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Leukocyte glucose index as a novel biomarker for COVID-19 severity

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The severity of coronavirus disease 2019 (COVID-19) quickly progresses with unfavorable outcomes due to the host immune response and metabolism alteration. Hence, we hypothesized that leukocyte glucose index (LGI) is a biomarker for severe COVID-19. This study involved 109 patients and the usefulness of LGI was evaluated and compared with other risk factors to predict COVID 19 severity. LGI was identified as an independent risk factor (odds ratio [OR] = 1.727, 95% confidence interval [CI]: 1.026–3.048, P = 0.041), with an area under the curve (AUC) of 0.749 (95% CI: 0.642–0.857, P < 0.0001). Interestingly, LGI was a potential risk factor (OR = 2.694, 95% CI: 1.575–5.283, $P_{corrected}$ < 0.05) for severe COVID-19 in female but not in male patients. In addition, LGI proved to be a strong predictor of the severity in patients with diabetes (AUC = 0.915 (95% CI: 0.830–1), sensitivity = 0.833, and specificity = 0.931). The AUC of LGI, together with the respiratory rate (LGI + RR), showed a considerable improvement (AUC = 0.894, 95% CI: 0.835–0.954) compared to the other biochemical and respiratory parameters analyzed. Together, these findings indicate that LGI could potentially be used as a biomarker of severity in COVID-19 patients.

Since December 2019, coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has been rapidly spreading all over the world[1]. As of 5 July 2020, the COVID-19 pandemic caused more than 582 000 deaths and infected more than 11 million people in over 200 countries[2].

The clinical spectrum of COVID-19 includes mild disease, severe pneumonia, multiple-organ failure, leading in some cases to death. Some risk factors associated with severe outcomes of SARS-CoV-2 infection are male gender, older age, and the presence of comorbidities such as cardiovascular disease, diabetes, hypertension, and obesity[3]. In turn, several studies have identified biomarkers for diabetes and other comorbidities[4]. These clinical features contribute to severe respiratory failure in COVID-19 patients, requiring their admission to the intensive care unit for mechanical ventilation[5]. During the inflammatory response in COVID-19 pneumonia, there is dysregulation of circulating biomarkers such as C-reactive protein (CRP), D-dimer, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLT), and blood urea nitrogen/creatinine ratio (BUN/Cr)[6–8]. These biochemical parameters, together with respiratory parameters: respiratory rate (RR), peripheral oxygen saturation (SpO$_2$), partial pressure of oxygen (PaO$_2$), the fraction of inspired oxygen (FiO$_2$), and respiratory rate oxygenation (ROX) index, have been reported as indicators of the COVID-19 prognosis[9,10].

Blood leukocytes and glucose are inexpensive, standard, and broadly used markers of inflammation[11], and they are involved in the severe COVID-19[12,13], where the inflammation inflicts multi-organ damage leading to organ failure[14]. In this regard, these parameters and the leukocyte glucose index (LGI), calculated from measurements of blood leukocytes count and glucose levels, have predictive values for acute myocardial infarction, coronary artery bypass grafting, and pneumonia after acute ischemic stroke[15–18]. Taken together, we hypothesized that LGI should be contemplated as another clinical tool for determining the severity of SARS-CoV-2 infection.

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| Variable	Severe group (n = 36)	Non-severe group (n = 73)	P value
Demographic characteristics			
Gender, female	22 (61.11%)	28 (38.36%)	**0.041**
Age, years old	51.94 (16.3)	58.78 (14.26)	0.068
Height, meters	1.6 (0.07)	1.64 (0.08)	**0.007**
Weight, Kg	68 (9.59)	72.07 (8.83)	**0.020**
BMI, Kg/m^2	26.62 (3.73)	26.77 (2.73)	0.548
Comorbidities, n (%)			
CKD	11 (30.56%)	15 (20.55%)	0.360
Diabetes	18 (50%)	29 (39.73%)	0.416
COPD	2 (5.56%)	7 (9.59%)	0.726
Clinical and laboratory data			
Onset of Symptom to Hospital admission, days	7.56 (3.59)	7.11 (5)	0.074
RR, beats per minute	32.92 (9.61)	23.29 (4.49)	**< 0.0001***
SpO$_2$, %	73.19 (21.33)	91.48 (9.02)	**< 0.0001***
FiO$_2$, %	45.22 (21.18)	31.3 (12.86)	**< 0.001**
SaO$_2$, %	71.5 (19.38)	88.05 (8.72)	**< 0.0001**
PaO$_2$, mmHg	66 (31.12)	91.03 (60.82)	**0.001**
HCO$_3^-$, mmol/L	17.61 (7.16)	25.22 (7.16)	**< 0.0001***
pH	7.28 (0.14)	7.4 (0.08)	**< 0.0001***
Diarrhea, n (%)	12 (33.33%)	2 (2.74%)	**< 0.0001**
Arthralgia, n (%)	11 (30.56%)	2 (2.74%)	**< 0.0001***
Leukocytes, × 10^9/L	14.1 (4.15)	10.09 (3.43)	**< 0.0001***
Lymphocytes, × 10^9/L	7.67 (5.72)	9.45 (7.98)	0.459
Neutrophils, × 10^9/L	84.69 (7.13)	78.58 (11.94)	**0.018**
RBC, × 10^{12}/L	3.54 (0.59)	3.48 (1.13)	0.430
Hemoglobin, g/dL	10.53 (2.55)	12.37 (2.34)	**< 0.001**
Glucose, mg/dL	204.67 (100.48)	156.15 (93.5)	**0.008**
NLR	15.25 (7.52)	10.36 (8.02)	**0.001***
LGI	2.94 (1.63)	1.61 (1.17)	**< 0.0001***
ROX index	6.74 (4.65)	15.12 (6.31)	**< 0.0001***
PAFI, mmHg	174.77 (120.55)	317 (180.13)	**< 0.0001***
SAFI, mmHg	191.95 (100.59)	336.5 (119.33)	**< 0.0001***
CO-RADS 3	1 (2.8%)	15 (20.5%)	
CO-RADS 4	5 (13.9%)	31 (42.5%)	**< 0.0001***
CO-RADS 5	30 (83.3%)	27 (37.0%)	

Table 1. Clinical characteristics and laboratory findings in patients with non-severe and severe COVID-19. Data are presented as mean ± SD or number (%). Statistically significant *P* values (< 0.05) are highlighted in bold. Variables that remained significant after considering gender are indicated with asterisk in the *P* value (*). *RR* respiratory rate, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, FiO$_2$ fraction of inspired oxygen, SpO$_2$ peripherical oxygen saturation, SaO$_2$ oxygen saturation, PaO$_2$ partial pressure of oxygen, HCO$_3^-$ arterial bicarbonate, *pH* potential hydrogen, *RBC* red blood cells, *NLR* neutrophil to lymphocyte ratio, *LGI* leukocyte glucose index, *ROX* index respiratory rate oxygenation index, *PAFI* PaO$_2$/FiO$_2$, *SAFI* SaO$_2$/FiO$_2$, *CO-RADS* the COVID-19 Reporting and Data System.

Therefore, in this study, we analyzed the clinical data of 109 patients to evaluate the potential of LGI as a novel predictor of COVID-19 severity and compared its usefulness with previously reported biochemical and respiratory markers.

Results

Patient characteristics. A total of 109 patients with confirmed COVID-19 were enrolled in the present study, where were including 36 severe and 73 non-severe COVID-19 cases. Two patients were previously excluded from the analysis due to their elevated blood glucose levels. The mean (SD) age and body mass index (BMI) in patients diagnosed with severe infection were 56.5 (15.2) years and 26.7 (3.1) kg/m^2, respectively. Table 1 shows the baseline characteristics of all patients. There were no significant differences regarding age, weight, and BMI between severe and non-severe COVID-19 groups ($P_{corrected} = 1$).

Gender was statistically associated with COVID-19 severity ($P = 0.04$); however, it did not remain significant when multiple hypothesis correction was performed ($P_{corrected} = 1$). A similar effect was observed in hematocrit
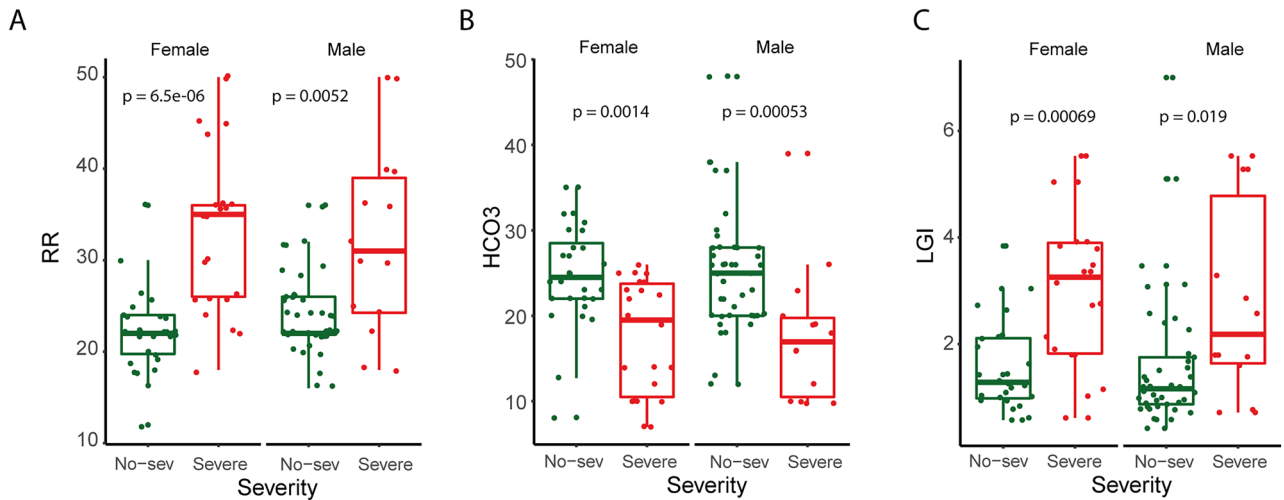
Figure 1. Clinical parameters associated with COVID-19 severity after adjusting gender. Box plot showing the difference of (**A**) RR, (**B**) HCO_3^-, and (**C**) LGI between non-severe and severe groups in female (left) and male (right) patients. Groups were compared using Mann U Whitney test, $P < 0.05$. RR: respiratory rate; HCO_3^-: arterial bicarbonate; LGI: leuko-glycemic index.

($P = 0.001$; $P_{corrected} = 0.05$), temperature ($P = 0.003$; $P_{corrected} = 0.1$), sodium ($P = 0.006$; $P_{corrected} = 0.3$), myalgia ($P = 0.01$; $P_{corrected} = 0.5$), and HR ($P = 0.03$; $P_{corrected} = 1$) (Supplementary Table S1online). The mean of days from onset of symptoms to hospital admission was seven days in both groups ($P_{corrected} = 1$). Regarding comorbidities, hypertension was the most frequent (57.8%), followed by diabetes (43.2%) in all the patients. There were no significant differences between the severe and non-severe groups regarding diabetes, CKD, hypertension, and COPD. The CO-RADS, a scoring system previously reported to be a predictor of COVID-19 severity, was showed a significant difference between both groups ($P_{corrected} < 0.001$). The leukocytes count, LGI, and FiO_2 were significantly higher in the severe group while the ROX index, RR, SpO_2, SAFI, PAFI, HCO_3^-, pH, SaO_2, and hemoglobin ($P_{corrected} < 0.05$) were significantly lower. Diarrhea and arthralgia were symptoms significantly associated with severity being present in roughly 30% of severe patients. Levels of glucose, NLR, PaO_2, neutrophils, RBC, and lymphocytes were found no significant between both groups, like other variables included in this study (Supplementary Table S1 online).

Since a significantly higher proportion of females with severe COVID-19 (61.11% vs. 38.36%, $P = 0.04$) was observed, we evaluated whether all 15 previous significant variables remained significant when data were adjusted by gender. In this regard, 12 variables remained significant in both male and female groups. Some of these variables, such as SAFI and PAFI, had been previously reported as predictors of severe COVID-19[19]. However, new variables such as RR, HCO3-, and LGI among others also were associated with the COVID-19 severity regardless the gender (Fig. 1A-C). Therefore, these results indicated that LGI was significantly higher in the severe group, independent of gender.

Identification of candidate predictors for severe COVID-19. According to the previous outcomes, the 15 statistically significant characteristics were selected to perform univariate logistic regression analysis in patients with COVID-19. As shown in Table 2, the univariate analysis revealed that all of them were significant with a $P < 0.001$ and $P_{corrected} < 0.05$. We found that the variables with the highest OR [95% CI] values were diarrhea (17.749, 4.440–119.459, $P_{corrected} < 0.005$), arthralgia (15.619, 3.862–105.574, $P_{corrected} = 0.009$), and CO-RADS (5.494, 2.513–14.189, $P_{corrected} = 0.001$). LGI showed an OR of 1.923 [1.421–2.719] which was higher than the ORs [95% CI] from ROX index (0.765 [0.677–0.843]), SAFI (0.988 [0.983–0.993]), RR (1.220 [1.132–1.335]), PAFI (0.991 [0.986–0.995]), leukocytes (1.323 [1.171–1.531]), and hemoglobin (0.734 [0.608–0.871]) among others (Table 2).

In order to evaluate the predictive value of the parameters involved in the COVID-19 severity, ROC curves analysis was performed. The AUC and the optimal cut-off values of each variable are shown in Table 3. ROX index showed the highest AUC of 0.863 (95% CI 0.791–0.935, $P < 0.000005$) with an optimal cut-off value of 9.09 (sensitivity, 0.833; specificity, 0.780) while SAFI had an AUC of 0.816 (95% CI 0.7280.904, $P < 0.000005$) and their optimal cut-off value was 235 mmHg (sensitivity, 0.805; specificity, 0.712). RR (AUC = 0.809 [95% CI 0.712–0.907]) and SpO_2 (AUC = 0.804 [95% CI 0.709–0.900]) also showed high values of AUC. PAFI, leukocytes, HCO_3^-, pH, and SaO_2 showed an AUC higher than 0.750. Moreover, LGI had an AUC of 0.749 (95% CI 0.642–0.857, $P = 0.00006$) and an optimal cut-off value of 1.764 (sensitivity, 0.777; specificity, 0.726).

Interestingly, we identified that these predictors of severity differed in female and male patients infected with SARS-CoV-2. In the male group, the leukocytes (OR 1.359, 95% CI 1.145–1.696, $P_{corrected} = 0.025$), ROX index (OR 0.816, 95% CI 0.700–0.919, $P_{corrected} < 0.05$), and hemoglobin (OR 0.610, 95% CI 0.439–0.796, $P_{corrected} = 0.013$) showing an AUC higher than 0.750. On the contrary, the best predictors of severe COVID-19 in the female group with an AUC higher than 0.750 were ROX index (OR 0.704, 95% CI 0.553–0.828, $P_{corrected} = 0.006$), SaO_2 (OR

| Predictors	OR [95% CI]	P value	Adjusted P value
Diarrhea	17.75 [4.440–119.459]	<0.001	**0.004**
Arthralgia	15.62 [3.862–105.574]	<0.001	**0.009**
CO-RADS	5.494 [2.513–14.189]	<0.0001	**0.001**
LGI	1.923 [1.421–2.719]	<0.0001	**0.001**
Leukocytes, $\times 10^9$/L	1.323 [1.171–1.531]	<0.0001	**0.0004**
RR, beats per minute	1.220 [1.132–1.335]	<0.0001	**<0.0001**
FiO_2, %	1.051 [1.024–1.084]	<0.001	**0.006**
PAFI, mmHg	0.991 [0.986–0.995]	0.0001	**0.001**
SAFI, mmHg	0.988 [0.983–0.993]	<0.0001	**<0.0001**
S_pO_2, %	0.9163 [0.876–0.950]	<0.0001	**<0.001**
SaO_2, %	0.9161 [0.877–0.949]	<0.0001	**0.0001**
HCO_3^-, mmol/L	0.847 [0.780–0.908]	<0.0001	**<0.001**
ROX index	0.765 [0.677–0.843]	<0.0001	**<0.0001**
Hemoglobin, g/dL	0.734 [0.608–0.871]	<0.001	**0.010**
pH	0.0000258 [0.000000872–0.002]	<0.0001	**<0.001**

Table 2. Risk factors associated with severity for COVID-19 patients. Univariable logistic regression analysis was performed using the 15 variables that had statistically significant difference when multiple hypothesis correction was performed ($P_{corrected} < 0.05$). Odds ratios (OR) and 95% Confidence Interval (CI 95%) are reported. Statistically significant *P* values (<0.05) are highlighted in bold. *CO-RADS* the COVID-19 Reporting and Data System, *LGI* leukocyte glucose index, *RR* respiratory rate, FiO_2 fraction of inspired oxygen, *PAFI* PaO_2/FiO_2, *SAFI* SaO_2/FiO_2, SaO_2 oxygen saturation, HCO_3^- arterial bicarbonate, *ROX* index respiratory rate oxygenation index.

Parameters	AUC	95% CI	P value	Optimal cut-off	Sensitivity	Specificity
ROX index	0,8632	79.129 to 93.510	**<0.0001**	9.0909	0.8333	0.7808
SAFI, mmHg	0.8165	72.823 to 90.494	**<0.0001**	235	0.8055	0.7123
RR, beats per minute	0.8099	71.241 to 90.745	**<0.0001**	30	0.6388	0.9041
S_pO_2, %	0.8049	70.976 to 90.020	**<0.0001**	89	0.7777	0.7671
PAFI, mmHg	0.7949	70.271 to 88.709	**0.0001**	202.5	0.8055	0.7260
Leukocytes, $\times 10^9$/L	0.7931	69.914 to 88.723	**<0.0001**	12	0.8055	0.7260
HCO_3^-, mmol/L	0.7838	69.136 to 87.636	**<0.0001**	19	0.5833	0.8767
pH	0.7821	68.351 to 88.078	**<0.0001**	7.33	0.7222	0.8219
SaO_2, %	0.7684	65.779 to 87.911	**<0.0001**	80	0.6944	0.7945
LGI	0.7498	64.202 to 85.759	**<0.0001**	1.764	0.7777	0.7260
Hemoglobin, g/dL	0.7258	62.214 to 82.952	**<0.001**	11.5	0.6944	0.7671
FiO_2	0.7045	60.545 to 80.360	**<0.001**	40	0.7777	0.5890

Table 3. Cut-off values of the risk factors for COVID-19 severity. Statistically significant *P* values (<0.05) are highlighted in bold. *RR* respiratory rate, SpO_2 peripheral oxygen saturation, HCO_3^- arterial bicarbonate, *pH* potential hydrogen, SaO_2 oxygen saturation, *LGI* leukocyte glucose index, FiO_2 fraction of inspired oxygen.

0.869, 95% CI 0.783–0.932, $P_{corrected} < 0.05$), RR (OR 1.297, 95% CI 1.143–1.561, $P_{corrected} = 0.011$), HCO_3^- (OR 0.838, 95% CI 0.735–0.926, $P_{corrected} < 0.05$), and LGI (OR 2.694, 95% CI 1.575–5.283, $P_{corrected} < 0.05$) (Supplementary Table S2online). This analysis showed that LGI could better distinguish severity in female than male patients with SARS-CoV-2 infection.

Since LGI was statistically significant between non-severe and severe groups, their predictor value was compared with other blood parameters (NLR, glucose, ROX index, leukocytes), previously reported as predictors of disease severity[6,10,20–22]. The AUC of LGI was higher than that for glucose and leukocytes, in contrast with the ROX index and NLR (Fig. 2A). Although, diabetes was not related to COVID-19 severity ($P = 0.41$) (Table 1), LGI was statistically higher in the severe group of patients with diabetes ($P < 0.0001$) while no significance was found in patients without diabetes ($P = 0.13$) (Fig. 2B). To further explore the usefulness of LGI, a ROC analysis for LGI and other blood parameters was performed in patients with diabetes. The results obtained demonstrated that LGI had an AUC higher than when all patients were considered. The AUC of LGI was 0.915 (95% CI 0.830–1, [sensitivity, 0.833; specificity, 0.931]) being higher than for the AUC of NLR (0.832), glucose (0.816), and leukocytes (0.858) and almost equal to the ROX index (0.925) (Fig. 2C). Although the optimal cut-off of LGI was different between the patients with diabetes alone (3.15) and all patients (1.764), the cut-off points for
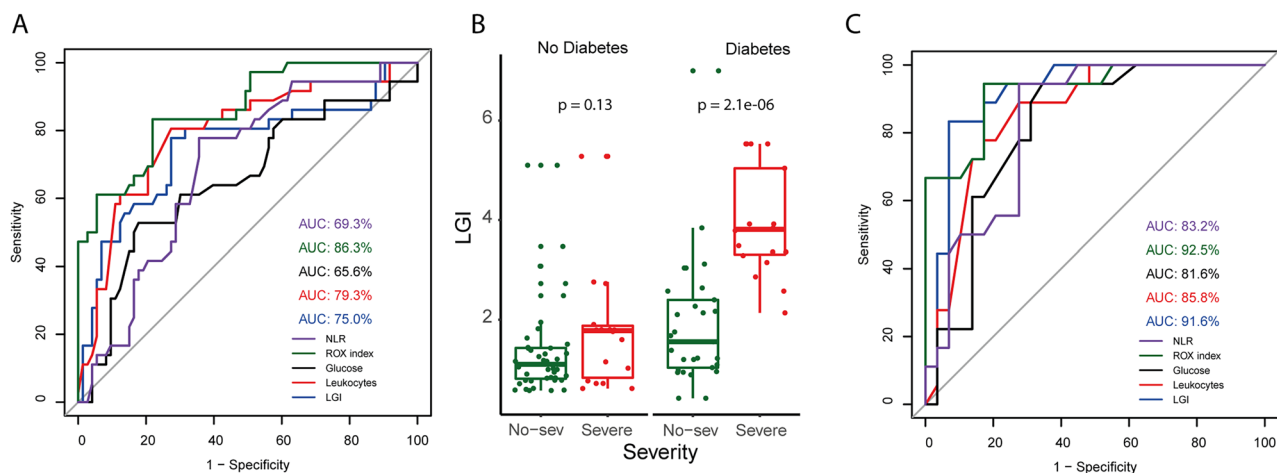
Figure 2. ROC analysis and LGI levels in diabetic patients with severe COVID-19. Comparison of ROC curve of NLR, ROX index, glucose, leukocytes, and LGI for predicting severe COVID-19 in all patients (**A**) or patients with diabetes (**C**). LGI levels in patients with non-severe or severe COVID-19 after adjusting the data for diabetes (**B**). The AUC of NLR, ROX index, glucose, leukocytes, and LGI were represented with purple, green, black, red, and blue lines, respectively. AUC: Area under the curve; NLR: neutrophil to lymphocyte ratio; LGI: leuko-glycemic index.

Predictor	OR [95% CI]	*P* value
Hemoglobin	0.505 [0.315—0.713]	**<0.001**
HCO$_3^-$	0.862 [0,741—0.969]	**0.026**
FiO$_2$	1.070 [1.010—1.150]	**0.034**
LGI	1.727 [1.026—3.048]	**0.041**
RR	1.165 [1.014—1.376]	**0.044**
SaO$_2$	0.940 [0.861—1.012]	0.125
CO-RADS	2.825 [0.828—12.736]	0.126
SpO$_2$	0.957 [0.898—1.010]	0.133

Table 4. Independent predictors for COVID-19 severity. Candidate predictors with statistically significant difference ($P < 0.05$) in univariate logistic analysis were included a multivariable logistic regression. Odds ratios (OR) and 95% Confidence Interval (CI 95%) are reported. Statistically significant *P* values (< 0.05) are highlighted in bold. HCO$_3^-$: arterial bicarbonate; FiO$_2$: fraction of inspired oxygen; LGI: leukocyte glucose index; RR: respiratory rate; SaO$_2$: oxygen saturation; CO-RADS: the COVID-19 Reporting and Data System; SpO$_2$: peripherical oxygen saturation.

ROX index, RR, leukocytes, pH, and FiO$_2$ were the same in both groups. (Supplementary Table S3 online). This finding suggested that LGI is a strong predictor of COVID-19 severity in diabetes patients.

LGI as a strong predictor of the COVID-19 severity.   A multivariate logistic regression with step-wise procedure was performed to determine the predictors of COVID-19 severity, considering all 15 variables with statistically significant difference ($P < 0.05$), obtained from the univariate analysis. Interestingly, the LGI remained significant together with other 4 variables (Table 4). Results showed that LGI was independent risk factor for severe COVID-19 with a OR value of 1.727 (95% CI 1.026–3.048; $P = 0.041$). Other risk factors for severe infection included RR (OR = 1.165; 95% CI 1.014–1.376; $P = 0.044$), FiO$_2$ (OR = 1.070; 95% CI 1.010–1.150; $P = 0.034$), HCO$_3^-$ (OR = 0.862; 95% CI 0.741–0.969; $P = 0.026$), and hemoglobin (OR = 0.505; 95% CI 0.315–0.713; $P = 0.0007$) (Table 4).

The addition of RR and SaO2 to LGI improved the predictive value for severe COVID-19.   In other to determine the utility of RR and SaO$_2$ in addition to LGI for the prediction of COVID-19 patients at high risk of progression to severe disease, a ROC curve analysis was performed (Fig. 3). The model including RR and LGI improved the predictive performance for COVID-19 severity showing an AUC of 0.894 [95% CI 0.835–0.958]. This AUC was higher compared to the ROX index (AUC = 0.863, 95% CI 0.791–0.935). The inclusion of SaO$_2$ with LGI showed an AUC of 0.855 [95% CI 0.769–0.941]; however, it was lower compared to the AUC of the ROX index. Finally, the AUC of RR and SaO$_2$, in addition to LGI, resulted in a considerable improvement of the predictive performance (AUC = 0.903, 95% CI 0.847–0.958) compared to LGI alone (AUC = 0.749) and ROX index (Fig. 3).
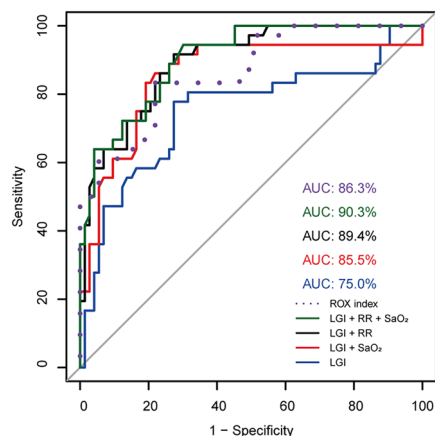
Figure 3. ROC analysis of LGI associated with other biomarkers AUC comparison of ROX index (dashed line), LGI (blue line), RR in combination with LGI (black line), SaO$_2$ in combination with LGI (red line), and the combination of SaO$_2$, RR, and LGI (green line). AUC: Area under the curve; LGI: leuko-glycemic index; RR: respiratory rate; SaO$_2$: oxygen saturation.

Discussion

The current study proposes a novel factor to predict severity of patients with COVID-19. High levels of leukocytes and glucose have been associated with inflammatory response, acute myocardial infarction, and pneumonia in acute ischemic stroke[16–18]. The SARS-CoV-2 infection produces an aggressive inflammatory response strongly implicated in pneumonia and multi-organ damage leading to organ failure, especially in the cardiac and nervous systems[14,23]. The LGI, which considers leukocytes count and blood glucose level, has been shown to have a predictive value in coronary artery disease, a pathology associated with an increased risk of several clinical complications in COVID-19 patients[15,24]. Hence, this study explored the usefulness of LGI in the prediction of severe COVID-19.

We found a significantly higher proportion of females with severe COVID-19. After the multiple hypothesis correction, the gender was not significantly different between the severe and non-severe groups. This observation could be due to the relatively small sample size. A multiple hypothesis testing correction is recommended to avoid false positives when multiple variables are analyzed. For example, a previous study used the Benjamini–Hochberg procedure as they analyzed several biomarkers[4]. We applied the Bonferroni correction, a more stringent procedure, to discard the slightly significant variables. Moreover, a clear explanation that men have a higher risk of severe COVID-19 than women has not been established yet[25]. Biological and immunological pathways, socio-behavioral, and cultural aspects could be involved in COVID-19 severity in a sex-dependent manner[26].

The results showed that the most common symptoms found were the same as reported previously[27], including arthralgia and diarrhea. Comorbidities such as diabetes were not associated with the COVID-19 severity, agreeing with a previous multi-center study[28]. Although symptoms such as diarrhea and arthralgia, and CO-RADS were three main predictors for admission (univariate analysis), they could not prove to be effective severity indicators. The ROX index showed that highest AUC (0.863); however, leukocytes, LGI, RR, FiO2, FAPI, SAFI, SaO2, HCO3, ROX index, and hemoglobin were also candidates to predict COVID-19 severity. A retrospective study reported the potential predictive value of ROX index for deterioration in 186 patients with COVID-19 (AUC = 0.848)[10]. Even though the ROX index is a simple model based solely on three respiratory parameters ([SpO2/FiO2]/RR)[10] and LGI can be easily calculated with two biochemical parameters, our results suggests that both parameters are good predictors. The ROX index had greater predictive validity than LGI (AUC = 0.749); however, the multivariate analysis revealed that the ROX index was not an independent factor that aided in predicting the disease severity. This could probably be because the other variables considered in the multivariate analysis were sufficient to predict the COVID-19 severity and the ROX index was not adding significative information. This suggests that ROX index is a good sole predictor, but a pair of biomarkers could have a better performance as shown in the case of LGI + RR (Fig. 3). In contrast, RR, FiO2, hemoglobin, HCO3-, and LGI remained after the stepwise procedure indicating that they are independent predictors of severe disease conditions. RR and FiO$_2$ (involved in calculating ROX index), hemoglobin, and HCO$_3^-$ have been reported to be associated with COVID-19 severity[10,29,30]. Nevertheless, the OR for the LGI was higher than the other parameters when were considered all (1.727, 95% IC 1.026–3.048) or only female patients (2.694, 95% IC 1.575–5.283). As an independent risk factor, LGI had the highest AUC of 0.915 (95% IC 0.830–1), with a sensitivity of 0.833 and a specificity of 0.931, in patients with diabetes. This result may be due to the blood glucose levels correlate with clinical outcomes in patients with COVID-19 and pre-existing diabetes[13,20]. Furthermore, high glucose levels in monocytes directly promote cytokine production, viral replication, subsequent T cell dysfunction, and lung epithelial cell death[31]. Leukocytes $> 5.37 \times 10^9$/L count has been associated with a higher risk of death and shorter survival time in patients with COVID-19 and diabetes[12]. Thus, the link between blood glucose levels and leukocytes counts in the COVID-19 severity suggests that LGI should be analyzed as a new predictor. Interestingly, the LGI showed to be an excellent predictor for COVID-19 severity in patients with diabetes, being higher than the AUC of D-dimer (0.909) for mortality risk[32]. The optimal LGI cut-off for severe COVID-19 was 1.764 in all patients, while in

patients with this condition and diabetes was 3.15. This cutoff was similar to a previous study that reported an optimal cut-off of 2 for LGI in postoperative coronary artery bypass grafting[15]; indicating that high levels of LGI are associated with different diseases. Due to the predominant respiratory features of COVID-19 and that RR is a physiological variable associated with a significant increase in the odds ratio for the ROX index[10], we analyzed the combined effect of RR and LGI (LGI + RR) in predicting for severity. The AUC of LGI + RR (0.894) was higher compared with the combined effect observed in other studies such as the combination of (a) procalcitonin (PCT), CRP and NLR (AUC = 0.84)[33]; (b) NLR, platelet count and CRP (AUC = 0.774)[6]; and (c) CD4+ T cell count, NLR, and D-dimer (AUC = 0.865)[34]. Therefore, LGI + RR showed to be a strong predictor and its easy implementation makes it a valuable marker.

Until now, there has been a paucity of research that has combined respiratory and biochemical parameters to find a strong predictor of COVID-19, particularly in the severity The models from Zhou, King, Ji, Haimovich, and Altschul, with AUC of 0.862, 0.79, 0.91, 0.89, and 0.798, respectively, have also been suggested to predict the COVID-19 outcome[35–39]. Nevertheless, their candidate predictors require a complicated composite of patient-related risk factors, which makes challenging to operationalize. Moreover, machine learning-based predictors are not straightforward to be widely implemented[40,41]. The predictive model from Patel et al. was performed considering only 5 of 72 variables for predicting intensive care unit (ICU) need (CRP, D-dimer, PCT, SpO$_2$, and RR), obtaining an AUC of 0.79[40]. In contrast, the Cheng et al. model identified 20 predictive variables to ICU transfer in hospitalized COVID-19 patients[41]. These variables were related to progressive respiratory failure (RR and SaO$_2$), markers of systemic inflammation (leukocytes count and CRP), among others, resulting in an AUC of 0.799[41]. RR was a significant variable[40] and had the highest predictive value, followed by leukocytes[41]. Hence, these findings confirm the usefulness of leukocytes and RR in predicting COVID-19 severity, supporting the result obtained here, where the predictive value of LGI increased when the effect of RR and LGI were combined, LGI + RR.

The severe COVID-19 is associated with an uncontrolled inflammatory response[42]. In this sense, the NLR, blood urea nitrogen/creatinine ratio, and platelet-lymphocyte ratio (PLR) are reliable indicators of the COVID-19 severity[6,8,43]. Nevertheless, we not find any positive association between these parameters and severe COVID-19. Regarding the NLR, a most recent study conducted in 76 patients with COVID-19 revealed that this biochemical parameter (NLR ≥ 3.59) was not an independent risk factor for death[33]. Xu et al. study may suggest why our finding did not show a positive correlation between NLR and severe disease. Lymphocyte, neutrophil, and platelet counts, used to calculate NLR and PLR, are part of the system immune-inflammation index (SII), a good index to reflect the immune response and systemic inflammation[44]. However, these parameters were also not associated with the COVID-19 severity in this study. NLR is an independent risk factor for severe disease or mortality, with an AUC of 0.737 (Shang et al.), 0.69 (Xu et al.), and 0.87 (Ok et al.)[6,8,33]. Thus, a simple index as LGI (two biochemical parameters: blood leukocytes and glucose) in combination with RR (respiratory parameter), LGI + RR (AUC = 0.894) can outperform inflammatory biomarkers in predicting the severe COVID-19. Glucose is the primary energy source, and its homeostasis is maintained by pancreatic β cells through insulin secretion. A recent study demonstrated that the β-cells were permissive to SARS-CoV-2 infection and replication, affecting glucose responsiveness[45]. Furthermore, high glucose highly induces viral replication and cytokine production during SARS-CoV-2 infection. Therefore, targeting glucose metabolism may offer a new practical antiviral approach[31,46]. Other molecules such as HDL-cholesterol and triglycerides, low and high concentrations, respectively, are strong predictors of a severe course of the COVID-19[47]. Since the host-inflammatory response and the regulation of metabolism are intimately connected with the COVID-19 severity, LGI (blood leukocytes count and glucose levels) appears to be a potent risk biomarker.

This study has limitations: (1) the study had a retrospective design and was conducted at a single center; (2) the sample size was small, which may affect the generalization of the results due to the limitation of enrolled patients. Although this study included a small sample, the results could be compared to other studies, with a similar number of patients, performed to determine clinical predictors for COVID-19 outcomes[9,33,34]. Nevertheless, the results of this study should be validated with additional studies or future efforts focused on the prospective analyses to strengthen our understanding of the predictive utility of LGI and LGI + RR. Other limitations are: (3) Since pharmacological therapies implemented during the hospitalization may affect the biochemical and respiratory parameters, the laboratory and clinical findings on the day of admission were selected to minimize the adverse impact of subsequent treatments; and (4) The respiratory and biochemical factors were not monitored regularly, thus, could not longitudinally evaluated the association between the dynamic changes of the factors and the severity during the disease course.

On the other hand, the current study had some strengths points. First, the evidence obtained on LGI as a biomarker for COVID-19 severity. Second, this study considered patients from Mexico, while other studies are based on cases from different countries, which is relevant since the outcomes for COVID-19 are known to be dependent on demographics[40].

In conclusion, we demonstrate that values of just two or three features, namely, leukocytes, glucose, and RR, can predict the severe disease accurately obtained from all 51 variables included in this study. LGI and LGI + RR could serve as independent risk factors for predicting the COVID-19 severity and as an objective tool to support clinicians in their decision. These findings need to be further validated in a larger population of multi-center study.

Methods

Study design and participants.
We conducted a retrospective observational study at a third level reference hospital (Unidad Médica de Alta Especialidad (UMAE), Hospital de Especialidades No. 14, Centro Médico Nacional (CMN) "Adolfo Ruiz Cortines", Mexican Social Security Institute (IMSS)) from Veracruz, Mexico. A

total of 109 COVID-19 patients with a positive nucleic acid test for SARS-CoV-2 from April to July 2020 were included. The clinical sample collection, processing, and COVID-19 testing for all patients were based on WHO guidelines[48].

The COVID-19 patients who met any of the following criteria were excluded from the study: (1) pregnancy patients; (2) patients ages ≤ 18 years; (3) patients having severe medical conditions, including chronic renal dysfunction, malignant tumor, acquired immune deficiency syndrome, and liver cirrhosis; (4) patients with elevated blood glucose levels (> 600 mg/dL)[49]; and (5) patients with essential information deficits. Given the retrospective nature of the research, the Research Ethical Committee of the UMAE, Hospital de Especialidades No. 14, CMN "Adolfo Ruiz Cortines" from Mexican Social Security Institute (Registry code: CONBIOÉTICA-30-CEI-003–20,180,412; COFEPRIS 17CI30193067) approved the wavier for informed consent.

Disease severity was defined according to "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia, issued by the Chinese Centers for Disease Control and Prevention[50]. Patients with a confirmed diagnosis of COVID-19 were classified into four types: (1) mild, patients with slight clinical symptoms and no imaging finding of pneumonia; (2) moderate, patients with fever and respiratory symptoms, and signs of pneumonia on radiologic assessment; (3) severe, patients met any of the following criteria (a. shortness of breath, RR ≥ 30 times/min; b. oxygen saturation ≤ 93% at rest; and c. partial pressure of oxygen (PaO_2)/fraction of inspired oxygen ($PaO_2/FiO_2 ≤ 300$ mmHg); d. pulmonary imaging showing the significant progression of lesion > 50% within 24 to 48 h); and (4) critical, patients showing any of the following conditions (respiratory failure requires mechanical ventilation, shock, combined with other organ failure requires intensive care and treatment. For further analysis in this study, the patients were grouped as "non-severe" (classified as mild or moderate type) and "severe" (classified as severe or critical type) according to other reports where some factors were used to predict severe COVID-19[34,51].

Data collection. All data from the patients meeting the inclusion criteria were abstracted from the electronic medical records. Clinical parameters included age, sex, comorbidities, signs and symptoms, laboratory results, and vital signs were collected on admission.

Definitions. All the biochemical parameters were determined at the hospital admission of the patients. The leukocyte glucose index (LGI) is defined as the product between blood leukocytes counts and glucose levels divided by 1000[15–18]. NLR was calculated by dividing the total absolute neutrophil counts over total lymphocyte counts[33]. PAFI was obtained as the ratio between partial pressure of oxygen (PaO_2) and the fraction of inspired oxygen (FiO_2)[19,52]. SAFI was determined as the ratio between the oxygen saturation (SaO_2) and the FiO_2[19,52]. The respiratory rate oxygenation (ROX) index was calculated using the following formula: ROX index = (SaO_2/FiO_2)/respiratory rate (RR)[53]. The COVID-19 Reporting and Data System (CO-RADS) is a categorical assessment scheme that includes a five-point scale for chest computed tomography in patients suspected of having COVID-19[54].

Statistical analysis. The data are presented as the mean ± standard deviations (SD) or numbers and frequencies (%). The Shapiro–Wilk test was used to evaluate the normality assumption of quantitative variables. We considered the standardized normal probability plots to analyze the dispersion and assess non-normality. The Chi-square test was performed to evaluate associations between categorical variables. Mann-Whiney U test and Kruskal–Wallis test were used to compare numerical variables between groups. Spearman's rank correlation test was used to determine the correlations between continuous variables. Univariate and multivariate logistic regression analyses were performed to determine the variables affecting the severity of COVID-19. For multivariate logistic regression, a step-wise method was considered. The Odds Ratios (OR) were estimated with 95%CI. Receiver Operator Characteristic (ROC) curves were performed to evaluate and compare the Area Under the Curve (AUC) of LGI and other relevant variables associated with COVID-19 severity (adjusted $P < 0.05$). A predictor with an AUC above 0.7 was considered valuable, whereas an AUC between 0.8 and 0.9 indicated good diagnostic accuracy.

Logistic regression models were used to generate receiver operative curves for the variables of LGI, LGI + RR, LGI + SaO2, and LGI + RR + SaO2. We defined statistical significance as $P < 0.05$. P values were adjusted using the Bonferroni corrections ($P_{corrected}$) to compensate the effect of multiple hypothesis testing. The variables were filtered using 0.05 as a significance cut-off[55]. The optimal cut-off points were determined considering the Youden index by showing the trade-off between sensitivity and specificity. All statistical analyses were performed with R v4.03 statistical software (R Foundation, Vienna, Austria).

Ethics approval

Data availability

The datasets generated and analyzed during the study are available from the corresponding author upon reasonable request.

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Author contributions

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Competing interests

The authors declare no competing interests.

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