, Median(IQR)	2.6(1.6)	2.7(1.5)	2.3(1.6)	0.270
RBS, Mean(SD)	177(76)	182(78)	164(70)	0.140
Urea, Median(IQR)	94(100)	69(72)	102(129)	0.009
Creatinine, Median(IQR)	1(1.3)	1.2(4.5)	2.6(4)	
Na, Median(IQR)	135.1(5.8)	135(4.6)	135.4(7.2)	0.270
K, Median(IQR)	4.2(1)	4.1(0.8)	4.4(1.2)	0.303
D-Dimer				
CRP, Median(IQR)	23.1(60.9)	12.8(24.3)	68.4(107.45)	<0.001
After 1st week				
Hb, Mean(SD)	12.4(2.4)	12.8(2.3)	12(2.6)	0.089
ANC, Median(IQR)	11043(8546)	9570(4686)	15359(9796)	<0.001
ALC, Median(IQR)	732(955)	1247(1387)	537(501)	<0.001
NRL, Median(IQR)	14.8(26.5)	8.4(9.4)	34(20.9)	<0.001
Platelets, Median(IQR)	2.5(1.4)	2.8(1.2)	2.2(1.3)	0.019
RBS, Mean(SD)	169(67)	164(70)	174(64)	0.575
Na, Median(IQR)	133.5(8.4)	133.6(4.7)	133.2(11.5)	0.444
K, Median(IQR)	4.4(1)	4.3(1.0)	4.6(1.2)	0.22
D-Dimer				
CRP, Median(IQR)	24.6(79.7)	13(23)	85.6(125)	<0.001

In our study, the sex distribution of the patients was heavily skewed towards males, with 66.4% of the patients being male and 33.6% being female. In terms of survival, the overall survival rate was found to be 60.1%, while the 14-day survival rate was higher at 69.3%. These results highlight the potential impact of sex on COVID-19 outcomes and provide important information for clinicians when managing patients with COVID-19. The results are summarized in table 1.

In this study, we analyzed the laboratory findings of patients with COVID-19 at different stages of the disease, with a focus on the differences between survivors and non-survivors. The results of lab parameters were collected at three different time frames during hospitalisation of the patient: at admission, within the first week, and after the first week of hospitalization. The results are summarized in table 2.

At admission, the median age of all patients was 67 years (IQR: 26), with survivors having a significantly lower median age of 65 years (IQR: 25) compared to non-survivors at 73 years (IQR: 22) ($p < 0.001$). Significant differences between survivors and non-survivors were observed in absolute neutrophil count (ANC), absolute lymphocyte count (ALC), neutrophil-to-lymphocyte ratio (NLR), urea, creatinine, and C-reactive protein (CRP) levels (all $p < 0.05$). Notably, D-dimer levels were significantly higher in non-survivors (median: 1930, IQR: 3008) than in survivors at the time of admission(median: 927, IQR: 1230) ($p < 0.001$).

Within the first week of hospitalization, significant differences between survivors and non-survivors were observed in ANC, ALC, NLR, urea, creatinine, and CRP levels (all $p < 0.05$). No significant differences were found in hemoglobin (Hb), random blood sugar (RBS), sodium (Na), and potassium (K) levels between the two groups.

After the first week of hospitalization, significant differences between survivors and non-survivors persisted in ANC, ALC, NLR, platelet count, and CRP levels (all $p < 0.05$). Although there were differences in Hb, RBS, Na, and K levels between the two groups, these differences were not statistically significant.

In summary, our results highlight the importance of certain laboratory parameters in predicting the clinical outcome of patients with COVID-19. Elevated D-dimer and CRP levels at admission, as well as persistently high ANC, low ALC, increased NLR, and high CRP levels during the course of hospitalization, were significantly associated with a higher risk of mortality. These findings can help guide the clinical

management and of patients with COVID-19, thus contributing to improved patient outcomes.

DISCUSSION

This study examined the laboratory parameters and mortality outcomes among 238 severe COVID-19 patients admitted to the ICU at a tertiary care hospital, Chazhikattu Memorial Hospital, in Kerala. Out of these patients, 143 (60.1%) survived and were discharged in a stable condition to their homes. All patients were isolated throughout their treatment, and healthcare workers followed appropriate infection control measures using disposable personal protective equipment (PPE). The patients were treated according to ICMR guidelines, and their clinical severity was categorized accordingly. Treatment involved the use of antivirals, corticosteroids, anticoagulants, bronchodilators, and supplemental oxygen therapy. Non-invasive ventilation (NIV) and mechanical ventilation were provided as needed.

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Our findings highlight the significance of certain laboratory parameters in predicting the clinical outcomes of severe COVID-19 patients. Elevated D-dimer and CRP levels at admission, as well as persistently high ANC, low ALC, increased NLR, and high CRP levels during hospitalization, were significantly associated with a higher risk of mortality. These results are consistent with previous studies that have reported associations between these laboratory parameters and COVID-19 severity or mortality (1-3).

A meta-analysis by Huang et al.4 demonstrated that an increased NLR was associated with higher odds of severe COVID-19 infection and mortality. Our study supports these findings, as we observed a significantly higher NLR in non-survivors compared to survivors, both within the first week and after the first week of hospitalization.Elevated D-dimer levels have been reported to be associated with a higher risk of mortality in COVID-19 patients, as shown by Zhang et al.. Our study concurs with these findings, as we observed significantly higher D-dimer levels in non-survivors at the time of admission compared to survivors.

In line with previous studies, we found that higher CRP levels at admission and during the course of hospitalization were associated with an increased risk of mortality. This suggests that CRP levels may be a valuable prognostic marker for severe COVID-19 patients.

These findings are also similar to the findings from other studies done on Indian population by Ramkumar et.al 5., Pujani et.al 6., Bairwa et.al 7. and Gupta et.al 8. with a sample size of 60, 506, 249 and 200 respectively. There were some differences from the above studies as well. We did not get any statistically significant association between low potassium and mortality as noted by Bairwa et.al. It is also to be noted that among these 4 studies, only the one by Ramkumar et.al was done on COVID patients admitted to the ICU. The rest of the studies were on both moderate and severe cases admitted to the hospital wards and ICU's respectively.

This study provides valuable insights into the management of severe COVID-19 patients in a tertiary care setting in India. The multidisciplinary approach to treatment, including the use of antivirals, corticosteroids, anticoagulants, and other supportive measures, reflects the evolving understanding of COVID-19 and its management. The high survival rate of 60.1% in our cohort indicates the effectiveness of the management strategies employed.

In conclusion, our study highlights the importance of monitoring laboratory parameters, such as D-dimer, CRP, ANC, ALC, and NLR, to predict clinical outcomes in severe COVID-19 patients. This information can guide healthcare providers in risk stratification, allowing for the allocation of resources and personalized management strategies for patients at higher risk of mortality. Future studies should continue to investigate the role of these and other emerging biomarkers in predicting COVID-19 outcomes and guiding treatment decisions.

The management of severe COVID-19 patients remains a challenge for healthcare systems globally. Timely identification of patients at risk of poor outcomes, as well as the implementation of evidence-based treatment strategies, are crucial for improving patient prognosis. The findings of our study contribute to the growing body of evidence on the prognostic value of laboratory parameters in severe COVID-19 patients, emphasizing the importance of close monitoring and timely intervention.

LIMITATIONS

Lastly, it is important to recognize the limitations of our study, which include its single-center design, retrospective nature, and the lack of availability of certain other lab parameters including D-Dimer at within first week and after week, LDH, Troponin levels, etc. Despite these limitations, our study provides valuable insights into the prognostic utility of laboratory parameters in severe COVID-19 patients, which may inform clinical decision- making and improve patient outcomes. In addition to the aforementioned biomarkers, it is important to consider other factors that may contribute to the clinical outcomes of severe COVID-19 patients. The latest ICMR guidelines as of January 2023 state that for adult patients with COVID-19, medications such as Lopinavir- ritonavir, Hydroxychloroquine, Ivermectin, Neutralizing monoclonal antibody, Convalescent plasma, Molnupiravir, Favipiravir, Azithromycin, and Doxycycline should not be administered for treating COVID-19. It should be noted that during the study period, some of these medications, including Ivermectin, Favipravir, Molnupiravir, Azithromycin, and Doxycycline, were used in patients in accordance with the then guidelines issued. As a result, our study findings may have been restricted to some extent.

CONCLUSION

In conclusion, this study on laboratory parameters and mortality among severe COVID-19 patients in the ICU at Chazhikattu Memorial Hospital, a tertiary care hospital in Kerala, provides significant insights into the clinical course and outcomes of these patients. Our study's primary findings suggest that advanced age, elevated levels of CRP and D-dimer, high ANC and low ALC levels, higher Urea and Creatinine levels and a high neutrophil-to-lymphocyte ratio (NLR) at admission, along with higher levels of ANC, Urea, creatinine, and CRP, and lower levels of ALC within the first week and after the first week of hospitalization are significantly linked to increased overall in-hospital mortality in severe COVID patients in India.

The outcomes of our study emphasize the importance of closely monitoring these parameters in order to optimize patient care and management. Our findings are consistent with previous studies that have reported similar associations between laboratory parameters and mortality among COVID-19 patients.

In summary, our study contributes valuable information to the ongoing efforts to manage and treat severe COVID-19 cases. By identifying the significant associations between older age, we hope to improve patient care and resource allocation in ICUs during this unprecedented global pandemic.

Future research should focus on exploring additional factors that could further refine the prediction of mortality and investigating the underlying mechanisms of the observed associations. This could lead to the development of more targeted therapies and better clinical decision-making for severe COVID-19 patients.

CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

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