Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Intensive Care Unit

Association between Inflammatory Markers and the Outcome of Critically Ill COVID-19 Patients

Dr. Md. Mahade Hassan[1*], Dr. Shafatujjahan[2], Dr. Reshma Sharmin[3], Dr. Md. Saif Uddin Azad[4], Dr. Anjan Bal[5]

[1]Assistant Professor, Department of Intensive Care Unit, Chattogram Maa Shishu Hospital Medical College, Chattogram, Bangladesh
[2]Associate Professor, Radiation Oncology, Chattogram Maa O Shishu Hospital Medical College, Chattogram, Bangladesh
[3]Medical Officer, OCC, Chittagong Medical College Hospital, Chattogram, Bangladesh
[4]Registrar ICU, Chattogram Maa O Shishu Hospital Medical College, Chattogram, Bangladesh
[5]Junior Consultant, Department of Anesthesia, Chittagong Medical College Hospital, Chattogram, Bangladesh

DOI: 10.36347/sjams.2022.v10i10.003 | **Received:** 24.07.2022 | **Accepted:** 20.08.2022 | **Published:** 04.10.2022

***Corresponding author:** Dr. Md. Mahade Hassan
Assistant Professor, Department of Intensive Care Unit, Chattogram Maa Shishu Hospital Medical College, Chattogram, Bangladesh

Abstract **Original Research Article**

Background: Coronavirus disease (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2(SARS-CoV-2). It had emerged from Wuhan, China and has rapidly spread around the world. In critically ill patients, the mortality rates are significantly high. This study analyzed the various inflammatory markers and their association with patient mortality, thus helping to identify critically ill patients with a high possibility of worsening prognosis. ***Materials and Methods:*** In this multicenter, prospective study, 85 patients were included and were followed until either of two outcomes was achieved: patients were successfully discharged or patients expired at the ICU. Correlation between the patient outcome and inflammatory markers were analyzed. Cut-off values for patients with worse prognosis were speculated through ROC curve. ***Results:*** Significantly, mortality was associated with CRP (P<0.001), d-dimer (P<0.001)., LDH (P=0.001), IL-6(P<0.001), serum ferritin(P=0.001), procalcitonin (P<0.001)along with neutropenia (P<0.001) and lymphocytosis (P<0.001). ***Conclusion:*** With the following inflammatory markers such as CRP, d-dimer, LDH, IL-6, procalcitonin and serum ferritin, patients who have a worse prognosis can be identified among the critically ill patients at the ICU. Hence, close monitoring and early management of such patients can help improve their prognosis.

Keywords: COVID-19, respiratory syndrome coronavirus2, procalcitonin, serum ferritin.

INTRODUCTION

Covid-19 is a disease caused by the severe acute respiratory syndrome coronavirus2 also known as the SARS- CoV-2. It was first identified in the middle of December 2019 in Wuhan, China and has spread rapidly across the globe resulting in over 4.7 million deaths worldwide [1, 2]. The virus causes a severe respiratory illness that is usually characterized by fever, cough and shortness of breath. Although many of the infected individuals display mild symptoms, a certain percentage of infected patients require hospital admissions for severe illness. Furthermore, a significant portion of the hospitalized patients develop acute respiratory distress syndrome for which they require management at intensive care units (ICU).

In Bangladesh, the first case of COVID 19 was diagnosed on 8th March 2020, followed by rapid dissemination of infection across the different districts including Chattogram district. With the increase in number of critically ill COVID-19 patients, the ICU capacity as well as hospital care resource allocations was subsequently increased. However, there is a dearth in knowledge about the allocation of appropriate services based on patient need. Even worse, scientific data about the course of disease and the outcome of critically ill COVID-19 ICU patients among the population of Bangladesh is limited. For the management of severe and life threatening COVID-19 cases, evidence-based therapy as well as supportive care in the ICU is of utmost importance [3].

Many laboratory-based studies have showed a number of test parameters to be characteristically altered in COVID-19 patients and its use in categorizing patients as mild, moderate or severe. However, very few studies have been conducted that associated altered laboratory parameters with patient prognosis. Since

inflammation plays a major role in the pathogenesis and progression of COVID-19,changes in the levels of different inflammatory markers such as C- reactive protein (CRP), interleukin 6 (IL-6), lactate dehydrogenase enzyme (LDH), procalcitonin and serum ferritin can be expected. In fact, studies have shown significant association of different inflammatory markers with severity of COVID-19 infection. To reduce mortality in ICU settings, careful monitoring of the patient as well as timely interventions are necessary and inflammatory markers play an important role in this regard. Hence, the purpose of this study is to identify the different inflammatory markers that are characteristically altered in critically ill COVID-19 patients admitted at an intensive care unit; and their potential prognostic value.

MATERIALS AND METHODS

This is a prospective study that was conducted among patients admitted to the intensive care units of three different hospitals between periods of October 2020 to February 2021. The hospitals were Chattogram Maa O Shishu Hospital, Islami Bank Hospital and Imperial Hospital. On admission to the ICU, patient history was taken and necessary investigations were given. Clinical signs and symptoms were confirmed from patient caretaker after seeking permission to conduct the study and the results were recorded in a data collection sheet. The investigation results used included hematological profile and inflammatory markers among patients admitted to the ICU with a confirmed diagnosis of COVID-19 using rt-PCR.

RESULTS

A total of 85 patients were included in this study. The mean age of the respondents was 52 ±15.8 years with a female: male ratio of 1:2.7. Out of the total 85 patients, 20 expired while the rest were discharged with or without complications. The average length of stay among the study group was 9.5 ± 4.6 days. All patients admitted to the ICU had shortness of breath. Other common symptoms observed were fever (n=76), cough (n=57), tachypnea (n=32), diarrhea (n=20), headache (n=18), anosmia (n= 13). Among patient comorbidities, the most common observed were hypertension (n=42), diabetes mellitus (n= 39), ischemic heart disease (n=20), hypothyroidism (n=6), COPD (n=6), CKD (n=5) and CVD (n=4).

In case of hematological profile some of the parameters showed significant difference when compared between survivors and non-survivors among the study subjects. The table below summarizes these findings.

Table 1: Hematological profile based on patient outcome

Parameters	Survived	Non-survived	p value
Hemoglobin	12.4±1.5	11.4±0.9	0.001
Total WBC	9286.1± 4194.1	14066.5±5937.17	0.03
Neurophils%	57.7±12.3	73.4±16.1	<0.001
Lymphocytes %	22.3±8.8	10.7±4.6	<0.001
N:L ratio	3.2±2.0	8.2±3.8	< 0.001

Analysis of the hematological profile showed that the cohort which did not survive had a significantly higher level of neutrophils and lower level of lymphocytes. Although within normal limits, a significant difference in the levels of hemoglobin was observed between the dead and alive cohort. Also, the total WBC counts were significantly raised in the patients who expired.

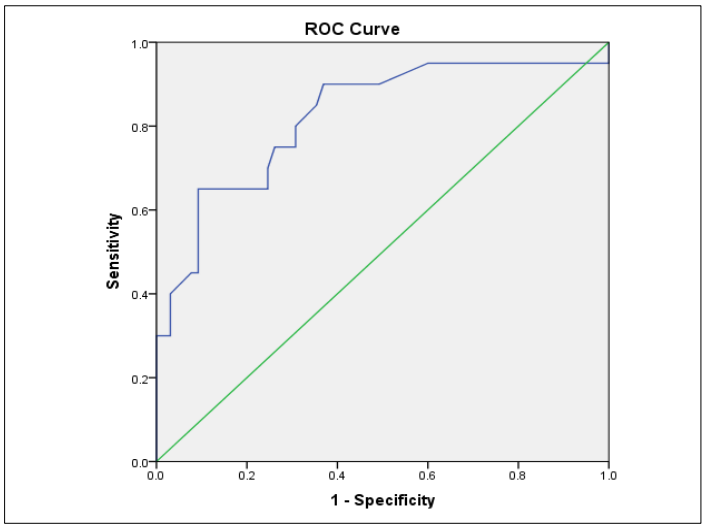
Both these groups were further compared for inflammatory markers. The findings are summarized in the next table.

Table 2: Inflammatory markers based on patient outcome

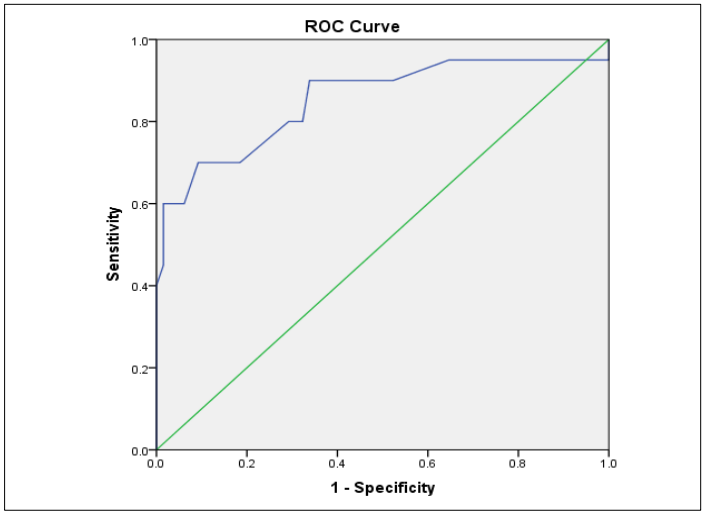
Parameters	Survived	Died	p value
C-reactive protein	45.8±29.5	98.8±51.9	< 0.001
D-dimer	0.7±0.5	1.9±0.9	< 0.001
LDH	286.9±111.5	394.5±156.7	0.001
IL-6	36.6±27.2	100.5±60.9	< 0.001
S. Ferritin	472.8±185.7	801.9±389	0.001
Trop- I	3.8±8.4	6.8±8.9	0.183
S. creatinine	1.0±0.3	1.6±0.3	< 0.001
Procalcitonin	0.2±0.3	0.9±0.5	< 0.001

Inflammatory markers such as CRP, D-dimer, LDH, IL-6, serum ferritin, serum creatinine and procalcitonin were significantly raised among the patients who expired as compared to the ones who survived. Only troponin I showed no significant difference between the two cohorts.

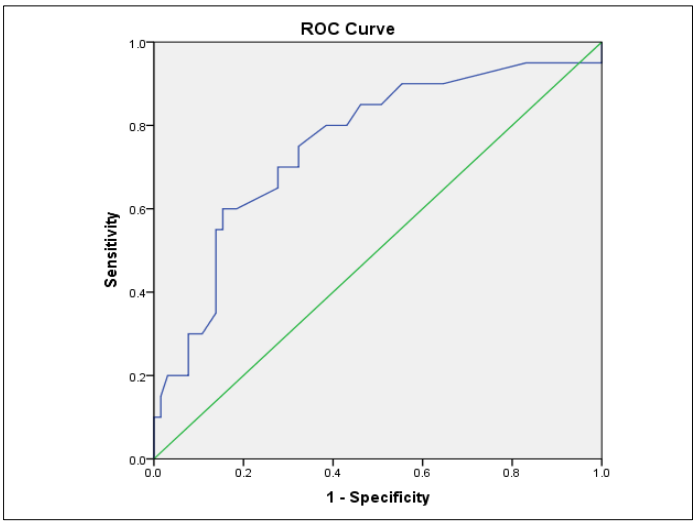
To better detect the disease outcome, the ROC curve of the various inflammatory parameters was administered and the results in listed in Figure 1.



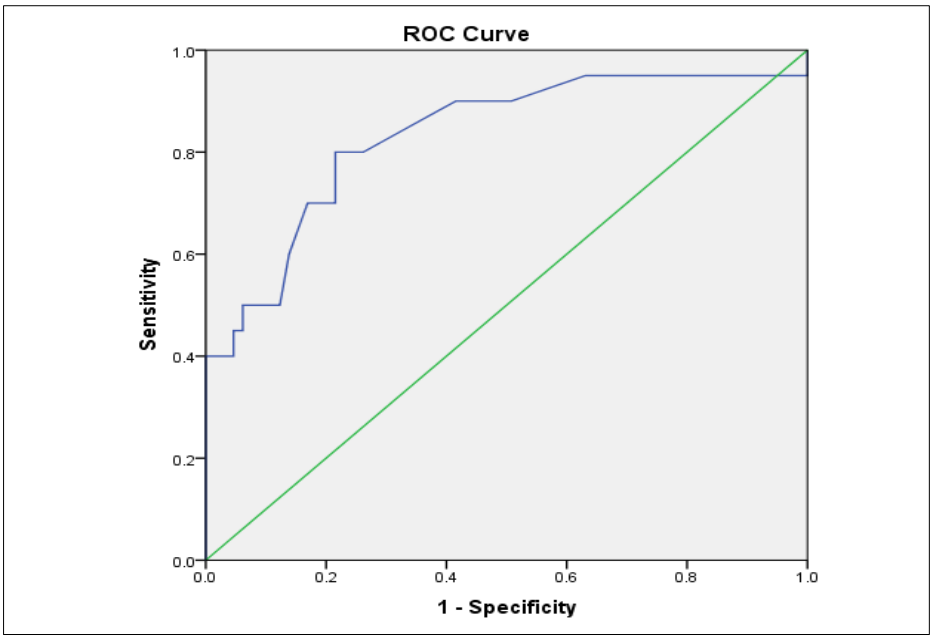
(a)



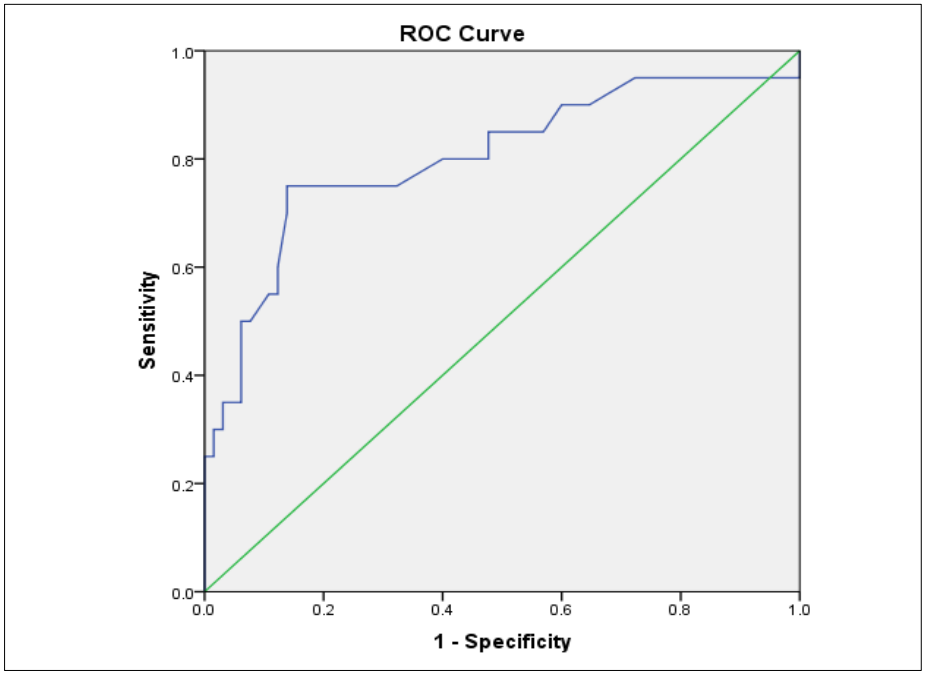
(b)



(c)



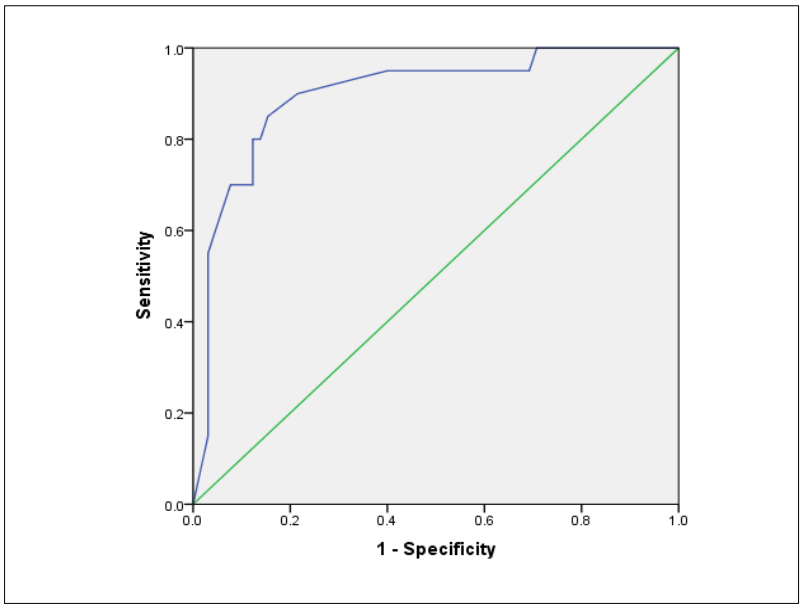
(d)



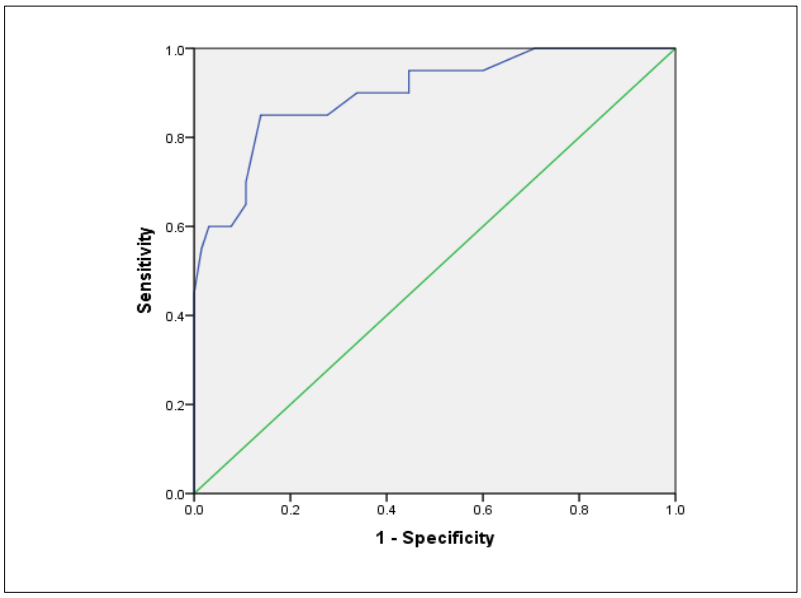
(e)

Figure 1: ROC curve of indicators between alive and dead patients. a) CRP, b) D-dimer, c) LDH, d) IL-6, e) Serum ferritin

The ROC curve for C - reactive protein (AUC= 0.823, 95% CI: 0.708-0.939, P< 0.001) suggested the best cut-off point to be 52mg/dl sensitivity of 80% and a specificity of 69%. For d-dimer the ROC curve (AUC= 0.853, 95% CI: 0.739 -0.968, P< 0.001) suggested the best cut-off point was 1.035µg/ml with a sensitivity of 80% and a specificity of 71%. The best cut-off point for lactate dehydrogenase (AUC= 0.754, 95% CI: 0.627 -0.881, P= 0.001) was315.5 U/L with a specificity of 62% and a sensitivity of 80%. The ROC curve of interleukin 6 (AUC= 0.832, 95% CI: 0.718 -0.947, P< 0.001) recommended best cutoff point was 53.5pg/ml with a sensitivity of 80% and a specificity of 79%. The best cut-off point for serum ferritin level was 542µg/L with a sensitivity of 80% and a specificity of 60%.



(a)



(b)

Figure 2- ROC curve of indicators between alive and dead patients. a) Serum creatinine b) Procalcitonin

In Figure 2 above, we displayed the ROC curve of serum creatinine and procalcitonin to predict patient outcome. For serum creatinine, ROC curve suggests that the best cut-off point for serum creatinine (AUC= 0.898, 95% CI: 0.817 -0.979, P< 0.001) was 1.15 with a sensitivity of 90% and a specificity of 79%. In case of procalcitonin (AUC= 0.899, 95% CI: 0.818 - 0.981, P< 0.001), the best cut-off point was recommended to be 0.27ng/ml with a sensitivity of 90% and a specificity of 66%.

The chest X ray findings of all study subjects admitted to the ICU showed evidence of bilateral lung congestion. For further analysis, HRCT was conducted and the level of significance between patients who died and ones who survived was p= 0.054.

Table 4: Association between RT-PCR results and patient outcome

RT-PCR	Patient outcome		Total	P value
	Dead	Survived		
Positive	9	53	62	0.002
Negative	11	12	23	
Total	20	65	85	

The table above shows the association between RT-PCR results and patient outcome. Here, patients who were RT-PCR positive for Covid-19 had a significantly higher rate of survival than patients who were symptomatic, but RT-PCR negative for COVID-19 (p=0.002).

DISCUSSION

The COVID-19 outbreak that began in late 2019 continues to infect people worldwide. Although the number of cases has risen to an alarming rate, most of the patients tend to experience mild to moderate severity of disease. However, for patients who develop severe disease and become critically ill, chances of survival become limited and mortality rates are noticeably higher in this group of individuals. Hence, it is essential to identify critically ill patients early and manage them accordingly to increase survival.

In this study, the relationship between critically ill patient outcome and inflammatory markers were comprehensively analyzed. Most of the critically ill patients were older and had associated comorbidities. This is consistent with a study by Wang *et al.*, [4] which included 143 cases of COVID-19 cases and a cutoff point of 52-year- old age depicted disease severity on their ROC curve. Another study [5] that prospectively included 138 patients with COVID-19 found advanced age and comorbidities to be significantly associated with poor patient outcome.

In case of hematological parameters, levels of lymphocyte counts and neutrophil counts were significantly associated with poor outcome of the patients. Additionally, a high neutrophil- lymphocyte ratio also suggests increased mortality among the study subjects. Besides, we also found a significant increase in CRP, D-dimer, LDH, IL-6, serum ferritin, serum creatinine and procalcitonin among the patients who expired as compared to the ones who survived. On administering an ROC curve for the individual parameters, the best cut-off points were 52mg/dl, 1.035µg/ml, 315.5 U/L, 53.5pg/ml, 542 µg/L, 1.15 and 0.27ng/ml respectively.

The hematological parameters were similar to studies conducted by Wang *et al.*, [4], Liu *et al.*, [6] and Wan *et al.*, [7], where lower lymphocyte counts and higher neutrophil counts were associated with disease severity. Similarly, CRP was also significantly raised in this study which is suggestive of infection. Along with lymphopenia and leucocytosis, elevated D-dimers and procalcitonin were observed to be associated with mortality in another study [8]. Procalcitonin levels are usually raised when there are severe fungal, bacterial or systemic inflammatory responses; however, they are usually not raised in viral infections [4]. Rise in levels among the patients who expired suggest a likelihood of multiple infections. A significant increase in LDH levels were also observed in a few studies and were suggestive of organ damage. One study found a cut-off value of 245U/L to be suggestive of progression to critical illness [4]. In our study the value was much higher (315.5 U/L). This could be due to the fact that all of our patients were critically ill and our ROC curve for each of the parameters showed outcome of patient among the critically ill. Interleukin-6 was significantly raised among the patients who died as compared to the ones who survived. The best cut- oof point was IL-6 >53.5pg/ml, that was suggestive of poor patient outcome. This was comparable to another study by Ruan *et al.*, [9] where significantly higher levels of IL-6 were reported among the patients who died. Lu *et al.*, [10] developed an ACP risk grade where age and levels of CRP were used to predict patient outcome earlier in the course of the disease. Our study shows many other markers that may be used to assess patient outcome.

Covid-19 progresses rapidly for some critically ill patients. Hence close monitoring and timely treatment is necessary to improve patient outcome. The survival rate of critically ill COVID-19 patients was found to be 70.6% in this study. Similar results were observed in a study from Netherlands [11] where the survival rate was slightly higher at 76% and in the UK [12] where survival rates in ICU patients was 80.4%. The improvements in survival rates are most likely due to advancements in clinical management of cases and reduction in strain on critical care units across the study period [12].

In our study we did not excluded cases that had a negative RT-PCR test result provided they had symptoms and an HRCT thorax study suggestive of COVID-19. According to He *et al.*, [13], it is wiser to conduct both a chest CT as well as an RT-PCR in patients highly suspicious for COVID-19 since there are chances of false-negative results on RT- PCR. One observation noted in our study was that patients with a false negative result on RT-PCR had a significantly lower chance of survival than patients who were RT-PCR positive. This could be due to the lack of timely transfer to the ICU or lack of sufficient rescue equipment for these patients when complications such as respiratory failure, shock or multiple organ dysfunctions ensued, especially since this cohort was kept out of focus. False negative results made up around 27% of our study population. This was similar to another study by Fang *et al.*, [14] where around 29% of COVID-19 patients had a false negative test on their first RT-PCR. Another study by Li *et al.*, [15] reported that around 20% of false-negative incidences of COVID-19 were constantly found in their hospitals. While the diagnosis of COVID- 19 cases is not limited to RT-PCR positive results, disease progression among critically ill patients is alsonot limited to inflammatory markers alone. In fact, it is the amalgamation of the various tests and the clinical features, along with proper

decision-making skills of the attending physician that improve survival of such patients.

CONCLUSION

Early detection and proper management of critically ill COVID-19 patients is essential to ensure a better outcome. Laboratory markers play an important role in predicting immediate outcome of critically ill COVID-19 patients and can be used to identify cases with a poor prognosis. This, in turn, could alert the attending physicians so that such cases can be prioritized and managed accordingly.

LIMITATIONS

The study has quite a few limitations. Since data was collected from three different ICUs, there could have been variations in management of patients. Still, since all ICUs implemented the national treatment protocol, chances of variations in treatment are low except for decisions made by the attending physicians. This may have had some impact on patient outcome. The sample size is limited to 85 and a better result can be obtained with a larger sample size. Laboratory tests were not conducted in a single laboratory setting and hence there may be slight variations in results obtained.

REFERENCES

1. Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., ... & Feng, Z. (2020). Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. *New England journal of medicine*.
2. World Health Organization. WHO coronavirus (COVID-19) dashboard.2021. [Accessed on 26/9/2021]. [Available at https://covid19.who.int/]
3. Li, L., Li, R., Wu, Z., Yang, X., Zhao, M., Liu, J., & Chen, D. (2020). Therapeutic strategies for critically ill patients with COVID-19. *Annals of intensive care*, *10*(1), 1-9.
4. Wang, D., Li, R., Wang, J., Jiang, Q., Gao, C., Yang, J., ... & Hu, Q. (2020). Correlation analysis between disease severity and clinical and biochemical characteristics of 143 cases of COVID-19 in Wuhan, China: a descriptive study. *BMC infectious diseases*, *20*(1), 1-9.
5. Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., ... & Peng, Z. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *Jama*, *323*(11), 1061-1069.
6. Liu, J., Li, S., Liu, J., Liang, B., Wang, X., Wang, H., ... & Zheng, X. (2020). Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine*, *55*, 102763.
7. Wan, S., Yi, Q., Fan, S., Lv, J., Zhang, X., Guo, L., ... & Chen, Y. (2020). Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). *MedRxiv*.
8. Shao, L., Li, X., Zhou, Y., Yu, Y., Liu, Y., Liu, M., ... & Zhou, F. (2020). Novel insights into illness progression and risk profiles for mortality in non-survivors of COVID-19. *Frontiers in medicine*, *7*, 246.
9. Ruan, Q., Yang, K., Wang, W., Jiang, L., & Song, J. (2020). Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive care medicine*, *46*(5), 846-848.
10. Lu, J., Hu, S., Fan, R., Liu, Z., Yin, X., Wang, Q., ... & Hou, J. (2020). ACP risk grade: a simple mortality index for patients with confirmed or suspected severe acute respiratory syndrome coronavirus 2 disease (COVID-19) during the early stage of outbreak in Wuhan, China. *MedRxiv*.
11. Aleva, F. E., Van Mourik, L., Broeders, M. E. A. C., Paling, A. J., & de Jager, C. P. C. (2020). COVID-19 in critically ill patients in North Brabant, the Netherlands: patient characteristics and outcomes. *Journal of critical care*, *60*, 111-115.
12. Bateson, M. L., & McPeake, J. M. (2022). Critical care survival rates in COVID-19 patients improved as the first wave of the pandemic developed. *Evidence-Based Nursing*, *25*(1), 13-13.
13. He, J. L., Luo, L., Luo, Z. D., Lyu, J. X., Ng, M. Y., Shen, X. P., & Wen, Z. (2020). Diagnostic performance between CT and initial real-time RT-PCR for clinically suspected 2019 coronavirus disease (COVID-19) patients outside Wuhan, China. *Respiratory medicine*, *168*, 105980.
14. Fang, Y., Zhang, H., Xie, J., Lin, M., Ying, L., Pang, P., & Ji, W. (2020). Sensitivity of chest CT for COVID-19: comparison to RT-PCR. *Radiology*, 296(2), E115-117.
15. Li, D., Wang, D., Dong, J., Wang, N., Huang, H., Xu, H., & Xia, C. (2020). False-negative results of real-time reverse-transcriptase polymerase chain reaction for severe acute respiratory syndrome coronavirus 2: role of deep-learning-based CT diagnosis and insights from two cases. *Korean journal of radiology*, *21*(4), 505-508.