INTRODUCTION

The SARS-CoV-2 virus produces COVID-19, which in 15% of cases progresses to severe forms with a mortality rate of 3%-10%.¹ This disease is associated with significant inflammation in different systems with the influx of neutrophils to the lungs and the sustained release of anti-inflammatory cytokines that lead to lymphopenia which seems to be related to mortality.²

In the attempt to provide a prognostic indicator of evolution, the neutrophil/lymphocyte ratio (NLR)³,⁴ has been proposed, which is a marker of inflammation which predicts the severity and mortality due to disease at admission to hospital.⁵–⁷ It has also
been suggested that it can predict endothelial damage associated with inflammation.⁸

In studies that have evaluated the NLR, it has been found that in survivors this ratio was less than 1.95 (1.43–2.58) while in those who died it was greater than 13.87 (7.50–24.82); similarly, in those with severe and non-severe disease it was 6.88 (3.54–11.18) and 2.21 (1.51–9.85), respectively.⁷ In patients with severe COVID-19, the NLR was higher than in those with mild to moderate disease (6.29 vs 2.33), as were D-dimer levels (315 vs 190 g/L).¹⁰ Similarly, in another study, the NLR values between the group with severe and mild COVID-19 were 6.6 and 3.3 respectively.¹¹ Lymphopenia with consequent elevation of NLR was the most consistent alteration in blood count in patients with COVID-19.¹²

In addition, a meta-analysis, a higher NLR was found in patients with severe COVID-19 than in those with non-severe disease (standard mean difference [SMD] 2.80, 95% confidence interval [CI] 2.12–3.48, \( P < 0.00001 \)) and the NLR was higher in those who did not survive (SMD 3.72, 95% CI 0.53–6.90, \( P = 0.02 \)).¹³

There was also a significant difference when comparing the NLR in general patients and those with severe pneumonia (2.88 [1.77–5.55] vs 8.78 [5.76–25.10], \( P < 0.001 \)) and it has been reported that a NLR of 11.75 was associated with a 44-fold increase in death risk.¹⁴ In another study comparing patients with COVID-19 who were discharged from hospital with those who remained, the NLR was discrete but significantly higher in the former, with the authors suggesting that an appropriate inflammatory process is necessary to get rid of the infection.¹⁵

In one study, the sensitivity of the NLR to predict severity has been reported to be 81% (95% CI 58–95) with specificity of 67% (95% CI 58–66), negative predictive value (NPV) of 95%, and positive predictive value (PPV) of 32% (95% CI 20–46),¹⁶ whilst another study has mentioned a sensitivity of 38% and a specificity of 97%.¹⁷

The NLR can be modified by the time that has elapsed since onset of symptoms and the collection of the blood sample.¹⁸

Regarding the platelet/lymphocyte ratio (PLR), the reports are contradictory since in one study it failed to predict mortality,¹⁹,²⁰; however, in another study with a larger sample number it could predict it.²¹ Thus the objective of the present work was to determine the differences in the NLR and PLR in pregnant women with and without COVID-19.

2 MATERIALS AND METHODS

This was an observational, cross-sectional, retrospective, comparative, open, controlled study from January to April 2021 at the UMAE Hospital de Gineco Obstetricia “Luis Castelazo Ayala” Instituto Mexicano del Seguro Social, Mexico City, Mexico, in which two groups of pregnant women were initially studied, those with a negative test for COVID-19 and those with a positive test. Subsequently, the group with a positive test was divided according to the severity of the disease, resulting in a total of four groups: Group 1 negative test for COVID-19, Group 2 with positive test and mild disease, Group 3 with positive test and moderate disease, and Group 4 with positive test and severe disease. Postpartum women were not included. The protocol was authorized by the Ethics in Research Committee and the Local Research in Health Committee with registration number R-2021-3606-022 and the patients signed an informed consent form.

COVID-19 disease was defined as mild when signs and symptoms were present without dyspnea or abnormal images on chest x-radiography, moderate when lower respiratory tract disease was present by clinical and/or radiological evaluation, with oxygen saturation greater than 90%, temperature 38°C, respiratory frequency greater than 22 and less than 30 breaths per minute, normal blood pressure, requiring oxygen therapy through nasal tips, and severe when disease in the lower respiratory tract was present, with respiratory frequency greater than 30 breaths per minute, oxygen saturation less than 93% with the need for non-mechanical ventilation.

A history of diabetes, chronic hypertension, asthma, smoking, lung disease, heart disease, nephropathy, and immunodeficiency secondary to HIV were investigated in all patients and if they were present those patients were not included in the study.

Age (years), weight (kg), height (m), and body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) were documented for each patient. The number of pregnancies, deliveries, abortions, and cesarean deliveries as well as gestational age in the current pregnancy were investigated. Also, the presence of cough, headache, dyspnea, myalgia, arthralgia, odynophagia, nasal constipation and/or rhinorrhea, conjunctivitis, chest pain, and anosmia were investigated.

From the blood count, the total number of leukocytes, neutrophils, lymphocytes, and platelets were compiled, and the NLR (total number of neutrophils/total number of lymphocytes) and PLR (total number of platelets/total number of lymphocytes) were calculated.

For statistical analysis, SPSS version 20 (IBM) was used. Central tendency and dispersion measures (median, minimum, and maximum), frequencies, and percentages were used. For the comparisons between the groups of the continuous variables, the Kruskal-Wallis test was used. To determine the differences between each one of the groups Mann-Whitney \( U \) test was used and for the nominal ones, contrast of proportions (chi-squared test) was used. A \( P \) value less than 0.05 was considered statistically significant. To define the cutoff point, the receiver operating characteristic curve was used to calculate the area under the NLR and PLR curves. Sensitivity, specificity, PPV, NPV, and odds ratio (OR) were calculated.

The sample size was calculated using Medcalc version 18.5. An \( \alpha \) error of 0.01, a \( \beta \) error of 0.1, were considered with a mean difference of 364, a standard deviation in group 1 of 97 and of 523
in group 2 with a 1 to 2 relationship, so 18 and 36 patients were needed for group 1 and 2 respectively.

3 | RESULTS

Seventy-seven patients were studied, 24 with a negative test for COVID-19 and 53 with a positive test, with the latter group later being subdivided according to the severity of the disease, resulting in four final groups as follows: Group 1 negative test for COVID-19 (n = 24), Group 2 (n = 33) with positive test and mild disease, Group 3 positive test and moderate disease (n = 10) and Group 4 positive test and severe disease (n = 10).

When comparing healthy (COVID-19 negative) and COVID-19 positive women, no statistically significant differences between the groups were found in weight, height, and BMI, nor in the number of pregnancies, births, abortions, and cesarean deliveries.

Fever (0 vs 20.8%, P < 0.014), cough (37.5% vs 79.2%, P < 0.001), myalgias (25% vs 58.5%, P < 0.008), rhinorrhea (37.5% vs 66%, P < 0.026), chest pain (4.2% vs 41.5%, P < 0.001), and anosmia (8.3% vs 50.9%, P < 0.001) presented in a higher proportion in those with COVID-19 (Table 1). The median of heart rate was significantly lower in the group of women without COVID-19 (87 (65–150) vs 101 (70–151), P < 0.004, and oxygen saturation was higher in this same group 96 (88–98) vs 95 (45–98) P < 0.004.

Leukocyte, lymphocyte, and neutrophil counts were significantly higher in healthy patients, while the PLR was higher in the group with COVID-19 (Table 2).

When comparing healthy patients and the groups with different degrees of severity due to COVID, no statistically significant difference was found between the groups in age, number of pregnancies, and gestational age (Table 3).

Temperature, heart rate, and respiratory rate were significantly higher with greater severity of the disease and oxygen saturation was significantly lower with greater severity (Table 4).

Fever, cough, dyspnea, rhinorrhea, chest pain and anosmia were significantly different between groups, with a higher proportion of patients presenting with greater severity of the disease (Table 5).

In the hematological parameters, a statistically significant difference was found between the groups in the number of leukocytes, lymphocytes, neutrophils, platelets, PLR, and D-dimer. The number of neutrophils and lymphocytes was significantly higher in the healthy women group. The NLR was not different between the groups and the PLR was significantly higher in the group with severe disease (Table 6).

The proportion of patients with fever and elevated PLR (cutoff point 221) was 72% versus 35.7% (P < 0.013).

When analyzing healthy and sick patients without dividing by degree of severity and considering an NLR with a value of 5.1, the sensitivity was 38%, the specificity 63%, PPV 69%, and NPV 31% (OR 1.01, 95% CI 95 0.37–2.73), and with a PLR of 221 the sensitivity was 47%, specificity 83%, PPV 86%, and NPV 42% (OR 4.46, 95% CI 1.34–14.80) (Table 7).

With the NLR with cutoff point 5.1 and in the group with severe disease, sensitivity of 70%, specificity 63%, PPV 44%, and NPV 83% were found (OR 3.89, 95% CI 0.80–19.0). With the PLR with a cutoff point of 221 and in the group with severe disease, the sensitivity was

### Table 1: Symptom presentation by group among healthy pregnant women and pregnant women with COVID-19

| Symptom                  | Healthy (n = 24) | COVID-19 (n = 53) | P value |
|--------------------------|-----------------|-------------------|---------|
| Fever                    | 0               | 11 (20.8)         | 0.014   |
| Cough                    | 9 (37.5)        | 42 (79.2)         | 0.001   |
| Headache                 | 13 (54.2)       | 27 (50.9)         | 0.811   |
| Dyspnea                  | 5 (20.8)        | 18 (34.0)         | 0.292   |
| Myalgia                  | 6 (25.0)        | 31 (58.5)         | 0.008   |
| Arthralgias              | 4 (16.7)        | 21 (39.6)         | 0.066   |
| Odynophagia              | 9 (37.5)        | 25 (47.2)         | 0.467   |
| Rhinorrhea               | 9 (37.5)        | 35 (66.0)         | 0.026   |
| Conjunctivitis           | 0               | 2 (3.8)           | 0.337   |
| Chest pain               | 1 (4.2)         | 22 (41.5)         | 0.001   |
| Diarrhea                 | 7 (29.2)        | 10 (18.9)         | 0.377   |
| Anosmia                  | 2 (8.3)         | 27 (50.9)         | 0.001   |

Values are given as number (percentage) of patients. Analysis by χ² test.

### Table 2: Laboratory tests in healthy pregnant women and pregnant women with COVID-19

| Parameter                | Healthy (n = 24) | COVID-19 (n = 53) | P value |
|--------------------------|-----------------|-------------------|---------|
| Leukocytes per mm³       | 9255 (4120–19290) | 7000 (3600–15800) | 0.006   |
| Lymphocytes per mm³      | 1525 (213–3410)  | 1030 (112–2530)   | 0.004   |
| Neutrophils per mm³      | 6495 (2440–16920) | 4790 (270–9640)    | 0.005   |
| Platelets per μL         | 247 500 (35 000–386 000) | 222 000 (132 000–645 000) | NS     |
| NLR                      | 3.95 (1.5–22.5)  | 3.92 (0.3–56.6)   | NS      |
| PLR                      | 166.25 (23.6–638.5) | 215.5 (79.8–2053.6) | 0.016   |
| Fibrinogen (mg/dl)       | 656 (459–930)    | 658.5 (192–921)   | NS      |
| D-dimer (ng/ml)          | 450 (74–949)     | 606.5 (197–1935)  | NS      |

Abbreviations: NLR, neutrophil/lymphocyte ratio; NS, not significant; PLR, platelet/lymphocyte ratio. Values are given as median (minimum and maximum). Analysis by Mann-Whitney U test.
90%, specificity 83%, PPV 69% and NPV 95%, OR 45 (4.40–461.7) (Table 8).

4 | DISCUSSION

In the present study, pregnant women with COVID-19 were studied and NLR and PLR were analyzed. In this study, fever, cough, dyspnea, rhinorrhea, chest pain, and anosmia were more frequent with greater severity of the disease, similar to that reported in a study in a nonpregnant population in which the patients who worsened were those who upon admission had fever, chills, myalgia, and dyspnea.22 As has already been reported, the heart and respiratory rates are higher and oxygen saturation was lower in patients with COVID.21 When comparing between healthy women and all the COVID-19 positive women, a significant difference was found between the groups in leukocytes, lymphocytes, neutrophils, and PLR. Likewise, greater lymphopenia was found with greater severity of COVID-19, as has already been described in the nonpregnant population.23 The NLR was not different between the four groups and the PLR was significantly higher in the group with severe disease.20 Regarding D-dimer, significant differences were found between healthy women and those with moderate and severe disease, between those with mild and moderate disease, and between those
with mild and severe disease, which is consistent with reports in the literature indicating that the D-dimer rises as severity does.24

The proportion of patients with fever and elevated PLR was 72%; this association may be useful in the diagnosis of patients.

Regarding the NLR, it was found that a value of 2.65 had a sensitivity of 79% but a specificity of 25%, while with 5.1 the sensitivity was 38% and the specificity 63%, which is similar to other studies in terms of sensitivity.17

The PLR with a value of 193.5 had a sensitivity of 60% and a specificity of 67%, and when it was 221, the sensitivity was 47% and the specificity of 83%. The OR for NLR and severe disease with a cutoff point of 5.1 was 3.89 and for the PLR at a cutoff point of 221 was 45.

It is worth mentioning that the ideal cutoff points for NLR and PLR have not been defined.25 The weakness of this study is that there were not enough cases with severe disease; moreover, since fortunately there were no deaths, the usefulness of these ratios to predict mortality could not be calculated.

Therefore, it is possible to conclude that the PLR more than the NLR is useful to detect pregnant patients with COVID-19 who have severe disease, but further studies are needed to confirm these results.

### TABLE 5 Symptom presentation by group in healthy and COVID-19 patients according to the severity of the disease

| Symptom          | Healthy (n = 24) | Mild (n = 33) | Moderate (n = 10) | Severe (n = 10) | P value |
|------------------|-----------------|--------------|------------------|----------------|---------|
| Fever            | 0 (0)           | 1 (3)        | 5 (50)           | 5 (50)         | 0.001   |
| Cough            | 9 (37.5)        | 25 (75.8)    | 8 (80)           | 9 (90)         | 0.004   |
| Headache         | 13 (54.2)       | 20 (60.6)    | 3 (30)           | 4 (40)         | 0.316   |
| Dyspnea          | 5 (20.8)        | 9 (27.3)     | 2 (20)           | 7 (70)         | 0.027   |
| Myalgia          | 6 (25.0)        | 20 (60.6)    | 5 (50)           | 6 (60)         | 0.051   |
| Arthralgias      | 4 (16.7)        | 12 (36.4)    | 5 (50)           | 4 (40)         | 0.202   |
| Odynophagia      | 9 (37.5)        | 13 (39.4)    | 7 (70)           | 5 (50)         | 0.310   |
| Rhinorrhea       | 9 (37.5)        | 26 (78.8)    | 4 (40)           | 5 (50)         | 0.009   |
| Conjunctivitis   | 0 (0)           | 0 (0)        | 1 (10)           | 1 (10)         | 0.119   |
| Chest pain       | 1 (4.2)         | 11 (33.3)    | 6 (60)           | 5 (50)         | 0.003   |
| Diarrhea         | 7 (29.2)        | 6 (18.2)     | 1 (10)           | 3 (30)         | 0.531   |
| Anosmia          | 2 (8.3)         | 15 (45.5)    | 7 (70)           | 5 (50)         | 0.002   |

Values are given as number (percentage) of patients. Analysis by Pearson chi square.

### TABLE 6 Laboratory tests in healthy pregnant women and pregnant women with three severity stages of COVID-19 disease

| Test                          | Healthy (n = 24) | Mild (n = 33) | Moderate (n = 10) | Severe (n = 10) | P value |
|-------------------------------|-----------------|--------------|------------------|----------------|---------|
| Leukocytes per mm$^3$         | 9255 (4120–19 290)$^{a,c}$ | 6300 (4010–12 160)$^a$ | 6605 (3600–11 600)$^c$ | 8230 (4160–15 800) | 0.016   |
| Lymphocytes per mm$^3$        | 1525 (213–3410)$^{d}$ | 1350 (600–2530)$^{m,p}$ | 855 (370–1200)$^{m,z}$ | 568.5 (112–1120)$^{p,t}$ | 0.001   |
| Neutrophils per mm$^3$        | 6495 (2440–16 920)$^{b,e,j}$ | 4790 (2700–9640)$^b$ | 5080.5 (270–9500)$^g$ | 4196 (1420–9266)$^j$ | 0.043   |
| Platelets 10$^3$ per µl       | 247.5 (35–386)$^j$ | 227 (146–346)$^n$ | 182.5 (149–452)$^{j,s}$ | 221 (132–645) | 0.161   |
| NLR                           | 3.95 (1.5–22.5) | 3.4 (1.5–14.7)$^q$ | 5.27 (0.3–10.9) | 6.85 (1.3–56.6)$^{q,t}$ | 0.169   |
| PLR                           | 166.25 (23.6–638.5)$^{k,x}$ | 195.6 (79.8–465)$^y$ | 226.93 (148.6–567.6)$^{k}$ | 539.7 (141.1–2053.6)$^{k,r}$ | 0.001   |
| Fibrinogen (mg/dl)            | 656 (459–930) | 659.5 (340–877) | 598.5 (192–822)$^u$ | 783.5 (475–921)$^u$ | 0.200   |

Abbreviations: NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio. Values are given as median (minimum and maximum). Kruskal-Wallis analysis. Comparisons between each group Mann-Whitney U test.

Healthy vs mild: $^aP < 0.004$, $^bP < 0.013$.
Healthy vs moderate: $^cP < 0.021$, $^dP < 0.001$, $^eP < 0.049$, $^fP < 0.047$, $^gP < 0.034$, $^hP < 0.045$.
Healthy vs severe: $^iP < 0.001$, $^jP < 0.054$, $^kP < 0.001$, $^lP < 0.001$.
Mild vs moderate: $^mP < 0.006$, $^nP < 0.021$, $^oP < 0.011$.
Mild vs severe: $^pP < 0.001$, $^qP < 0.041$, $^rP < 0.001$, $^sP < 0.001$.
Moderate vs severe: $^tP < 0.034$, $^uP < 0.041$. 

### TABLE 5 Symptom presentation by group in healthy and COVID-19 patients according to the severity of the disease
CONFLICT OF INTEREST
The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS
SCL: Design, analysis, and manuscript writing. MGE: Design, sample recollection, and critical analysis.

ORCID
Sebastián Carranza Lira https://orcid.org/0000-0001-7199-264X

REFERENCES
1. Rizo-Téllez SA, Méndez-Garcia LA, Flores-Rebollo C, et al. The neutrophil-to-monocyte ratio and lymphocyte-to-neutrophil ratio at admission predict in-hospital mortality in Mexican patients with severe SARS-CoV-2 infection (Covid-19). Microorganisms. 2020;8(10):1-17.
2. Tatum D, Taghavi S, Houghton A, Stover J, Toraih E, Duchesne J. Neutrophil-to-lymphocyte ratio and outcomes in Louisiana COVID-19 patients. Shock. 2020;54(5):652-658.
3. Haghipoor JS, Vaseghi G, Manteghinejad A, Nasirian M. Neutrophil-to-lymphocyte ratio as a potential biomarker for disease severity in COVID-19 patients. J Glob Antimicrob Resist. 2020;22:862-863.
4. Ullah W, Basyal B, Tariq S, et al. Neutrophil-to-C-reactive protein ratio: a novel predictor of adverse outcomes in COVID-19. J Clin Med Res. 2020;12(7):415-422.
5. Qun S, Wang Y, Chen J, et al. Neutrophil-to-lymphocyte ratios are closely associated with the severity and course of non-mild COVID-19. Front Immunol. 2020;11:1-11.
6. Imran MM, Ahmed U, Usman U, Ali M, Shaukat A, Gul N. Neutrophil/Lymphocyte ratio – a marker of COVID-19 pneumonia severity. Int J Clin Pract. 2021;75(4):e13698. doi:https://doi.org/10.1111/ijcp.13698.
7. Wang S, Fu L, Huang K, Han J, Zhang R, Fu Z. Neutrophil-to-lymphocyte ratio on admission is an independent risk factor for the severity and mortality in patients with coronavirus disease 2019. J Infect. 2021;82(2):e16-e18.
8. Jimeno S, Ventura PS, Castellano JM, et al. Prognostic implications of neutrophil-lymphocyte ratio in COVID-19. Eur J Clin Invest. 2021;51(1):1-9.
9. Wang X, Li X, Shang Y, et al. Ratios of neutrophil-to-lymphocyte and platelet-to-lymphocyte predict all-cause mortality in patients with Coronavirus disease 2019 (COVID-19): a retrospective cohort study in a single medical center. Epidemiol Infect. 2020;148:E 211. doi:https://doi.org/10.1017/S0950268820002071.
10. Fu J, Kong J, Wang W, et al. The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19: a retrospective study in Suzhou China. Thromb Res. 2020;192:3-8.
11. Kong M, Zhang H, Cao X, Mao X, Lu Z. Higher level of neutrophil-to-lymphocyte is associated with severe COVID-19. Epidemiol Infect. 2020;9(148):e139. doi:https://doi.org/10.1017/S0950268820001557.
12. Khartabil TA, Russcher H, van der Ven A, de Rijke YB. A summary of the diagnostic and prognostic value of hemocytometry markers in COVID-19 patients. Crit Rev Clin Lab Sci. 2020;57(6):415-431.
13. Chan AS, Rout A. Use of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in COVID-19. J Clin Med Res. 2020;12(7):448-453.
14. Yan X, Li F, Wang X, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019. J Infect Chemother. 2020;26(2):109-115.
disease 2019: a retrospective cross-sectional study. J Med Virol. 2020;92(11):2573-2581.

15. Zhu C, Yu S, Zhao H, et al. Neutrophil-to-lymphocyte ratio predicts the clearance of SARS-CoV-2 RNA in mild COVID-19 patients - a retrospective analysis from Dongxihu Fangcang hospital in Wuhan, China. Clin Chem Lab Med. 2020;58(9):E167-170.

16. Basbus L, Lapidus Ml, Martingano I, Puga MC, Pollán J. Índice neutrófilo-linfocito como factor pronóstico de Covid-19. Med (B Aires). 2020;80:31-36.

17. Fois AG, Paliogiannis P, Scano V, et al. The systemic inflammation index on admission predicts in-hospital mortality in COVID-19 patients. Molecules. 2020;25(23):1-13.

18. Bedel C, Korkut M, Armağan HH. NLR, d-NLR and PLR can be affected by many factors. Int Immunopharmacol. 2021;90:107154. doi:https://doi.org/10.1016/j.intimp.2020.107154.

19. Xue G, Gan X, Wu Z, et al. Novel serological biomarkers for inflammation in predicting disease severity in patients with COVID-19. Int Immunopharmacol. 2020;89(Pt A):107065. doi:https://doi.org/10.1016/j.intimp.2020.107065.

20. Qu R, Ling Y, Zhang Y-H-Z, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol. 2020;92(9):1533-1541.

21. Carranza-Lira S, García-Espinosa M, Moreno-Álvarez O. Frecuencia de disfunción olfatoria en mujeres embarazadas con infección con SARS-CoV-2. Gac Med Mex. 2021;157:255-261.

22. Chang MC, Park YK, Kim BO, Park D. Risk factors for disease progression in COVID-19 patients. BMC Infect Dis. 2020;20:445. doi:https://doi.org/10.1186/s12879-020-05144-x.

23. Fathi N, Rezaei N. Lymphopenia in COVID-19: therapeutic opportunities. Cell Biol Int. 2020;44(9):1792-1797.

24. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. Expert Rev Hematol. 2020;13(11):1265-1275.

25. Kotani K, Morisawa Y, Yamada T. Using the neutrophil-to-lymphocyte ratio to estimate the severity of coronavirus disease 2019. Polish Arch Intern Med. 2020;130(7–8):716-718.

How to cite this article: Carranza Lira S, García Espinosa M. Differences in the neutrophil/lymphocyte ratio and the platelet/lymphocyte ratio in pregnant women with and without COVID-19. Int J Gynecol Obstet. 2022;157:296–302. https://doi.org/10.1002/ijgo.13840