Research article

Clinical and biomarker profile of COVID-19 patients admitted in a tertiary care hospitalArchana Bhat¹, Don Gregory Mascarenhas², Manjunath J.³, Anand Kumar R.⁴, Sucharitha Suresh⁵ Glenn Fernandes⁶¹Assistant Professor of Pathology, ²Associate Professor of Pulmonology, ³Professor and Head of Nephrology, ⁴MD Resident of Internal Medicine, ⁵Professor of Community Medicine and Statistics, ⁶Assistant Professor of Internal Medicine, Father Muller Medical College, Mangalore, Karnataka, India

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ABSTRACT

Introduction and Aim: A novel beta-coronavirus emerged in Wuhan, China during the early December 2019 and spread globally. The clinical signs and symptoms and the disease severity in people infected with COVID-19 can be varied. The present study was conducted to study the biomarker profile and their association with disease severity in COVID-19.

Materials and Methods: This was a single-centre Cohort study of data regarding epidemiological, clinical and biomarker parameters, and outcome of COVID-19 patients admitted in a tertiary care hospital in South India. CDC guidelines were followed for assessing disease severity.

Results: A total of 336 COVID-19 patients were admitted during the study period. Of these 16 were excluded and 320 cases were analysed. Mean age of patients was 44.82 years. A male predominance was observed. Diabetes mellitus was the most common co-morbidity. Asymptomatic, Mild, moderate, severe and critical disease was seen in 15%, 52.5%, 20.3%, 6.3% and 5.9% patients respectively. ICU care was required in 15.3%. Overall mortality was 5.3%. The mean NLR, ALC, CRP, LCR, LDH, Ferritin and D-dimer in the severe group vs non-severe group were 19.03 vs 4.2, 1025cells/cu mm vs 1740cells/cu mm, 185.8mg/L vs 31.7mg/L, 17.1 vs 996.3, 552.8IU/L vs 252.7IU/L, 2531.9ng/ml vs 414.1ng/ml and 2245.5ng/ml vs 339.4ng/ml respectively.

Conclusion: An increased NLR, CRP, LDH, Ferritin and D-dimer and a reduced ALC and LCR are significantly associated with disease severity, need for ICU and mortality. These biomarkers will be useful adjunct to clinical assessment in better categorising and management of COVID-19 patients.

Keywords: Biomarkers; COVID-19; CRP; D-dimer; NLR; ferritin; SARS.

INTRODUCTION

The world witnessed a surge of pneumonia cases of unknown etiology, emerging from Wuhan in Hubei province of China during the early December 2019 (1). The Chinese Centre for Disease Control and Prevention conducted high-throughput sequencing on the throat swab sample of patients with this disease and reported the etiology of pneumonia as a novel beta-coronavirus(2) which causes a disease resembling severe acute respiratory syndrome coronavirus(SARS-CoV; 3). Subsequently this pandemic disease was named as 2019-novel coronavirus disease (COVID-19) and the culprit virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organisation(WHO). The first case in India was reported on January 30, 2020 from Thrissur in Kerala. Of all the confirmed COVID-19 cases in India, 1009976 are active, 4025079 are discharged and 83198 deaths reported as on 17th September 2020 (5).

People infected with this pandemic causing virus may present with a myriad of clinical features in isolation or combination, ranging from mild symptoms like fever, anosmia, cough, myalgia, sputum production, headache, haemoptysis, diarrhoea to severe symptoms like dyspnoea, acute respiratory distress

syndrome(ARDS), acute cardiac injury or secondary infection(5,6). Due to such varied clinical presentation among patients infected with novel beta- coronavirus, subjectivity in assessing clinical condition and rapid deterioration in the disease course, the role of biomarkers becomes more important. Some of the biomarkers, which provide objective values through the disease progression, can help in interpretation of symptoms and better categorising of patients allowing earlier interventions (7, 8). Simple and cost-effective biomarkers, if found useful can be of great help especially in developing countries with limited resources catering to a large population. On the other hand, biomarkers are ordered routinely by some clinicians in COVID-19 patients. As such, it becomes important to understand the association between these biomarkers and disease. The dynamic fluctuation in the levels of the biomarkers and disease severity needs close follow-up through the entire course of the disease i.e., till recovery or death.

Hence, we conducted a complete follow-up study to explore the role of different biomarkers like the Neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), Ferritin, D-dimer, Lactate dehydrogenase (LDH), and Lymphocyte to CRP ratio

(LCR) in COVID-19 patients and their association with disease severity.

MATERIALS AND METHODS

This was a cohort study conducted in Father Muller Medical College Hospital, which is a tertiary care hospital located in Mangalore city of Dakshina Kannada district of Karnataka state in southern part of India. The institution ethical clearance was obtained. We included all consecutive COVID-19 patients admitted from June 1st 2020 to July 31st 2020. The paediatric patients and patients with lost follow-up were excluded. COVID-19 was confirmed microbiologically by reverse transcriptase polymerase chain reaction (RT-PCR) or by Cartridge Based Nucleic Acid Amplification Test (CB-NAAT).

Clinical data, laboratory parameters and outcome from consecutive patients with microbiologically confirmed COVID-19 were collected from the records. The hospital had no control over patient selection and patients of all severity were admitted. Patients were received and evaluated in screening areas like fever clinic and casualty. History related to travel, exposure and presence of co-morbidities was taken and documented. The patients were triaged and admitted in hospital as per the clinical assessment into isolation ward or the intensive care units (ICU). During the course of stay in ward, need for clinician depending on the patients disease severity, age and accompanying co-morbidities decided ICU.

All the patients were treated symptomatically according to the standard guidelines at that point of time. Treatment for pre-existing diseases was continued. Baseline laboratory investigations were done. From all the patients suspected of COVID-19, throat swab and nasopharyngeal samples were taken and sent to the molecular testing laboratory of our Hospital, in viral transport medium with proper packaging and all precautions. The samples were processed in a biological safety cabinet (BSC-type IIb). RNA extraction was done by reverse transcriptase-polymerase chain reaction (RT-PCR) and Qualitative RT-PCR targeting the envelope (E), open reading frame 1b (ORF-1b) and RNA-dependent RNA polymerase (RdRp2) genes of SARS-CoV-2 was performed.

The laboratory biomarkers namely the complete blood counts, CRP, LDH, D-dimer and Ferritin were done in

all patients at admission and before discharge and in between depending on the clinical condition of the patient. The worst value of these biomarkers was taken in our study. The patients clinical condition and severity was categorised using the Centre for Disease Control and Prevention (CDC) guidelines update as on June 30, 2020 (9) as Mild to moderate (Mild symptoms up to mild pneumonia) or Severe disease (dyspnoea, hypoxia or >50% lung involvement on imaging) or Critical illness (respiratory failure, shock or multiorgan failure). All the patients were followed-up till the end-point i.e., discharge or death. Severity was assessed during the entire course of hospital stay and the worst was recorded. Analysis was done between Severe vs Non-severe groups, ICU vs Non-ICU groups and Recovered/discharged vs Dead groups. Patients with mild or moderate disease were categorised into the Non-severe group, and patients with severe or critical disease were included in the severe group. Patients requiring ICU care at any point of their stay in the hospital were included in the ICU group. The outcomes were recorded as recovered or dead.

Statistical analysis

Continuous data were presented as mean and standard deviation (SD) for normally distributed data. For non-normally distributed data, median and interquartile range (IQR) were used. Categorical variables were presented by frequency and percentages (n%). Comparability between groups was analysed by Mann Whitney U test. The IBM SPSS version 23 software was used for statistical analyses. Receiver operating characteristic (ROC) curve was plotted for NLR, CRP, LDH and Ferritin. Area under the curve (AUC) and cut-off values were calculated.

RESULTS

A total of 336 with COVID-19 were hospitalised during the study period. Of these, 16 patients were not analysed (3 were paediatric cases, 4 were still admitted and 9 patients were either referred or discharged against medical advice).

Of the 320 cases, 197 patients (61.6%) were males. Mean age of patients was 44.82 years and 30% were below 30 years of age. The elderly (>60 years) contributed to 18.4% of the admissions (Table 1).

Table 1: Clinical and Demographic profile of patients admitted with COVID-19

		Number (percentage)
Age	30 and below	97 (30.3)
	31 - 40	41 (12.8)
	41 - 50	53 (16.6)
	51 - 60	70 (21.9)
	Above 60	59 (18.4)
Gender	Male	197 (61.6)
	Female	123 (38.4)
ICU And Non-ICU	Non ICU	271 (84.7)

	ICU	49 (15.3)
Severity	Asymp	48 (15.0)
	Mild	168 (52.5)
	Moderate	65 (20.3)
	Severe	20 (6.3)
	Critical	19 (5.9)
Outcome	Recovered	303 (94.7)
	Dead	17 (5.3)

Approximately one-third (31.8%) of the patients admitted had Diabetes mellitus as one of the co-morbidities. Mean age was 57 years. Severe and critical disease was observed in 22 of them. Mortality rate in this sub-group was 12.7%, which is more than two times the overall mortality rate.

The other co-morbidities, which were observed in patients, were Hypertension, Kidney disease, Heart disease, Hypothyroidism, Lung disease and Malignancies.

Using CDC criteria, 168 patients (52.5%) had mild disease. Moderate, Severe and Critical disease was seen in 65(20.3%), 20(6.3%) and 19(5.9%) patients respectively. Forty-eight (15%) of cases were

asymptomatic. ICU care was required for 49(15.3%) patients. Overall mortality was 5.3%. Among patients with severe and critical disease (12.2%), mortality was observed in 43% of cases. Mortality was 12.7% in diabetics and 20.8% in patients with heart disease.

CRP, LDH, Ferritin and D-dimer were found to be significantly elevated in patients who developed severe disease as compared to those with non-severe disease. (CRP - 185.82mg/L vs 31.77mg/L, LDH - 522.8IU/L vs 252.7IU/L, Ferritin - 2531.9ng/ml vs 414ng/ml, D-dimer - 2245.4ng/ml vs 339.4ng/ml).

The elevated biomarkers were significantly associated with need for ICU care and mortality (Table 2).

Table 2: Median and Inter-quartile range [IQR] of Biomarkers in patients admitted with COVID-19.

Biomarker Median [IQR]	Severe	Non- severe	ICU	Non-ICU	Recovered	Dead
Total White cell count in cells/cumm [IQR]	14400 [12100-18200]	5900 [4700-8550]	13700 [11950-17200]	5800 [4700-8300]	6000 [4800-9425]	16100 [13150-20050]
NLR(Neutrophil to Lymphocyte ratio) [IQR]	14.50 [7.9-19]	2.42 [1.41-4.33]	12.86 [7.32-18.90]	2.33 [1.39-4.13]	2.51 [1.47-5.51]	17.20 [12.79-31.00]
ALC (Absolute lymphocyte count in cells/cumm) [IQR]	896 [660-1176]	1565 [1117-2108]	910 [652-1222]	1585 [1122-2107]	1519 [1088-2100]	732 [550-977]
CRP in mg/L [IQR]	129.57 [64.77-264.69]	6.72 [1.55-44.34]	118.73 [60.07-238.56]	6.28 [1.44-38.53]	9.58 [1.78-54.83]	171.48 [117.58-293.71]
LCR(Lymphocyte to CRP ratio) [IQR]	7.4 [2.79-13.89]	230.28 [31.8-1193.88]	7.93 [2.98-15.09]	273.72 [39.58-1268.99]	170.62 [22.66- 1045.16]	2.97 [2.19-8.37]
LDH in IU/L [IQR]	508 [337.5-685]	222 [185.5-295.5]	421 [325-656]	219 [184-292]	228.50 [188-313.75]	637.50 [359.50-977.75]
Ferritin in ng/ml [IQR]	901.95 [493.38-2116.25]	213.9 [74.88-486.10]	760.10 [380.45-1598.50]	207.40 [73.39-473.35]	234.50 [80.56-523.40]	1338 [599.18-4320.50]
D-dimer in ng/ml [IQR]	916.5 [307-3647]	156 [100-326]	901 [307-2817]	146.5 [100-305]	163 [100-396]	1426 [673-3353]

ManWhitney test P value <0.001 was highly significant for all the biomarkers for Severe vs Non-severe, ICU vs non-ICU and Recovered vs Dead.

An increased total WBC count and NLR was significantly associated with severe disease, need for ICU, and mortality. Decreased ALC and LCR were significantly associated with severe disease, ICU requirement and mortality. An inverse correlation was noted between ALC, LCR and other biomarkers.

Elevated levels of CRP, LDH, Ferritin, D-dimer were significantly associated with increased severity, need for ICU care and mortality. AUC for four biomarkers namely NLR, CRP, LDH and Ferritin were found to be significantly different between severe vs non-severe, ICU vs non-ICU and recovered vs dead groups. (Fig. 1, 2, 3).

Fig. 1: ROC – Recovered vs Dead

AUC and Cut-off values for Biomarkers: Recovered vs Dead			
Biomarkers	Area under curve	Std. Error	Cut-off value
NLR	.941	.017	7.78
CRP	.944	.016	104.9
LDH	.918	.030	297
Ferritin	.873	.050	670

Fig. 2: ROC Severe vs Non-severe groups

AUC and Cut-off values for Biomarkers: Severe vs Non-severe groups			
Biomarkers	Area under curve	Std. Error	Cut-off value
NLR	.902	.027	5
CRP	.918	.019	57.5
LDH	.910	.022	322.5
Ferritin	.823	.041	391.5

Fig. 3: ROC – ICU vs Non-ICU groups

AUC and Cut-off values for Biomarkers: ICU vs Non-ICU groups			
Biomarkers	Area under curve	Std. Error	Cut-off value
NLR	.886	.027	4.2
CRP	.907	.019	44.7
LDH	.875	.026	291.5
Ferritin	.798	.037	294.5

DISCUSSION

We reported the epidemiological profile, disease severity, biomarkers and outcome of a cohort of 320 consecutive patients admitted in a tertiary care hospital in southern part of India. The mean age of our patients was 44.82 years, which is comparable to an Indian study (10) and lower as compared to studies from other countries (4, 11-14). Our study had a male predominance (61.6%) which was comparable to studies from other countries (Table 3).

Table 3: Mean age of COVID-19 patients from various studies

Study	Mean age (year)	Males, n (%)	Outcomes
Huang <i>et al.</i> , 4 (n=41)	49	30 (73)	ICU - 32%; Death – 15%
Mohan A <i>et al.</i> , 10 (n=144)	40.1	134 (93.1)	ICU – 2.8%; Death – 1.4%
Guan <i>et al.</i> , 11 (n=1099)	47	637(58.1)	67 patients reached composite end point of which 15 died
Wang D <i>et al.</i> , 12 (n=138)	56	75(54.3)	ICU – 36(26.1%) 6 died, 11 were in ICU
Chen N <i>et al.</i> , 13 (n=99)	55.5	67(68)	ICU – 23(23%) 11(11%) died and 57(58%) were still in hospital
Richardson <i>et al.</i> , 14 (n=5700)	63 (52-75)	3437(60.3)	2634 reached study end-point. 373(14.2%) in ICU, 553(21%) died.
Present study (n=320)	44.82	197(61.6%)	ICU - 15.3% Death – 5.3%

However, a study from Northern India reported a male predominance of 93.1%. The authors attribute this to the fact that a significant number of their patients were part of a public gathering mainly attended by men, which was identified as a hotspot, and patients were identified by active screening (10).

Severe disease was seen in 12.2% of our patients, which is lower than that of other studies where severe disease was seen in 15.7 to 29 % of all patients.(4, 11-13). However, an Indian study reported a lower percentage (2.8%) of severe disease among their study patients which the authors attribute to selection bias as majority of their patients were identified by active screening(10).

The rate of ICU admission among coronavirus infected patients ranges from 3% to 100% as shown in a meta-analysis. The meta-analysis included thirty-seven studies with a total of 32,741 participants, conducted in different countries. The pooled rate of ICU admission was 32% with subgroup analysis that showed a rate of 32%, 57% and 26% for SARS-COV, MERS and SARS-COV-2 respectively. The authors say that one of the limitations of their meta-analysis is limited studies from few countries. There are no Indian studies included in the meta-analysis (15). The rate of ICU admission in our study was 15.3%. The mortality rate and ICU requirement in our study and another Indian study (10) is less than studies done in other countries (Table 3).

Studies on White blood cell count (WCC) in COVID-19 patients have shown variable results. Patients with RT-PCR positive COVID-19 disease had a significantly lower WCC as compared to RT-PCR negative suspect COVID-19 patients in a study of 200 patients.(16) In a retrospective study, an increase in WCC in severe group as compared to the non-severe group(5.6 vs 4.9 x 10⁹/L; p<0.001). A greater neutrophil-to-lymphocyte ratio (NLR) of 5.5 was observed in severe group as compared to 3.2 in non-severe group. (17) Another Chinese study concluded similar findings of high NLR in severe patients suggesting a role of NLR as a potential biomarker for severity in COVID-19.(12) In our study a significantly increased WCC and NLR were associated with increased severity, need for ICU care and mortality.

Absolute lymphocyte count (ALC) were reported to be lower in majority of COVID-19 patients in a descriptive study (13). Another study reported a lower lymphocyte count in critical patients suggesting a poor prognosis (18). In our study, a significantly lower ALC was associated with increased severity, ICU admission and death.

CRP is an acute phase reactant used as a biomarker in various inflammatory conditions. Though it is non-specific, a rise in CRP levels is associated with increased disease severity (8). In a retrospective cohort study conducted in Wuhan, China, that included

COVID-19 patients, a significantly higher CRP levels were observed among severe patients (57.9mg/L) as compared to non-severe patients (33.2mg/L) with a p<0.001 (17). Another retrospective cohort study on progression in severity of COVID-19 patients, it was found that CRP levels greater than 41.8mg/L was associated with increased likelihood of severe disease (19). In a study on computed tomography(CT) findings and CRP levels between two groups, one of COVID-19 patients and the other of influenza A or B patients, it was observed that the CRP levels was a better early predictor of severe COVID-19 disease with a sensitivity of 83% and a specificity of 91% (20). In a retrospective cohort study of 150 COVID-patients, that studied disease outcomes and biomarker levels, it was observed that CRP levels were significantly associated with mortality (21). Our study also showed similar results.

Lactate dehydrogenase (LDH) is another biomarker, which has convincing evidence between its serum levels and severity in COVID-19 in a Italian study involving 141 patients (22). In a single- centre retrospective cohort study involving 42 COVID-19 patients, a significant positive correlation was observed between LDH, CRP, Erythrocyte sedimentation rate and the severity of pneumonia as assessed on the initial CT images (23). In a retrospective study of 155 COVID-19 patients categorised into general and refractory groups, a higher level of LDH (p=0.017), CRP (p=0.001), AST and neutrophil count were reported in the refractory group. These findings are consistent with our results.

Some studies have observed elevated levels of D-dimer in COVID-19 patients requiring ICU admission and invasive ventilation (4, 11). In a follow-up study of 183 patients with an overall mortality rate of 11.5%, a significantly higher levels of D-dimer and fibrin degradation product levels were observed in the non-survivors (25). Our study also found that elevated D-dimer was associated with poor outcomes. Higher D-dimer levels predict poor prognosis and can therefore serve as an early biomarker and help the clinician in better management (26, 27).

Studies on platelet count and severity in COVID-19 have shown variable results. A lower platelet count was found to be associated with increased severity and mortality in COVID-19 patients.(28, 29) Contrary to these studies a higher platelet count was observed in the severe group of patients with COVID-19 (4, 30). Our study found no association between platelet count and disease severity.

In a retrospective study conducted in China, increased serum ferritin levels were seen in 63% of COVID-19 cases with a mean level of 808.7ng/ml (13). We also found that elevated serum ferritin levels had association with severity, ICU admission and mortality.

Limitation

This is a single-centre study and only the hospitalised patients are included.

CONCLUSION

To conclude, the biomarkers like NLR, CRP, Ferritin, D-dimer, LDH and LCR are associated with disease severity, need for ICU care and mortality. These biomarkers can be performed routinely in all COVID-19 patients and can be used as an adjunct to clinical examination in better categorising patients who need ICU care and aggressive management.

CONFLICTS OF INTEREST

Authors declare no conflict of interest.

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