Neutrophil–Lymphocyte Ratio in Patients with COVID-19 as a Simple Tool to Predict Requirement of Admission to a Critical Care Unit

Sagar S Maddani1, Nitin Gupta2, Shashikiran Umakanth3, Sowmya Joylin4, Kavitha Saravu5

ABSTRACT

Introduction: Coronavirus disease-2019 (COVID-19) pandemic has overloaded the healthcare system beyond its functional capacity. Late referral to higher levels of care may be one of the factors associated with higher mortality. Therefore, we aimed to find simple demographic and laboratory parameters which predict the requirement of admission to a critical care unit.

Materials and methods: A case–control study was undertaken in adult age population >18 years, admitted in a dedicated COVID hospital in South India. A total of 50 patients with severe disease (cases) were compared with 143 mild or asymptomatic cases (controls). Those demographic and laboratory parameters that were found to be significant on univariate analysis were used for multiple logistic regression analysis.

Results: Univariate analysis of demographic and laboratory data showed higher age, male sex, presence of diabetes mellitus, higher values of C-reactive protein, ferritin, D-dimer, neutrophil–lymphocyte ratio (NLR), and lactate dehydrogenase to be significantly associated with cases. Multivariate logistic regression analysis of these significant variables showed NLR and ferritin to be the independent predictors of the requirement of admission to a critical care unit. The receiver-operating characteristic curve showed an NLR value of 5.2 and a ferritin value of 462 μg/L that were able to predict the requirement of admission in critical care units.

Conclusion: High ferritin and NLR were independent predictors of the requirement of admission in critical care units. NLR is a simple tool that can be used in resource-limited settings for triage and early referral to higher levels of care.

Keywords: Coronavirus disease-2019, C-reactive protein, Ferritin, Neutrophil–lymphocyte ratio.

ORIGINAL RESEARCH

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Majority of the patients with COVID-19 have a mild or asymptomatic presentation. These patients mainly require strict isolation to prevent transmission of the disease in the community. Around 5–15% of COVID-19 patients may present with or progress to severe symptoms requiring higher levels of care. In a report of 44,500 patients from China, the mortality rate was found to be 2.3%. Early anticipation of the progression of the disease and prompt referral to higher centers for initiation of treatment in moderate to severe cases will prevent mortality. Due to the heavy burden of COVID-19 on the Indian healthcare system, many patients with COVID-19 are being managed in small healthcare centers without an adequate facility for providing intensive care. Late referral to higher levels of care may be one of the factors associated with mortality. Therefore, the study aimed to find simple demographic and laboratory parameters that predict the requirement of admission to a critical care unit.

MATERIALS AND METHODS

A case–control study was conducted in adult age-group population >18 years, at Dr TMA Pai Hospital, Udupi, Karnataka, between March and August 2020 after taking permission from the Institutional Ethics Committee. Those patients requiring admission in the critical care unit and clinically categorized as severe (pneumonia, with respiratory rate >30/minute or SpO2 <90% on room air) according to the definition given by World Health Organisation were grouped as “cases.” The hospital numbers of all the patients admitted in hospital wards with asymptomatic or mild disease (no clinical signs of pneumonia and no hypoxia) were compiled. Random sampling was done using the random number table to select three times the number of cases. These were designated as “controls.” The demographic, clinical parameters, laboratory parameters, and treatment and outcome of both cases and controls were recorded for each of the enrolled patients in a separate predefined case-record form.
Statistical Analysis
A univariate analysis was done to find demographic and laboratory parameters that were significantly associated with the requirement of admission to a critical care unit. For categorical variables, a chi-square test was used. For continuous variables, independent t-test and Mann–Whitney U test were done. Those with a p-value of <0.05 were included in the multivariable logistic regression analysis to find the independent predictors of critical care unit admission. A receiver operating characteristic (ROC) curve was generated for quantitative predictors that were significant on multivariable analysis to determine their optimal cutoffs that can help in predicting individuals requiring critical care admission.

Results
A total of 53 patients were categorized as severe and required admission in the critical care unit. Of these, three patients were excluded because of lack of sufficient data. For these 50 cases, 150 control patients were selected from the asymptomatic or mild category; eight patients were excluded because of lack of sufficient data. A total of 142 patients were taken as controls in the final analysis. A total of 35 patients had a history of travel, while 75 patients had a history of contact with a positive patient. A total of 19 patients were pregnant among the included patients. The details of stay, examination findings, and treatment of patients in the severe and mild categories have been summarized in Table 1. Following complications were noted in patients admitted in critical care unit: acute kidney injury (n = 13), the requirement of dialysis (n = 3), hepatitis (n = 9), myocarditis (n = 2), stroke (1), myocardial infarction (1), and shock (3). In patients admitted in the critical care unit, noninvasive ventilation was given to 20 patients, while five patients required oxygen through a high-frequency nasal cannula. Of these patients, 10 patients required invasive mechanical ventilation. There was only one mortality in this group. Five cases were transferred to another center.

The demographic and laboratory parameters of cases and controls are described in Table 2. The result of a univariate analysis comparing cases and controls is also described in Table 2. The presence of diabetes mellitus (DM) and higher duration of illness at presentation were significantly associated with admission to a critical care unit (Table 2). The mean age of cases was significantly higher when compared to controls (Table 2). The incidence of severe disease was higher in males (Table 2). The mean total leucocytes and neutrophil–lymphocyte ratio (NLR) was higher in cases when compared to controls. Similarly, D-dimer, ferritin, C-reactive

| Table 1: Details of stay, examination, and treatment of COVID-19 patients requiring critical care admission (cases) as compared to those who did not (controls) |
|---------------------------------|--------|--------|--------|
| Days of stay | 19.8 (8.4) | 8.29 (3.67) | <0.001 |
| Systolic blood pressure | 128.8 (18.6) | 124.7 (17) | 0.006 |
| Diastolic blood pressure | 77.2 (11.6) | 79.8 (11.7) | 0.001 |
| Respiratory rate | 24.9 (3.4) | 18.23 (2.7) | 0.003 |
| SpO2 | 90.5 (4.6) | 97.7 (1.18) | <0.001 |
| Hospital-acquired infection | 4 | 1 | 0.005 |
| Antibiotics | 31 | 5 | <0.001 |
| Hydroxychloroquine | 27 | 5 | <0.001 |
| Steroids | 47 | 13 | <0.001 |
| Remdesivir | 17 | 1 | <0.001 |
| Death | 1 | 0 | <0.001 |

Table 2: Univariate analysis of demographic and laboratory parameters that can predict the requirement of admission to a critical care unit

| Age | 55.22 (13.75) | 44.22 (17.42) | 0.023 |
| Female sex | 14 (28%) | 67 (47.2%) | 0.018 |
| Duration of illness* | 4.50 [3.00, 5.00] | 2.00 [1.00, 4.00] | <0.001 |
| DM | 33 (66%) | 35 (24.6%) | <0.001 |
| CKD | 3 | 2 | 0.08 |
| HIV | 1 | 0 | 0.09 |
| Malignancy | 2 | 2 | 0.270 |
| Asthma/COPD | 2 | 10 | 0.445 |
| TLC (/µL) | 9762.00 (4582.84) | 6784.51 (2218.95) | <0.001 |
| NLR* | 8.45 [5.40, 13.88] | 2.32 [1.50, 3.48] | <0.001 |
| Platelet count (thousand/µL) | 298 (133.8) | 283.2 (93.9) | 0.394 |
| D-dimer* (µg/mL) | 0.90 [0.32, 1.80] | 0.30 [0.20, 0.50] | <0.001 |
| Ferritin* (µg/L) | 761.50 [465.75, 1119.00] | 137.50 [76.00, 257.85] | <0.001 |
| CRP*(mg/L) | 81.50 [43.00, 123.75] | 3.00 [1.00, 13.25] | <0.001 |
| LDH* (/U/L) | 411.00 [348.00, 652.00] | 262.00 [220.75, 309.00] | <0.001 |

Qualitative variables—percentages in the bracket; quantitative variables—mean (standard deviation); quantitative variables*—median (interquartile range)
DM, diabetes mellitus; CKD, chronic kidney disease; HIV, human immunodeficiency virus infection; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; TLC, total leucocyte count; NLR, neutrophil–lymphocyte ratio; LDH, lactate dehydrogenase
Table 3: Multivariable logistic regression of demographic and laboratory parameters that can predict the requirement of admission to a critical care unit

|                                | Cases (n = 50) | Controls (n = 142) | Unadjusted OR (95% confidence interval) | Adjusted OR (95% confidence interval) | p value |
|--------------------------------|---------------|--------------------|----------------------------------------|--------------------------------------|---------|
| Age                            | 55.22 (13.75) | 44.22 (17.42)      | 1.04 (1.02–1.06)                       | 1.05 (0.98–1.13)                     | 0.16    |
| Female sex                     | 14 (28%)      | 67 (47.2%)         | 0.435 (0.216–0.876)                    | 0.21 (0.03–1.66)                     | 0.14    |
| Duration of illness*           | 4.50 (3.00, 5.00) | 2.00 (1.00, 4.00) | 1.47 (1.26–1.71)                       | 0.95 (0.62–1.45)                     | 0.81    |
| DM                             | 33 (66%)      | 35 (24.6%)         | 5.93 (2.95–11.9)                       | 0.12 (0.01–1.14)                     | 0.065   |
| TLC (/µL)                      | 9762.00 (4582.84) | 6784.51 (2218.95)  | 1 (1–1)                                | 1.00 (1.00–1.00)                     | 0.66    |
| NLR*                           | 8.45 (5.40, 13.88) | 2.32 (1.50, 3.48) | 1.78 (1.48–2.13)                       | 0.67 (0.46–0.97)                     | 0.036   |
| CRP* (mg/L)                    | 81.50 (43.00, 123.75) | 3.00 (1.00, 13.25) | 1.03 (1.02–1.03)                       | 1.01 (0.99–1.02)                     | 0.29    |
| D-dimer* (µg/mL)               | 0.90 (0.32, 1.80) | 0.30 (0.20, 0.50)  | 3.51 (1.56–7.93)                       | 0.97 (0.45–2.08)                     | 0.93    |
| Ferritin* (µg/L)               | 761.50 (465.75, 1119.00) | 137.50 (76.00, 257.85) | 1 (1–1)                                | 1.00 (0.99–1.00)                     | 0.02    |
| LDH* (U/L)                     | 411.00 (348.00, 652.00) | 262.00 (220.75, 309.00) | 1.01 (1.01–1.02)                       | 1.00 (0.99–1.00)                     | 0.16    |

Qualitative variables—percentages in the bracket; quantitative variables—mean (standard deviation); quantitative variables*—median (interquartile range)
DM, diabetes mellitus; CRP, C-reactive protein; TLC, total leucocyte count; NLR, neutrophil–lymphocyte ratio; LDH, lactate dehydrogenase

Fig. 1: ROC curve for NLR and determination of cutoff to distinguish patients who require critical care admission from those who do not need admission and those who did not. Although several international studies have been published on this subject, it is important to study these parameters in Indian subjects as studies have shown a disparity in outcomes among various races/ethnicities. Various Indian studies related to COVID-19 have been published, but very few of these studies have systematically studied the risk factors for severity.

An ROC curve was generated for both NLR and ferritin. The optimal cutoff for NLR was found to be 5.2 which gave a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 76% (95% confidence interval (CI), 62–87%), 90.6% (95% CI, 84–95%), 74.5% (95% CI, 60–86%), and 91.2% (95% CI, 85–95%), respectively (Fig. 1). The area under the curve (AUC) for NLR was 0.91 (95% CI, 0.86–0.95). The optimal cutoff for ferritin was found to be 462 µg/L which gave a sensitivity, specificity, PPV, and NPV of 79.6% (95% CI, 66–90%), 89.8% (95% CI, 82–95%), 79.6% (95% CI, 66–90%), and 89.8% (95% CI, 82–95%), respectively (Fig. 2). The AUC for ferritin was 0.88 (95% CI, 0.81–0.94).

**Discussion**

Our case–control study demonstrates the difference in demographic and laboratory parameters between patients requiring critical care admission and those who did not. Although several international studies have been published on this subject, it is important to study these parameters in Indian subjects as studies have shown a disparity in outcomes among various races/ethnicities. Various Indian studies related to COVID-19 have been published, but very few of these studies have systematically studied the risk factors for severity. Also, none of these studies are from the southern states of India. Those studies where risk factors for severity or mortality were analyzed have been summarized in Table 4. Similar to other published studies, age and male gender were associated with a higher incidence of severe disease in our study. In a study from China, the rate of hospitalization varied between the different age-groups as follows: 1% (20–29 years), 4% (30–59 years), and 18% (>80 years). In another study, the risk of death was 20 times higher in those above 80 years of age compared to those between 50 and 59 years of age. Several studies have shown that the male gender has suffered worse outcomes comparatively. The presence of comorbidities like DM affects the disease severity as well as mortality. In a study from Italy, among the people who died, most patients had one or more comorbidities. The mean number
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Table 4: Comparing various studies related to COVID-19 patients in India

| Sl. No. | Author | Study design | Study population | Sample size | Predictors of severity/mortality | Mortality(%) |
|---------|--------|--------------|------------------|-------------|----------------------------------|-------------|
| 1       | Soni et al. Chandigarh | Prospective, observational study | All severity (severe-18 patients) | 114 | High inflammatory parameters, NLR ratio of ≥3.5, hypalbuminemia, and deranged creatinine | 2.6 |
| 2       | Mahale et al., Pune | Retrospective study | Patients requiring oxygen and on immunomodulators | 134 | SpO2, PaO2/FiO2 ratio, leukocytosis, lymphopenia, and creatinine | 26.9 |
| 3       | Bhadade et al., Mumbai | Prospective observational study | Critically ill COVID-19 patients | 373 | Comorbidities, hypertension, low SpO2, low P/F ratio, high levels of blood sugar, LDH, ferritin, D-dimer, IL-6 | 18.5 |
| 4       | Sharma et al., Jaipur | Prospective observational study | All severity | 70 | Lymphopenia and higher age | 32.8 |
| 5       | Dosi et al., Indore | Retrospective study | All severity (oxygen requirement-53) | 365 | Comorbidities, lymphopenia | 8.4 |

of comorbidities in that study was 2.7.14 Similar to other published studies, DM was found to be associated with severe disease in this study (Table 4).

Similarly, laboratory parameters like increased CRP, D-dimer, ferritin, NLR, and LDH were associated with a higher incidence of severe disease. Higher the degree of the inflammatory state, higher will be the levels of inflammatory markers, and consequently, these markers may help in predicting severity and prognosis. Inflammatory markers like CRP, ferritin, and interleukin-6 were associated with a higher incidence of severe disease in several studies.15 The SARS-CoV-2 also affects the coagulation pathway and liver result in a prothrombotic state. This results in increased morbidity and mortality. As a consequence, raised D-dimer levels have been used as a predictor for severity/mortality.15 Similar findings were seen in other Indian studies as well (Table 4).

To negate the effect of covariates, we did a multivariable logistic regression analysis that showed that NLR and ferritin are independent predictors of disease severity. Lymphopenia has been commonly described in patients with COVID-19.2 This might have been because of the presence of receptors for SARS-CoV-2 on lymphocytes.16 The degree of lymphopenia has been described to be higher in those with severe COVID-19, which may be because of the cytokines mediated apoptosis of lymphocytes.16 High NLR value has been associated with severity of disease illness in several studies from China.17,18 Studies from India have also shown that lymphopenia or high NLR is seen more commonly in critically ill patients.10,11 Ferritin was the only inflammatory marker that was significant on multivariable analysis. Similar studies from China have shown an association between ferritin and increased severity.5,19 In our study the cutoff for ferritin was found to be 462 μg/L with a considerable AUC. However, the availability of ferritin testing facilities in primary care centers may be a cause for concern. On the other hand, NLR at a cutoff of 5.2 had a better AUC compared to ferritin and is also a simple test that is available in most primary centers. In centers where testing is easily available, and resource-limitedness is not an issue, other inflammatory markers (beyond NLR and ferritin) may also be of some help in prognostication and predicting the requirement of higher levels of care.

The pandemic has tested the limits of an already overburdened healthcare system in India. Most patients in India are managed in primary care centers or make-shift centers. These centers are staffed by healthcare professionals without sufficient experience in managing critically ill patients. It is, therefore, important to have simple predictors that may suggest the requirement of critical care. We, therefore, suggest that NLR can be used for early referral to centers with critical care support.

**Limitations**

Our study had few limitations, mainly being a single-centre case-control study, hence postulating the same results to the general population might not be accurate. Interleukin-6 and chest imaging characters were not included in our study as it was not done in most of the mild cases.

**Conclusion**

Older individuals, male sex, DM, and raised inflammatory parameters (CRP, D-dimer, ferritin, NLR, and LDH) were associated with a higher incidence of severe disease. Out of these, high ferritin and NLR were independent predictors of disease severity. These parameters can be used to identify high-risk patients at resource-limited settings and refer them to tertiary care centers for better outcomes.

**Orcid**

Sagar S Maddani @https://orcid.org/0000-0003-0700-0532
Nitin Gupta @https://orcid.org/0000-0002-9687-2836
Shashikiran Umakanth @https://orcid.org/0000-0001-5210-7457
Sowmya Joylin @https://orcid.org/0000-0002-5112-1262
Kavitha Saravu @https://orcid.org/0000-0001-6399-1129

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