A Proposed Multivariate Logistic Regression Model for Early Covid-19 Risk Triaging

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ABSTRACT

Background/Aim: COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. Most COVID-19 affected patients experience mild to moderate symptoms that spontaneously resolve without treatment. Unfortunately, few patients become seriously ill and require intensive medical attention. The aim of our study was primarily to construct a multiple logistic regression-based model that may facilitate us in admitted patients' severity grading and their mortality probabilities.

Methods: A retrospective study was conducted in Queen Alia Military Hospital, Royal Medical Services, Amman, Jordan which included affected COVID-19 patients in the isolation department during the period between Mar 2020 and Sep 2021. Several investigated variables were compared across the 2 dichotomized comparative cohorts; Mild-Moderate Cohort (**Cohort I**) or Severe-Critical Cohort (**Cohort II**). A multiple Logistic Regression was used to abstract the significant coefficients to construct the diagnostic and prognostic model. The Receiver Operating Characteristic and the Sensitivity analyses were used to explore the utility performances of the proposed composted 2 ratios.

Results: Our proposed and tested severity grade prognosticator was the only statistically significant among the 4 tested independent variables [1.034; 95% CI (1.029-1.039), p-Value=0.000. The final proposed constructed MLR model in this study for SARS-CoV-2 infected patients severity grading was constructed as [e (-7.929+0.034×FAR: LMR)/ 1+ e (-7.929+0.034× FAR: LMR)].

Conclusion: Depending on this study's proposed dual composited ratios, the Ferritin to Albumin ratio (FAR) to the Lymphocytes to Monocytes ratio (LMR), on the initial triaging of the admitted affected COVID-19 patients and on the predicting the probability of mortality, may help the clinicians for specifying the proper treatment for every case, reducing medical articles consumption, and saving the cost.

Keywords: Multivariate regression analysis; Risk modeling; Early prediction; severity triaging; COVID-19; SARS-CoV-2

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INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a pandemic infection has presented many therapeutic challenges; the increasing number of patients admitted to the hospital due to SARS-CoV-2 presents the need for understanding the clinical, radiological, and laboratory findings associated with greater disease severity and mortality. (1)

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Common symptoms of COVID-19 include Fever, Cough, Fatigue, and Dyspnea. Less common symptoms include headache, dizziness, abdominal pain, nausea, and vomiting. Patients may present with anosmia (loss of smell), dyspepsia (distortion or loss of taste), nausea, and diarrhea. However, a systematic review found the occurrence of the symptoms; Fever, Cough, Fatigue, Dyspnea, and the Sputum (81.2%, 58.5%, 38.5%, 26.1 and 25.8%, respectively). [(2)] Certain demographic factors are associated with a higher rate of a severe clinical course of COVID-19, a retrospective analysis in New York found that a higher age group, overweight, Hispanic ethnicity, and higher core body temperature associated with a higher need for mechanical ventilation. [(3)] Data also suggests that the male sex is a variable that is independently associated with COVID-19 severity. [(4)]

Comorbidities such as cardiovascular disease, chronic kidney disease, chronic lung diseases (particularly COPD), diabetes mellitus, hypertension, immunosuppression, obesity, and sickle cell disease are associated with an increased risk of intubation. [(5, 6)] Hypoxemia is also associated with poor clinical outcomes in COVID-19 patients; A retrospective cohort study conducted of 140 patients to conclude that hypoxemia is independently associated with in-hospital mortality. This may help the clinician in the management of severe COVID-19, particularly in settings requiring strategic allocation of limited critical care resources. [(7)]

Radiological findings such as chest x-ray (CXR) and computed tomography (CT) have a role in assessing the severity of the SARS-CoV-2 disease; the most common CT findings are ground-glass opacities or bilateral consolidation in the peripheral lower lung fields. [(8)] Certain laboratory findings may predict the severity and prognosis of the disease in COVID-19 patients, this includes D-dimer levels, C-reactive protein (CRP), LDH, ferritin level, albumin level WBCs counts, and high-sensitivity cardiac troponin. [(9)] These biomarkers act as indicators for coagulopathy, cardiac dysfunction liver injury, and renal dysfunction.

A meta-analysis of an electronic search in Medline (PubMed interface), Scopus, Web of Science, and China National Knowledge Infrastructure (CNKI); concluded and recommended that clinicians should closely monitor WBC count, lymphocyte count, platelet count, IL-6, and serum ferritin as markers for potential progression to critical illness. [(9)] Early identification of patients at high-risk COVID-19 may facilitate more individually aligned treatment plans and optimized utilization of medical resources. Feng, Z., Yu, Q., Yao, S. *et* al; multicenter retrospective study result in CT severity score is associated with inflammatory levels and that older age, higher neutrophil-to-lymphocyte ratio (NLR), and CT severity score on admission are independent risk factors for short-term progression. [(10)]

Prediction models for covid-19 are quickly entering the academic literature to support medical decision-making at a time when they are urgently needed Investigators are trying to create prediction models that incorporate several hematologic, biochemical, and immunologic biomarkers. In this study we aimed for initial triaging of the admitted affected COVID-19 patients and on the predicting the probability of mortality which may help the clinicians for specifying the proper treatment for every case, reducing medical articles consumption, and saving the cost.

METHODS

A retrospective study was conducted in Queen Alia Military Hospital, Royal Medical Services, Amman, Jordan. It included all affected COVID-19 patients in the isolation department during the period between Mar 2020 and Sep 2021. All data were retrieved from our electronic medical record system (Hakeem). The study was approved by the institutional ethical review board (IRB) in Royal Medical Services. In addition, it includes all infected patients from moderate to severe cases with variable comorbidities. All patients were diagnosed and categorized according to ‘’The diagnostic and therapeutic protocol for COVID-19 which was issued by the Jordanian Ministry of Health. According to our protocol, cases could be confirmed case; positive PCR or suspected case; which has negative PCR with specific criteria of related symptoms.

Both confirmed and suspected cases were further categorized into two Cohorts: Mild-Moderate Cohort (Cohort I) or severe-Critical Cohort (Cohort II). Mild to moderate cases were admitted to the ward whereas severe-Critical admitted to the critical care unit (CCU) or intensive care unit (ICU). The 2 categorized cohorts were statistically compared and analyzes via Chi Square test and the results were presented as rates with counts, in addition to the odd ratios for the dichotomous investigated variables. Laboratory and radiological examinations were measured at baseline which particularly included, according to our protocol, complete blood counts (CBCs with deferential including lymphocytes and monocytes), standard chemistries, coagulopathy indices (prothrombin time and D-dimer), liver indices, antibiogram, radiological procedures (X-ray and high-resolution computed tomography (HRCT) if a patient with an SOB or suspected pneumonia). These biochemical and radiological examinations were repeated every 48 or 72 hours according to the opinion of the attending physician. Patients without symptoms for 10 days (regardless of PCR test) and patients who were admitted for at least 13 days (with last 3 days without symptoms) were considered as eligible criteria for discharging.

The Multivariate Logistic Regression Test was conducted to explore the degree of correlations, how much of the total variations in the dependent variable can be explained by the independent variables, and the quality of the prediction of the dependent variable. The Multivariate Logistic Regression Test was performed to ascertain the effects of age, BMI, gender, and baseline ferritin to albumin to monocyte ratio. The primary our tested composite severity grade was a predictor of the likelihood that admitted SARS-CoV-2 infected patients have a severe/critical grade. In addition, this test was conducted to abstract the necessary coefficients to collectively predict SARS-CoV-2 infected patient's severity grade and to present the final form of our proposed multivariate logistic regression model for the affected COVID-19 patients.

The Receiver Operating Characteristic (ROC) curve analysis for the investigated proposed novel prognosticator ratio, the Ferritin to Albumin ratio (FAR) to the Lymphocytes to Monocytes ratio (LMR), which was collectively abbreviated as FAR: LMR. was constructed against both the admitted SARS-CoV-2 infected patients' severity grouping [Mild/Moderate (0) and Severe/Critical (1)] and the overall mortality rate [Survivors (0) and Non-Survivors (1)]. The Sensitivity analysis was thereafter processed on a total of 781 processed cases [(388-case were processed as positive actual state, and 393-case were processed as a negative actual state) and (155-case were processed as positive actual state, and 626-case were processed as a negative actual state), respectively]. 0 processed cases were dealt with as missing data in both comparative scenarios. higher values of the test result variable(s) indicate stronger evidence for a positive actual state. The SPSS version 25 was used in this study's analysis and the p-Value <0.05 was considered the level of significance.

RESULTS

The overall eligible studied patients in this study were 781 patients which were categorized into 2 comparative-based severity grades cohorts; Mild-Moderate SARS-CoV-2 infected patients (Cohort I) and Severe-Critical SARS-CoV-2 infected patients (Cohort II). Approximately 51.2% of the overall eligible investigated patients (393 Mild-Moderate COVID-19 affected patients) was grouped to Cohort I and about 48.8% (388 Severe-Critical COVID-19 affected patients) was oppositely allocated to Cohort II.

The overall gender's distribution ratio (Male to Female ratio) in this study was 2.309: 1 and it was insignificant [0.891 (95% CI; 0.656-1.209, p-Value=0.459]. More female affected patients had Severe-Critical grade compared to Mild-Moderate grade [122 (31.4%) vs 114 (29.0%)] while more male affected patients had Mild-Moderate severity grade compared to Severe-Critical grade [279 (71.0%) vs 266 (68.6%)].

Approximately 79.9% (310 patients) of the Severe-Critical affected COVID-19 patients had a confirmed diagnosis of SARS-CoV2 related infection compared to 57% (224 patients) of the Mild-Moderate affected COVID-19 patients. In other side, approximately 43% (169 patients) of the Mild-Moderate grade had a suspected COVID-19 diagnosis compared to only 20.1% (78 patients) who had Severe-Critical severity grade. The odd ratio for the severity grades distribution across the Cohort I-II was 2.999 (95% CI; 2.180-2.124).

There were three modes for oxygen supply; Nasal Cannula (NC) with an Oxygen flow rate of 3-6 L/min, Non-Invasive Mechanical Ventilation (NIMV), and Invasive Mechanical Ventilation (IVM).166 (42.2%) patients were without any oxygen supply in the mild to moderate group and 150 (38.2%), 72 (18.3%), and 5(1.3%) patients with NC, NIMV, and IVM, respectively. Whereas patients in severe-critical group were with NC 11(2.8%), NIMV 131(33.8%), and IVM 173 (44.6%). Approximately 77.3% (300 patients) were given an oral paracetamol dose in the severe-critical group compared to 50.4% (198 patients) in the mild-moderate group. The mortality rate was significantly higher in the severe-critical affected COVID-19 patients compared to the Mild-Moderate SARS-CoV-2 infected patients [155 (39.9%) vs 0 (0.0%), respectively, p-Value=0.000]. The Chi Square results across the tested groups were presented in **Table I**.

The MLR Test was performed to ascertain the effects of age, BMI, gender and the primary our tested composite severity grade's predictor (FAR: LMR) on the likelihood that admitted SARS-CoV-2 infected patients had Severe/Critical grade. The MLR model was statistically significant [$\chi 2(8) = 56.099$, $p < .0005$]. The explained variation in the dependent variable based on our MLR model ranged from 43.1% to 57.5%, depending on the Cox & Snell R_2 or Nagelkerke R_2 methods, respectively, and correctly classified approximately 80% of the overall cases. Our proposed and tested severity grade prognosticator was the only statistically significant among the 4 tested independent variables [1.034; 95% CI (1.029-1.039), p-Value=0.000. The final proposed constructed MLR model in this study for SARS-CoV-2 infected patients severity grading was constructed as [e (-7.929+0.034×FAR: LMR)/ 1+ e (-7.929+0.034× FAR: LMR)]. Our proposed MLR related model's results were summarized in the **Table II** below.

As illustrated in **Figure 1** in this study, we revealed that the area under the ROC curve (AUROC±SEM) was higher for FAR: LMR against the overall mortality status when compared against the SARS-CoV-2 infected patients' severity grade [0.937±0.01 (95% CI; 0.911-0.95) vs 0.889±0.011 (95% CI; 0.866-0.911), respectively].

The optimal operating cutoff points for our tested FAR: LMR prognosticator was 232.6 ng/ml and 285.5 against the severity grading and the overall mortality, respectively, with sensitivity, specificity, and accuracy rates of 79.4%, 84.9%, and 82.2% versus 92.9%, 80.2%, and 82.7%, respectively. The ROC, and the sensitivity results were presented and **Table III**.

1.

Table I. The comparatively studied variables between Mild/Moderate SARS-CoV-2 infected patients Cohort (Cohort I) and Severe/Critical SARS-CoV-2 infected patients (Cohort II) among admitted affected COVID-19 patients at Queen Alia Military Hospital, Jordan between Mar 2020 and Sep 2021.

Studied Comparative Variables	Overall (N=781)	Cohort I (N=393, 51.2%)	Cohort II (N=388, 48.8%)	OD	P-Value
Gender					
F	236 (30.2%)	114 (29.0%)	122 (31.4%)	0.891 (95% CI; 0.656-1.209	0.459
M	545 (69.8%)	279 (71.0%)	266 (68.6%)		
M: F ratio	2.309:1	2.45: 1	2.18: 1		
O2 Supply strategy					
None	177 (22.7%)	166 (42.2%)	11 (2.8%)	NA	0.000
NC (3-6 L/min)	223 (28.6%)	150 (38.2%	73 (18.8%)		
NIMV	203 (26.0%)	72 (18.3%)	131 (33.8%)		

IMV	178 (22.8%)	5 (1.3%	173 (44.6%)		
COVID-19 status					
Suspected	247 (31.6%)	169 (43.0%)	78 (20.1%)	2.999	0.000
Confirmed	534 (68.4%)	224 (57.0%)	310 (79.9%)	(95% CI; 2.180-2.124)	
DEX (mg/day)					
None	376 (48.1%)	195 (49.6%)	181 (46.6%)	1.126	0.406
6 mg/day	405 (51.9%)	198 (50.4%)	207 (53.4%)	(95% CI; 0.85-1.49)	
CrCl (ml/min)					
0-39	378 (48.4%)	209 (53.2%)	169 (43.6%)	1.472	0.007
>=40	403 (51.6%)	184 (46.8%)	219 (56.4%)	(95% CI; 1.11-0.412	
PARA					
PO	498 (63.8%)	198 (50.4%)	300 (77.3%)	0. 298	0.000
IV	283 (36.2%)	195 (49.6%	88 (22.7%)	(95% CI; 0.219-1.95)	
MORT					
Survivors	626 (80.2%)	393 (100.0%)	233 (60.1%)	0.372	0.000
Non-survivors	155 (19.8%)	0 (0.0%)	155 (39.9%)	(95% CI; 0.336-0.412)	

Data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi Square Test (at p-value< 0.05) and expressed as Number (Percentage).

- Cohort I: Admitted SARS-CoV-2 infected patients who had a Mild-Moderate grade of COVID-19 disease severity.
- Cohort II: Admitted SARS-CoV-2 infected patients who had a Severe-Critical grade of COVID-19 disease severity.

- Significant (P-Value <0.05).
- N: Number of tested COVID-19 infected patients.
- NC: Nasal Canula on Oxygen flow rate of 3-6 L/min.
- NIMV: Non-Invasive Mechanical Ventilation.
- IMV: Invasive Mechanical Ventilation.
- DEX: Dexamethasone.
- MORT: Mortality.
- F: Female.
- M: Male.
- M: F: Male to Female ratio.
- 02: Oxygen.
- NA: Not statistically applicable and can't be computed.
- PARA: Paracetamol.
- PO: Orally.

Table II. The Multivariate Logistic Regression results for the 4 tested variables regarding SARS-CoV-2 infected patients' severity risk triaging at admission on Queen Alia Military Hospital, Jordan between Mar 2020 and Sep 2021.

Tested predictors	B±SEM	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
FAR: LMR	0.034±0.002	184.915	1	0.000	1.034	1.029	1.039
Gender	-0.229±0.217	1.109	1	0.292	0.795	0.519	1.218
Age (Yrs)	0.011±0.009	1.354	1	0.245	1.011	0.993	1.029
BMI (Kg/m^2)	-0.009±0.025	0.114	1	0.735	0.991	0.944	1.042
Constant	-7.929±1.087	53.243	1	0.000	0.000		

- The Multivariate Logistic Regression Test was performed to ascertain the effects of age, BMI, gender and the primary our tested composite severity grade's predictor on the likelihood that admitted SARS-CoV-2 infected patients have Severe/Critical grade. Also, this test was conducted to abstract the necessary coefficients to collectively predict SARS-CoV-2 infected patients severity grade and to present the final form of our proposed multivariate logistic regression model for the affected COVID-19 patients
- The Multivariate Logistic Regression Test was conducted to explore the degree of correlations, how much of the total variations in the dependent variable can be explained by the independent variables, and the quality of the prediction of the dependent variable. The logistic regression model was statistically significant, $\chi2(8) = 56.099$, $p < .0005$. The explained variation in the dependent variable based on our model ranges from 43.1% to 57.5%, depending on whether you reference the Cox & Snell R2 or Nagelkerke R2 methods, respectively, and correctly classified 80% of cases.

➢ Cohort I: Admitted SARS-CoV-2 infected patients who had a Mild-Moderate grade of COVID-19 disease severity.
➢ Cohort II: Admitted SARS-CoV-2 infected patients who had a Severe-Critical grade of COVID-19 disease severity.
➢

- **FAR: LMR:** Ferritin: Albumin to Lymphocytes: Monocyte's ratio
- **BMI:** Body mass index in kg per m^2

FAR: LMR vs SARS-CoV-2 infected patients' severity grade	FAR: LMR vs overall mortality rate

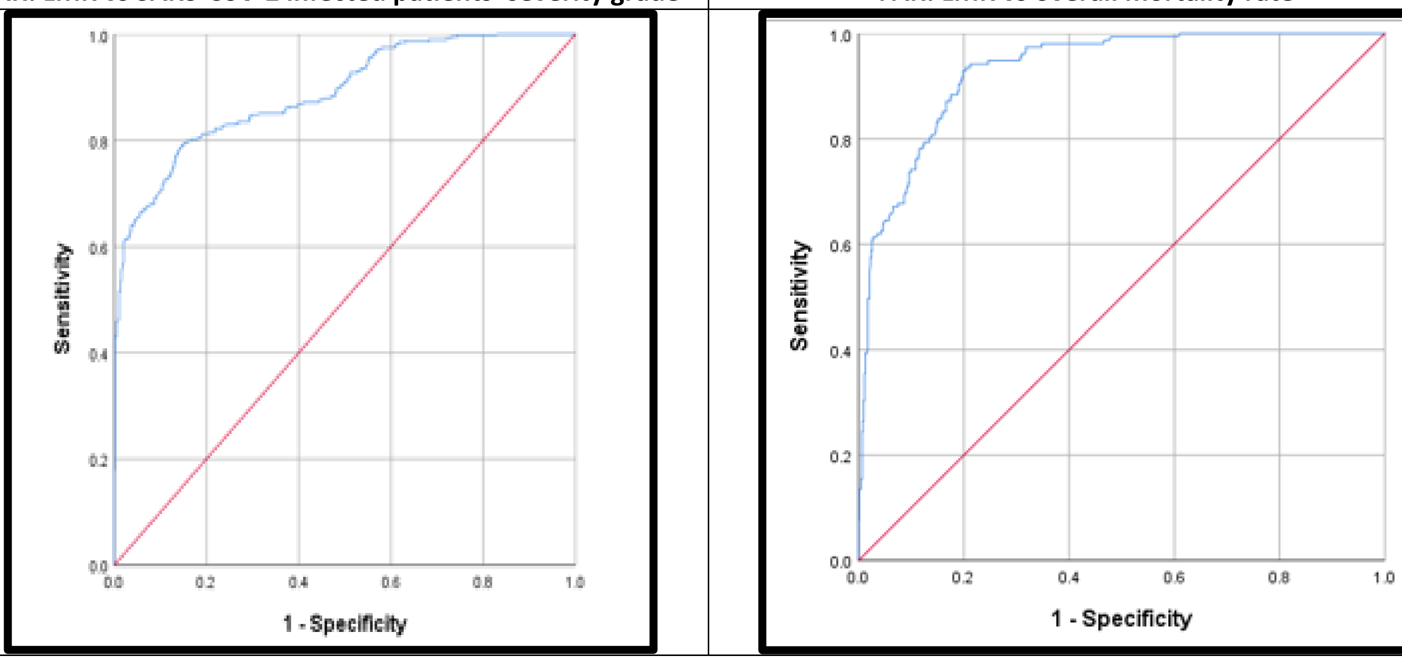

Figure 1. The Receiver Operating Characteristic (ROC) curve analysis for the investigated proposed novel prognosticator ratio, the Ferritin to Albumin ratio (FAR) to the Lymphocytes to Monocytes ratio (LMR) which was collectively abbreviated as FAR: LMR, to explore their corresponding AUROC. In this study, we revealed that the area under the ROC curve (AUROC) was higher for FAR: LMR against the overall mortality status when compared against the SARS-CoV-2 infected patients' severity grade [0.937±0.01 (95% CI; 0.911-0.95) vs 0.889±0.011 (95% CI; 0.866-0.911), respectively].

Table III. The optimal cut-off points, sensitivities, specificities, positive and negative predictive values, Youden and accuracy indices, and the negative likelihood ratios for FAR:LMR in triaging admitted SARS-CoV-2 infected patients' severity grade (Mild/Moderate vs Severe/Critical) and in prognosticating the overall mortality status (Survivors vs Non-Survivors).

Prognostic Indicator	Cutoff	TPR	FPR	YI	TNR	PPV	NPV	NLR	AI
SARS-CoV-2 infected patients' severity grade	232.6	79.4%	15%	64.4%	84.9%	83.9%	80.7%	24.3%	82.2%

Overall mortality	258.5	92.9%	19.8%	73.1%	80.2%	53.7%	97.9%	8.9%	82.7%
➢ The area under the receiver operating characteristic (ROC) analysis the Ferritin to Albumin ratio (FAR) to the Lymphocytes to Monocytes ratio (LMR), which was collectively abbreviated as FAR: LMR was constructed against both the admitted SARS-CoV-2 infected patients' severity grouping [Mild/Moderate (0) and Severe/Critical (1)] and the overall mortality rate [Survivors (0) and Non-Survivors (1)]. The Sensitivity analysis was thereafter processed on a total of 781 processed cases [(388-case were processed as positive actual state, and 393-case were processed as a negative actual state) and (155-case were processed as positive actual state, and 626-case were processed as a negative actual state), respectively]. 0 processed cases were dealt with as missing data in both comparative scenarios. higher values of the test result variable(s) indicate stronger evidence for a positive actual state.									
TPR: True positive rate (sensitivity). FPR: False positive rate. YI: Youden index. TNR: True negative ratio (specificity).			PPV: Positive predictive value. NPV: Negative predictive value. NLR: Negative likelihood ratio. AI: Accuracy index.						

DISCUSSION

Currently, there is no overview of available models for triaging suspected or confirmed COVID-19 cases. A systematic review of 37 421 titles and 169 studies describing 232 prediction models found that methodological guidance should be followed because unreliable predictions could cause more harm than benefit in guiding clinical decisions and the authors should adhere to the TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) reporting guideline. The Jehi diagnostic model and the 4C mortality score were identified as promising models. (11)

As the coronavirus disease 2019 (COVID-19) pandemic rages on, there is an urgent need for identification of clinical and laboratory findings for the progression of severe and fatal forms of this illness. Several biomarkers may potentially aid in risk stratification models for predicting the severity of COVID-19 were identified (9). In Our study, we aimed to evaluate the ability of hematologic, biochemical, and immunologic biomarkers in the early prediction of the disease's severity in a way that permits the early classification of the patients and selects the proper treatment with reduces the cost and reduces the overall mortality of COVID-19. The prediction model must be accurate and validated to estimate the risks and ultimately improve an individual's outcome or the cost-effectiveness of care. (12)

Several biomarkers that may aid in risk stratification models in the prediction of severe and fatal COVID-19, were identified. Patients with severe to critical COVID-19 should be closely monitored for WBC count, lymphocyte count, platelet count, serum ferritin, C-reactive protein, albumin level, ferritin to albumin ratio, and C-reactive protein to albumin ratio as markers for potential progression to critical illness. (13-14)

A meta-analysis, which included 21 studies, involved 3377 patients and 33 laboratory parameters. 18 studies (n = 2984) compared laboratory findings between patients with severe and non-severe COVID-19 and three studies (n = 393) compared survivors and non-survivors of the disease and were thus analyzed separately. Severe to critical COVID-19 infected patients had significantly increased white blood cell (WBC) count, and decreased lymphocyte and platelet counts compared to mild to moderate disease and survivors. Biomarkers of inflammation, cardiac injury, muscle injury, liver function, kidney function, and coagulation measures were also significantly elevated in patients with severe and fatal COVID-19. Interleukins 6 (IL-6) and 10 (IL-10) and serum ferritin were strong discriminators for severe disease. (15)

The effective triage, medical system, and timely supplement of medical resources have an important role in reducing the mortality of COVID-19. it is essential to ascertain the early predictors, which could help clinicians to identify the severity of patients with COVID-19 quickly at an early stage on admission. In our study, we identified Baseline Ferritin: Albumin to Lymphocytes: Monocyte ratio as independent risk factors for severe COVID-19 and mortality. However, venerable age, hypertension, lymphopenia, hypoalbuminemia, and elevated NLR hypoalbuminemia as risk factors for severe COVID-19 identified in previous studies as reported by Zhang et al. (16)

The majority of previous studies have reported that elderly patients with COVID-19 were more likely to progress to the severe stage and the mortality of elderly patients was higher than the other[1]4. However, venerable age was not an independent risk factor of severe COVID-19 in our study (P=0.245). [17-18]

The MLR analysis in this study was indicated that our proposed severity grades' prognosticator (FAR: LMR) Depending on the small sample size and the possibility of over-fitting in the multivariate logistic regression model, we adopted a forward stepwise method (probability for stepwise: entry P < 0.05, removal P > 0.1) for logistic regression analysis to reduce the number of independent variables entering the model thus reduce the probability of model over-fitting. The results showed that our tested prognosticator (FAR: LMR) was the independent early predictor for patients' severity risk triaging at admission. And the model was constructed as [e (-7.929+0.034×FAR: LMR)/ 1+ e (-7.929+0.034× FAR: LMR)]. In this study, the positive and negative predictive values of the FAR: LMR in triaging the SARS-CoV-2 infected patients' severity grade were 83.9% and 80.7% respectively. This study has several limitations, including particularly a single-center, relatively small sample, and the retrospective observational design study.

CONCLUSION

Depending on this study's proposed dual composited ratios, the Ferritin to Albumin ratio (FAR) to the Lymphocytes to Monocytes ratio (LMR), on the initial triaging of the admitted affected COVID-19 patients and on the predicting the probability of mortality, may help the clinicians for specifying the proper treatment for every case, reducing medical articles consumption, and saving the cost**.**

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