Assessment of inflammatory markers as predictor of outcome in COVID-19 patients on noninvasive ventilator in ICU setup

Dr. Vikas M
Junior Resident, Department of Anaesthesiology, Kasturba Medical College, Mangaluru, Manipal Academy of Higher Education, Manipal
Email: Vikas.kmcmg@learner.manipal.edu

Dr. Sonal Bhat
Additional Professor, Department of Anaesthesiology, Kasturba Medical College, Mangaluru, Manipal Academy of Higher Education, Manipal
Corresponding author email: sonal.bhat@manipal.edu

Dr. Sunil. B V
Additional Professor, Department of Anaesthesiology, Kasturba Medical College, Mangaluru, Manipal Academy of Higher Education, Manipal
Email: Sunil.bv@manipal.edu

Dr. Girish M
Associate Professor, Department of Medicine, Kasturba Medical College, Mangaluru, Manipal Academy of Higher Education, Manipal
Email: drmgirish@gmail.com

Abstract---According to the existing evidence, inflammatory reactions appear to have a significant impact on the emergence of COVID-19. This study aims to determine the severity of COVID-19-associated laboratory measures, particularly in patients receiving non-invasive ventilation. METHOD: This observational study involved 150 patients who were on non-invasive ventilation and tested positive for the Covid19 RTPCR/GENEXPERT gene. C reactive protein, D dimer, and ferritin examinations were frequently collected and Data were entered. Microsoft Excel, and SPSS software version 17.0 was used for the statistical analysis. The components of descriptive statistics are mean, standard deviation, frequency, and percentage. Student T-test was used to evaluate CRP, D Dimer, and ferritin between covid positive patients' outcome variables P<0.05 significant analysis will be done using SPSS software version 25. Result: CRP levels were above 10; 131 patients with bad outcomes (59) and 73 patients (55.7) survived. Thirty-five patients (39%) and 55 patients (61%) with D-dimer values

of 1 survived. 64 Patients (50.8%) with ferritin levels of more than 300 survived, while 62 Patients (48%) died. Conclusion: In our study population, elevated ferritin and D-dimer levels were found to be related to bad outcomes, whereas elevated CRP levels did not.

Keywords---COVID-19, laboratory parameters, C reactive, D dimer, ferritin.

Introduction

Coronavirus Disease 2019 (COVID-19), which emerged an outbreak in Wuhan, China and in short span of time and became pandemic worldwide. The COVID-19 infection were caused by Severe Acute Respiratory Syndrome Corona Virus 2. The COVID-19 pandemic has posed a huge threat to global public health and was declared a global public health emergency by World Health Organization.[1] It has high transmission rate and pathogenicity which made it to be a global concern.[2] Coronavirus caused multiple major public health events that had resulted in global epidemics, such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and corona virus disease 2019 (COVID-19). Coronavirus made a significant impact on people's health and lives.[3] The majority of patients infected with COVID-19 were found to be asymptomatic or reported mild influenza, however, some developed severe pneumonia, acute respiratory distress syndrome, multiorgan failure and even progressed to death.[4] The difference in severity among different individuals could be because of associated comorbidity, older age, increased exposure and compromised immune system. Laboratory markers have be en proposed for risk stratification.[5-8]

Accumulating evidence have suggested that inflammatory responses play a critical role in the progression of COVID-19. There are enough evidences that critically ill patients shows sign of hyperinflammation. Inflammatory responses are triggered by the rapid viral replication of SARS-CoV. There are some inflammatory markers having several trace and detecting accuracy for disease severity and fatality. Inflammatory markers such as procalcitonin (PCT), serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D Dimer and interleukin 6. Several inflammatory markers have been reported to be significantly associated with the high risks of the development of severe COVID19.[9]

The increase in inflammation markers will inibit the coagulation process which is the critical point underlying the systemic vasculitic processes and altogether will result into parenchymal lesions in the vital organs of the body. The CRP maker will be high in initial phase of the infection, is associated with severe disease development and predicts severity of COVID-19 at an early stage. The increase in cytokines inflammatory markers such as Interleukin-6, also known as Cytokin Storm, depicts acute lung injury, acute respiratory distress syndrome and can further lead to internal organs damage.[9]

The inflammatory markers were not only significantly associated with disease severity but also predict mortality. In many studies, it is concluded that non-

survivors had higher levels of inflammatory markers such as serum ferritin, C-reactive protein and interleukin-6 as compared to patients who survived to COVID. Laboratory biomarkers play a very vital role in a pandemic to detect the severity of COVID-19 infection and subsequently helps to plan an effective allocation of resources, especially in the context of respiratory support readiness. It will also facilitate risk stratification and guide clinical management. Therefore there is a dire need to find out the association of levels of inflammatory markers with the severity of the disease.

Hence, we performed an Observational study based on the current scientific literature to compare the levels of inflammatory markers among patients on Non Invasive Ventilation with COVID-19. This study will highlight the association of inflammatory markers such as CRP, D Dimer, Ferritin associated with the severity of COVID-19 and assist clinicians to monitor and evaluate the severity and prognosis of COVID-19 among patients on Non Invasive ventilation.

Materials and Methods

This was designed to be an observational study which was conducted at Kasturba Medical College Hospitals, Mangalore. The duration of the study was from August 2020 to July2022 with sampling conducted throughout the duration. For the sampling method, patients who fulfilled the inclusion criteria and did not fulfil the exclusion criteria for the observational study were included. The study was carried out in covid19 patients on non invasive ventilation admitted at KMC Hospitals. Dependent variable such as Age, Gender, Duration of hospitalization, Severity, Comorbidity, Smoking and BMI were noted Laboratory investigations such as CRP, D Dimer and ferritin were collected on the day of admission followed up regularly on every three days of admission and observed. The patients were chosen as per the inclusion criteria.

Sample size:
Calculated using the formula
$N= Z^2 pq/d^2$
Z=1.96 at 5% level of significnce
P=Prevalance = 74%[7]
q =1-p
d= 7% = Effect size
With 80% power and 95% confidence level,
The minimum number required for the study is 150.

Data Analysis

- Descriptive statistics is mean and standard deviation and frequency and percentage.
- To compare CRP, D Dimer and Ferritin between covid positive patients outcome variable Student T test performed.
- P<0.05 –significant Analysis will be done using SPSS software version 25.

Results

A hundred and fifty individuals on Non invasive ventilation who tested positive for covid 19 infection in ICU setup were included in this study. Data were entered into Microsoft Excel and statistical analysis was carried out in SPSS software version 17.0. Continuous parameters like Age, BMI, CRP, ferritin, D-dimer were categorised and presented as frequency and percentages. Qualitative variables like gender, smoking, and presence of co-morbidities and outcomes of covid in terms of survival or death were expressed as percentages. Bar diagram and pie charts were used for graphical representation of data. Differences in qualitative parameters like gender, CRP and ferritin categories with the outcome were assessed using chi square test. A p value of less than 0.05 was considered as statistically significant.

Age distribution

Out of all the included COVID patients in our study, more than half of them, 88 (58.7%) were belonged to less than 60 years of age and the remaining 62 (41.3%) were 60 years and above.

Age groups (years)	Number	Percentage
<60	88	58.7
≥60	62	41.3
Total	150	100.0

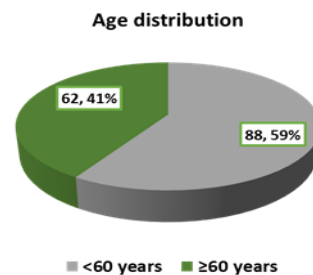
Tabe1: illustrates Age distribution among covid-19 patients.

Gender distribution

Out of 150 patients, 93 (62%) were men and 57 (38%) were women.

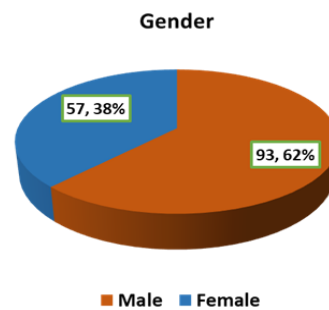| Gender	Number	Percentage
Male	93	62.0
Female	57	38.0
Total	150	100.0

Table 2: illustrates Gender distribution among covid-19 patients.

Severity outcome distribution

Out of the 150 patients admitted in non-invasive ventilator setup, 85 (56.7%) were recovered and the remaining 65 patients (43.3%) required invasive ventilation and expired.

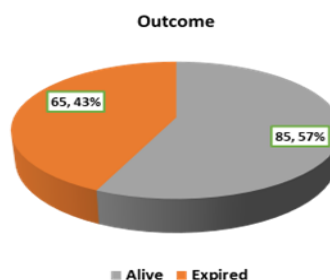| Severe Outcome	Number	Percentage
Patients Requiring Invasive Ventilation	85	56.7
Patients rceovered	65	43.3
Total	150	100.0

Table 4: illustrates the Outcome distribution among covid 19 patients.

Association between the outcome and CRP

In our study, there were 131 patients had a CRP level of >=10 and among them 73 (55.7%) were alive and 58 (44.3%) had expired. 19 patients had a CRP level of <10. Out of 19, 12 (63.2%) were alive and 7 (36.8%) had expired. The proportion that died was comparatively higher in CRP>=10 but this association was not statistically significant with the p value of 0.54.

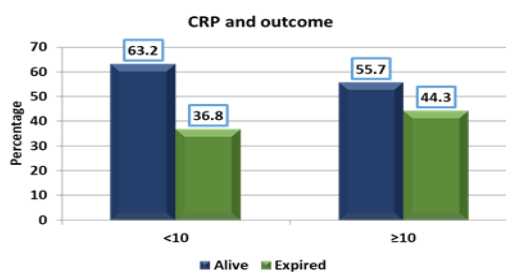| CRP	Alive		Expired		Total	P value
	n	%	n	%		
<10	12	63.2	7	36.8	19	0.54
≥10	73	55.7	58	44.3	131	
Total	85	56.7	65	43.3	150	

Table 5: illustrates CRP level association with Outcome

Association between the outcome and D dimer

We had categorised the d dimer values into less than 1 and more than 1. Around 83% of patients were alive and the remaining 17% had expired when their D-dimer values were <1. But nearly 61% of the patients had expired and 39% were surviving in D-dimer of ≥1 group. The proportion who had expired was high in ≥1 group than <1 (61% Vs17%) and this association was significant with the p value of <0.001.

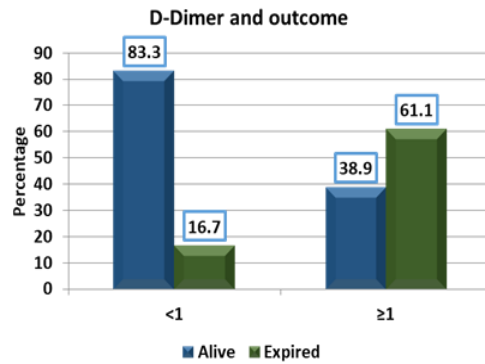| D Dimer	Alive		Expired		Total	P value
	n	%	n	%		
<1	50	83.3	10	16.7	60	<0.001*
≥1	35	38.9	55	61.1	90	
Total	85	56.7	65	43.3	150	

Table 6 illustrates D Dimer level association with Outcome.

Association between the outcome and ferritin

In patients who had a ferritin level of less than 300, 87.5% were alive and 3 (12.5%) had expired. If their ferritin level was 300 or more, nearly half were expired and half were alive. The proportion who had expired was more in ferritin level of ≥300 compared to <300 (49.2% Vs12.5%). There was significant association was observed between the ferritin level and patients survival.

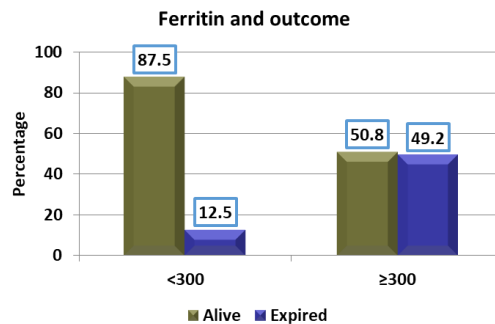| Ferritin	Alive		Expired		Total	P value
	n	%	n	%		
<300	21	87.5	3	12.5	24	0.001*
≥300	64	50.8	62	49.2	126	
Total	85	56.7	65	43.3	150	

Table 6 illustrates D Dimer level association with Outcome.

A hundred and fifty individuals on Non invasive ventilation who tested positive for covid 19 infection in ICU setup were included in this study. It was noted that: 131 Patients had a CRP level >10, 59 Patients had poor outcome and 73(55.7) survived. 55 Patients(61%) expired and 35 Patients(39%) survived with D-dimer

value of ≥1 . 62 Patients(48%) expired and 64 Patients(50.8%) survived with ferritin level >300. CRP was not statistically significant. Elevated D DIMER AND FERRITIN levels were associated with poor outcome of the patient requiring invasive ventilation proving to be statistically significant.

Discussion

In this study, the predictors of outcomes of non-invasive ventilation in 150 COVID-19 patients were evaluated. We also assessed the correlation of various laboratory parameters with outcomes of COVID-19 patients. We found that elevated D-dimer and ferritin levels, but not elevated CRP levels, were associated with poor outcomes in COVID-19 patients requiring invasive ventilation. It is necessary to predict the severity of COVID-19, especially in patients on non-invasive ventilation, in order to ensure resource allocation for respiratory support readiness. Various studies have reported numerous risk factors for mortality in COVID-19 patients, such as included elderly individuals, males, patients having concomitant diseases like diabetes, obesity, hypertension, heart diseases, etc. Among symptoms of fever, cough , hemoptysis, fatigue, dyspnea, transient loss of consciousness, respiratory distress, and syncope, various laboratory parameters have been attributed to poor prognosis in COVID-19. These include an elevated neutrophils to lymphocytes ratio and increased levels of various biomarkers like C-reactive protein, d dimer, ferritin, lactate dehydrogenase, and liver enzymes (alanine transaminase and aspartate transaminase).The elevated levels of inflammatory markers (CRP, ferritin, and D dimer) suggest hyperinflammatory status, and hence, poor prognosis.[10,11]

As an acute phase inflammatory peptide produced in the liver, the level of CRP gets elevated in several conditions, such as infection, inflammation, and cardiovascular disease. In a recent meta-analysis of 13 studies, it was found that patients having an elevated CRP level had severe COVID-19 requiring ICU admission; however, the same was not associated with a higher risk of death.[2] There is no consensus on the cut-off level of elevated CRP to determine an association with severe COVID-19. We found no association between raised CRP levels and risk of poor prognosis in patients with COVID-19. There are inconsistent findings in the literature regarding this. It was found that a raised CRP level was associated with 28-day mortality in COVID-19 patients.[12] Contrasting findings were also reported.[13] Inconsistencies in the results might be attributed to the non-uniform cut-off level of CRP used in these studies.[14] Another important issue is the time of measurement of CRP level after symptom onset. Serum CRP level rises initially after inflammation and the rise slows down after 72 hours. Other reason for CRP level falls is that dexamethasone administration could possibly reduce the levels. There are various other confounding factors resulting in an elevated CRP level, such as hyperlipidemia, hypertension, deranged liver function, smoking, obesity, etc.[3] However, CRP level can be an important biomarker in assessing prognosis in COVID-19 patients who are on non-invasive ventilation.[5] In these patients, a prophylactic anticoagulant needs to be immediately administered. Also, since CRP invariably rises in the presence of any inflammation, an elevated CRP level may not be a good predictor of poor outcome in these patients.[15]

We discovered in this study that a high D-dimer level was linked to a bad prognosis. A common biomarker for thrombotic diseases is D-dimer, a fibrin breakdown product. The development of COVID-19 disease has been shown to be accompanied by abnormal coagulation function, such as increased D-dimer. [16] Sepsis and coagulation dysfunction were frequent in cases of severe COVID-19 infection, which can develop into COVID-19. However, the rise in D-dimer levels may be an indirect sign of an inflammatory response because inflammatory cytokines may cause imbalances between coagulation and fibrinolysis in the alveoli, which could subsequently activate the fibrinolysis system and raise D-dimer levels. [17] According to a thorough investigation released in August 2020, COVID-19 individuals with high D-dimer readings were more likely to.[17] A thorough analysis released in August 2020 discovered that COVID-19 patients with high D-dimer values had a greater risk of fatal illness and severe sickness, and it also indicated that no reliable cutoff value had been established to predict adverse effects.[18]

In this study, we also found that an elevated ferritin levels were associated with a poor prognosis. The mechanism could be possibly explained by the presence of secondary hemophagocytic lymphohistiocytosis in these patients. Secondary hemophagocytic lymphohistiocytosis is a hyperinflammatory condition that leads to cytokine storm resulting in multi-organ failure and death.[19] Various viral infections commonly trigger this condition resulting in clinical worsening like the development of acute respiratory distress syndrome. Various authors have recommended the use of steroids to treat this potentially dangerous condition. However, a recent meta-analysis could not find adequate evidence on the routine use of steroids in patients with elevated ferritin levels.[20] On the contrary, some studies have reported beneficial results in the early administration of steroids in patients on non-invasive ventilation having elevated serum ferritin levels.[20]

The other prognostic factors that were studied in COVID-19 patients to predict poor outcomes include demographic characteristics, medical history, findings of physical examination (blood pressure, respiratory type and rate, body temperature, oxygen saturation in the peripheral blood at room air, heart rate, presence of respiratory distress, presence of fatigue/arthralgia/myalgia, abdominal pain, loss of appetite, hemoptysis, or hematemesis), laboratory markers (white blood cell count, platelet count, lymphocyte count, erythrocyte sedimentation rate, cardiac markers of myocardial infarction, serum lactate level, blood B-type natriuretic peptide level, blood urea nitrogen level, creatine kinase level, and serum bilirubin level), radiological markers (pleural effusion and consolidative infiltrates in the lungs), and a high sequential organ failure assessment (SOFA) score at baseline.[21] Non-invasive ventilation were widely used to treat COVID-19 patients with moderate to severe acute respiratory failure. It has been found that non-invasive ventilation can avoid intubation in almost half of the patients, reduce complications thereof, and reduce the duration of hospitalization. Based on our findings, D-dimer and ferritin levels must be estimated to predict poor outcomes in COVID-19 patients requiring invasive ventilation.[22] However, it has to be borne in mind that apart from laboratory biomarkers, monitoring of clinical parameters is essential in determining the severity, and hence, prediction of poor prognosis, in patients with COVID-19.

Conclusion

In this study, 150 patients receiving non-invasive ventilation had their levels of inflammatory markers as COVID-19 predictors evaluated. It was also investigated how the results of the patients correlated with different laboratory markers. Finally, we came to the conclusion that elevated CRP levels did not exhibit any association with bad outcomes as steroid were started soon after admission, whereas elevated D-dimer and ferritin levels were found to be related with poor outcomes in our study sample. Other criteria, such as demographics, medical history, physical exam results, and clinical characteristics, might be used to evaluate the results in addition to test indicators. Extremely high mortality is linked to severe COVID-19 pneumonia, particularly in environments with limited resources. A suitable model is required to evaluate the prognostic parameters and provide an accurate prognosis of the COVID-19 patients in an initial phase to avoid any severity later.

References

1. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet (London, England). 2020 Feb 15;395(10223):507–13.
2. Gopalan N, Senthil S, Prabakar NL, et al. Predictors of mortality among hospitalized COVID-19 patients and risk score formulation for prioritizing tertiary care-An experience from South India. PLoS One. 2022;17:e0263471.
3. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - A systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr. 2020 Jul 1;14(4):395–403.
4. Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis. 2020;14:1753466620937175.
5. Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): Systematic review and meta-analysis. J Intensive Care. 2020 May 24;8(1).
6. Izcovich A, Ragusa MA, Tortosa F, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PLoS One. 2020;15:e0241955.
7. Koozi H, Lengquist M, Frigyesi A. C-reactive protein as a prognostic factor in intensive care admissions for sepsis: a Swedish multicenter study. J Crit Care. 2020;56:73–79.
8. Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol. 2020;104370.
9. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 28;395(10229):1033–4.
10. Menzella F, Barbieri C, Fontana M, et al. Effectiveness of noninvasive ventilation in COVID-19 related-acute respiratory distress syndrome. Clin Respir J. 2021;15:779-787.

11. Poudel A, Poudel Y, Adhikari A, et al. D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. PLoS ONE. 2021;16:e0256744.

12. Pranata R, Huang I, Lim MA, Wahjoepramono EJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19-systematic review, meta-analysis, and meta-regression. J Stroke Cerebrovasc Dis. 2020 Aug 1;29(8):104949.

13. Pranata R, Huang I, Lukito AA, Raharjo SB. Elevated N-terminal pro-brain natriuretic peptide is associated with increased mortality in patients with COVID-19: systematic review and meta-analysis. Postgrad Med J. 2020 Jul 1;96(1137):387–91.

14. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, et al. Adult haemophagocytic syndrome. Lancet. 2014;383:1503–1516.

15. Shah S, Shah K, Patel SB, Patel FS, Osman M, Velagapudi P, et al. Elevated D-dimer levels are associated with increased risk of mortality in coronavirus disease 2019: a systematic review and meta-analysis. Cardiol Rev. 2020;28:295-302..

16. Sharifpour M, Rangaraju S, Liu M, et al; Emory COVID-19 Quality & Clinical Research Collaborative. C-Reactive protein as a prognostic indicator in hospitalized patients with COVID-19. PLoS One. 2020 Nov 20;15(11):e0242400.

17. Sharma A, Ahmad Farouk I, Lal SK. COVID-19: A Review on the Novel Coronavirus Disease Evolution, Transmission, Detection, Control and Prevention. Viruses. 2021 Feb 1;13(2).

18. Shivalkar S, Pingali MS, Verma A, Singh A, Singh V, Paital B, et al. Outbreak of COVID-19: A Detailed Overview and Its Consequences. Adv Exp Med Biol. 2021;1353:23–45.

19. Song J, Park DW, Moon S, et al. Diagnostic and prognostic value of interleukin-6, pentraxin 3, and procalcitonin levels among sepsis and septic shock patients: a prospective controlled study according to the Sepsis-3 definitions. BMC Infect Dis. 2019;19:968.

20. Tang N., Li D., Wang X. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J. Thromb. Haemost. 2020;18:844–847.

21. Veronese N, Demurtas J, Yang L, et al. Use of corticosteroids in coronavirus disease 2019 pneumonia : a systematic review of the literature. Front Med. 2020;7:1–6.

22. World Health Organization. Coronavirus Disease (COVID-19) Situation Reports [Internet]. World Health Organization. 2022 [cited 2022 Aug 26]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports