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ROLE OF CRP, LACTATE DEHYDROGENASE AND NEUTROPHIL TO LYMPHOCYTES RATIO AS PREDICTORS OF DISEASE SEVERITY AND OUTCOMES IN COVID-19 PATIENTS

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is an acute respiratory infective disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. However, it is still unclear which factors are the most sensitive and reliable indicators for predicting the prognosis of COVID-19 in the early stage. In the present study, we compared predictive power of lymphocyte percentage, C-reactive protein and lactate dehydrogenase for disease classification and prognosis in COVID-19 at our tertiary hospital. **Material and Methods:** Present study was a hospital based observational and descriptive study, conducted in individuals > 18 years with RT-PCR COVID-19 positive status admitted in SRI DEVARAJ MEDICAL COLLEGE and RL JALAPPA Hospital. **Results:** Total 89 patients were considered for present study. Male (66.29%) patients were more than female (33.71 %), male to female ratio was 2:1. Most common age group was 51-60 years (25.84 %) followed by age group 61-70 years (22.47 %) & 41-50 years (19.1 %). SpO_2 on admission was > 90% in most patients (43.82), followed by 81-90% (28.09). Other patients had SpO_2 as <40% (6.74 %), 41-50% (2.25 %), 51-60% (6.74 %), 61-70% (7.87 %) & 71-80% (4.49 %). HRCT score was <6 in most patients (78.65 %). NIV was required in 29.21 % patients while 21.35 % required mechanical ventilation. Total hospital stay was 08-10 days in 28.09 % patients, 11-15 days in 20.22 % patients & 6-7 days in 16.85 % patients. 69.66 % patients were discharged successfully while death was noted in 30.34 % patients. We noted a statistically significant difference for age (in years) between discharged patients & died patients. While statistically highly significant difference ($p < 0,001$) was noted for NL Ratio, LDH (U/L), CRP (mg/L), SpO_2(%), HRCT Score on admission & total hospital stay (days). **Conclusion:** Simple parameters such as neutrophil to lymphocytes ratio, C-reactive protein and lactate dehydrogenase NLR has good predictive values on mortality in patients with COVID-19 infection.

KEYWORDS : COVID-19, neutrophil to lymphocytes ratio , CRP, LDH

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an acute respiratory infective disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.[1] The COVID-19 pandemic has been spreading worldwide rapidly since March 2020. Current experience reveals that the majority of infected individuals (approximately >80%) are not severely affected and can recover without medical intervention, whereas a small number of cases need to be carefully treated and hospitalized.[2]

Patients with moderate COVID-19 and no underlying diseases can also develop the complications described above and progress to the severe or critically ill types.[3] The mortality rate for severe cases, particularly those that are critically ill, is quite high. It is therefore critical to identify reliable predictors for disease severity to improve outcomes and conserve medical resources.

Recent studies from different cohorts of patients have identified several factors, including viral load,[4] neutrophil to lymphocytes ratio, C-reactive protein (CRP),[5] interleukin-6 (IL-6) and lactate dehydrogenase[6] as warning indicators of prognosis in COVID-19 patients. However, it is still unclear which of these factors are the most sensitive and reliable indicators for predicting the prognosis of COVID-19 in the early stage. As interleukin-6 and procalcitonin are expensive and not readily available in our setting, so we studied simple parameters such as neutrophil to lymphocytes ratio, C-reactive protein and lactate dehydrogenase as early indicators for severe disease. In the present study, we compared predictive power of lymphocyte percentage, C-reactive protein and lactate dehydrogenase for disease classification and prognosis in COVID-19 at our tertiary hospital.

MATERIAL AND METHODS

Present study was a hospital based observational and descriptive study, conducted in SRI DEVARAJ MEDICAL COLLEGE and RL JALAPPA Hospital. Study duration was 1 month. Institutional ethical committee approval was taken. Study was explained to patients/relatives & a written informed consent was taken.

Inclusion criteria:
Individuals > 18 years with RT-PCR COVID-19 positive status admitted in SRI DEVARAJ MEDICAL COLLEGE and RL JALAPPA Hospital.

Exclusion criteria: Adults with
1. Type 2/ Type 1 Diabetes Mellitus
2. Hypertension
3. Cigarate smoking
4. Immunocompromised patients

Each subject was interviewed for complaints, medical/ surgical history including socioeconomic status & underwent physical examination, systemic examinations and relevant investigations. The levels of CRP, serum lactate dehydrogenase and neutrophil to lymphocytes ratio were measured in each patient on admission and corelated with disease severity and survival.

Data was entered into Microsoft excel data sheet and analyzed using SPSS 22 version software. Categorical data represented in the form of frequencies and proportions. Chi-square was used as test of significance. Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference. P value <0.05 was considered as statistically significant & p < 0,001 was considered as highly significant.

RESULTS

Total 89 patients were considered for present study. Male (66.29%) patients were more than female (33.71 %), male to female ratio was 2:1. Most common age group was 51-60 years (25.84 %) followed by age group 61-70 years (22.47 %) & 41-50 years (19.1 %).

Table No 1- Age wise distribution

Age in years	Male	Female	Total
≤20	0	8 (8.99 %)	8 (8.99 %)
21-30	4 (4.49 %)	2 (2.25 %)	6 (6.74 %)
31-40	5 (5.62 %)	2 (2.25 %)	7 (7.87 %)
41-50	13 (14.61 %)	4 (4.49 %)	17 (19.1 %)
51-60	15 (16.85 %)	8 (8.99 %)	23 (25.84 %)
61-70	15 (16.85 %)	5 (5.62 %)	20 (22.47 %)
71-80	5 (5.62 %)	1 (1.12 %)	6 (6.74 %)
>80	2 (2.25 %)	0	2 (2.25 %)
Total	59 (66.29%)	30 (33.71 %)	89

SpO$_2$ on admission was > 90% in most patients (43.82), followed by 81-90% (28.09). Other patients had SpO$_2$ as <40% (6.74 %), 41-50% (2.25 %), 51-60% (6.74 %), 61-70% (7.87 %) & 71-80% (4.49 %). HRCT score was <6 in most patients (78.65 %). NIV was required in 29.21 % patients while 21.35 % required mechanical ventilation. Total hospital stay was 08-10 days in 28.09 % patients, 11-15 days in 20.22 % patients & 6-7 days in 16.85 % patients. 69.66 % patients were discharged successfully while death was noted in 30.34 % patients.

Table No 2- General characteristics

	No. of patients (n=89)	Percentage
SpO$_2$ on admission		
<40%	6	6.74
41-50%	2	2.25
51-60%	6	6.74
61-70%	7	7.87
71-80%	4	4.49
81-90%	25	28.09
> 90%	39	43.82
HRCT SCORE		0
<6	70	78.65
6	19	21.35
NIV required	26	29.21
Use of mechanical ventilation	19	21.35
Total Hospital Stay (Days)		0
<5	19	21.35
6-7	15	16.85
08-10	25	28.09
11-15	18	20.22
16-20	2	2.25
21-30	5	5.62
31-40	5	5.62
Outcome		
DEATH	27	30.34
DISCHARGED	62	69.66

We noted a statistically significant difference for age (in years) between discharged patients & died patients. While statistically highly significant difference (p < 0,001) was noted for NL Ratio, LDH (U/L), CRP (mg/L), SpO$_2$(%), HRCT Score on admission & total hospital stay (days).

Table No 3- Comparison between discharged & died

Characteristics	Discharged patients (Mean ± SD)	Died patients (Mean ± SD)	p value
Age (in years)	43.82 ± 17.15	57.47 ± 13.19	0.012
NL Ratio	0.31 ± 0.14	0.53 ± 0.17	< 0.001
LDH (U/L)	266.50 ± 191.43	758.38 ± 386.49	< 0.001
CRP (mg/L)	3.83 ± 2.44	14.91 ± 11.25	< 0.001
SpO$_2$ (%)	90 ± 9.27	60.22 ± 19.18	< 0.001
HRCT Score on admission	3.84 ± 0.98	5.19 ± 0.79	< 0.001
Total hospital stay (days)	10.05 ± 8.17	3.17 ± 5.82	< 0.001

DISCUSSION

A significant proportion of patients with COVID-19 have mild symptoms, such as fever, muscle ache, cough, shortness of breath and fatigue, and about half of patients do not show any obvious symptoms.[7] However, some severe cases with severe pneumonia can develop into acute respiratory distress syndrome (ARDS), pulmonary oedema or multiple organ dysfunction syndrome (MODS), hence leading to a high mortality.[8]

Patients with cardiovascular diseases, diabetes, and other comorbidities are often subject to acute respiratory distress syndrome, shock, multi-organ failure, cytokine storm, and other serious complications in COVID-19. These patients commonly have a poor prognosis. The increase in inflammation markers is the critical point underlying the systemic vasculitis processes and the defects in the coagulation processes that cause most parenchymal lesions in vital organs.[5]

Increased levels of cytokines, chemokines, and Neutrophils to Lymphocyte Ratio (NLR) in severe cases suggest a possible hyper-inflammatory response role in the pathogenesis of COVID-19. [9,10] Some hematological parameters, including white blood cell (WBC), lymphopenia, CRP, and some biochemical parameters, such as LDH, creatine kinase (CK), and troponin were reported to be associated with COVID-19 severity.[9,10]

The CRP marker was found to be significantly increased in the initial phases of the infection for severe COVID-19 patients, also prior to indications of critical findings with CT. Importantly, CRP has been associated with disease development and is an early predictor for severe COVID-19.[11] The authors also reported by correlation analysis that CRP (R¼0.62, p<.01), erythrocyte sedimentation rate (ESR) (R¼0.55, p<.01) and granulocyte/lymphocyte ratio (R¼0.49, p<.01) were positively associated with CT severity scores.[11] Similar findings was noted in present study.

Xu JB et al.,[12] confirmed that baseline levels of procalcitonin (≥ 0.10 ng/mL) and CRP (≥ 52.14 mg/L) have been addressed as independent predictors of survival in patients with COVID-19, but the elevated NLR do not seem useful for discriminating the death in COVID-19 infected patients. While C. Tan et al.[11] noted that, compared to CT scans alone, CRP values are more reliable for earlier identification of case severity. Meta-analysis of 20 studies including 4843 COVID-19 patients, reporting impact of elevated CRP (>10 mg/L) on outcomes showed that there is nearly fourfold higher risk of poor outcomes in COVID-19 patients with elevated CRP.[13]

Neutrophil to lymphocytes ratio (NLR) is a rapid, inexpensive, and useful indicator that could be estimated via the complete blood count. A meta-analysis had shown that the NLR levels in severe patients with COVID-19 were increased compared with patients without severe disease.[14] Other six retrospective clinical studies examining the potential use of NLR as a prognostic marker for severe Covid-19 had consistently concluded that NLR is an independent risk factor of mortality in critically ill patients with Covid-19.[15-20] Similar findings was noted in present study.

Elevated lactate dehydrogenase (LDH) levels seems to reflect that the multiple organ injury and failure may play a more prominent role in this pathology in influencing the clinical outcomes in patients with COVID-19. Possible sources of elevated serum LDH levels during infection may be immunologic changes after SARS-COV-2 infection of the upper and lower respiratory tract which result in an early acute respiratory inflammatory response with consequent release of pro-inflammatory cytokines, including interleukin-

1β, followed by inflammasome activation and production of active mature interleukin-1β which is a mediator of lung inflammation and fibrosis.[21]

Henry BM et al.,[22] elevated LDH values were associated with 6-fold increased odds of severe COVID-19 disease. More importantly, elevated LDH was associated with a N16-fold increase in odds of mortality.

Many times diagnosis of severe and critically ill patients relies on complex procedures such as imaging tests and blood gas analysis. In a pandemic situation, it is difficult to perform these diagnostic examinations on all patients. It is therefore particularly important to identify more easily detectable and earlier predictors to achieve extensive screening of patients and optimize the allocation of medical resources.

Evaluating simple parameters such as neutrophil to lymphocytes ratio, C-reactive protein and lactate dehydrogenase can help clinicians identify potentially severe cases early, conduct early triage and initiate effective management in time, which may reduce the overall mortality of COVID-19. However larger studies are required to confirm our findings.

CONCLUSION

Simple parameters such as neutrophil to lymphocytes ratio, C-reactive protein and lactate dehydrogenase NLR has good predictive values on mortality in patients with COVID-19 infection.

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