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Differences in the neutrophil/lymphocyte ratio and the platelet/lymphocyte ratio in pregnant women with and without COVID-19

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Abstract

Objective: To determine the differences in the neutrophil/lymphocyte ratio (NLR) and the platelet/lymphocyte ratio (PLR) in pregnant women with and without COVID-19.

Methods: Observational, cross-sectional, retrospective, comparative, open, controlled study done from January to April 2021 at the UMAE Hospital de Gineco Obstetricia "Luis Castelazo Ayala" Instituto Mexicano del Seguro Social. Mexico City, Mexico: Patients were divided into those with a negative test for COVID-19 and those with a positive test, with the latter then being divided according to disease severity into mild, moderate, and severe groups. In all the NLR and PLR were calculated. Symptoms, vital signs, and oxygen saturation were documented. Statistical analysis: Central tendency and dispersion measures, Kruskal-Wallis test, Mann-Whitney *U* test, and chi-squared test were used. Sensitivity, specificity, positive predictive value, negative predictive value, and odds ratio (OR) were calculated.

Results: Seventy-seven patients were included, 24 without COVID-19 and 53 with COVID-19. There were 33, 10, and 10 patients in the mild, moderate, and severe disease groups, respectively. There was no difference in NLR between the groups and the PLR was significantly higher in the severe disease group. With a 5.1 NLR cutoff point, between normal and those with severe disease, the sensitivity was 70% and specificity 63%, whilst with a 221 PLR cutoff point, the sensitivity was 90% and the specificity 83% (OR 45, 95% CI 4.40–461.7).

Conclusion: PLR more than NLR was useful to detect pregnant patients with COVID-19 with severe disease.

KEYWORDS
COVID-19, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, severity

1 | 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.[9] 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 µg/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, in 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], $P < 0.001$)[6] 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℃, 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 nonmechanical 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 α error of 0.01, a β 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), $P < 0.002$, 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

TABLE 1 Symptom presentation by group among healthy pregnant women and pregnant women with COVID-19

	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 χ^2 test.

TABLE 2 Laboratory tests in healthy pregnant women and pregnant women with COVID-19

	Healthy (n = 24)	COVID-19 (n = 53)	P value
Leukocytes per mm^3	9255 (4120–19 290)	7000 (3600–15 800)	0.006
Lymphocytes per mm^3	1525 (213–3410)	1030 (112–2530)	0.004
Neutrophils per mm^3	6495 (2440–16 920)	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.

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 3 General data in healthy pregnant women and pregnant women with three stages of severity of COVID-19 disease

	Healthy (n = 24)	Mild (n = 33)	Moderate (n = 10)	Severe (n = 10)	P value
Age (years)	28.5 (16–43)	27 (19–47)[a]	24 (18–36)[b]	32 (25–41)[a,b]	0.072
Weight (kg)	75 (41–99)	72 (52–97)	79.5 (62–100)	71.1 (56–96)	0.337
Height (m)	1.59 (1.4–1.7)	1.57 (1.5–1.7)	1.57 (1.54–1.7)	1.59 (1.5–1.7)	1.0
BMI	30.1 (16.6–37.9)	28.1 (19.3–40.5)	30.5 (24–39.5)	29.1 (20–40)	0.629
Pregnancies	2 (1–5)	2 (1–5)	1 (1–3)[c]	2.5 (1–4)[c]	0.099
Deliveries	0 (0–2)	0 (0–3)	0 (0–2)	0.5 (0–2)	0.227
Abortions	0 (0–4)	0 (0–3)	0 (0–0)	0 (0–1)	0.032
Cesarean delivery	0 (0–2)	0 (0–1)	0 (0–1)	0 (0–1)	0.927
Weeks of gestation	26 (6–39)	31 (12–40)	33 (26.3–40)	27.8 (15.3–40)	0.287

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

Values are given as median (minimum and maximum).

Kruskal-Wallis analysis.

Mild vs severe: [a]$P < 0.031$.

Moderate vs severe: [b]$P < 0.019$, [c]$P < 0.043$.

TABLE 4 Vital signs and oxygen saturation in healthy pregnant women and pregnant women with three stages of severity of COVID-19 disease

	Healthy (n = 24)	Mild (n = 33)	Moderate (n = 10)	Severe (n = 10)	P value
Temperature (°C)	36.5 (35.6–36.9)[a,c,g]	36.7 (36.0–38.6)[a,n]	37.9 (36.3–39.0)[c]	37.9 (36.2–40.0)[g,n]	0.001
Systolic BP (mm Hg)	110 (73–130)	115 (95–140)	115 (95–144)	109 (90–126)	0.150
Diastolic BP (mm Hg)	70 (47–90)	70 (55–87)	73.5 (52–95)	66 (58–76)	0.437
Heart rate per minute	87 (65–150)[b,d,h]	97 (70–149)[b,k,o]	114 (85–151)[d,k]	121 (95–134)[h,o]	0.001
Respiratory rate per minute	20 (14–27)[e,i]	20 (17–25)[l,p]	25.5 (17–32)[e,l]	28.5 (20–38)[l,p]	0.001
Oxygen saturation	96 (88–98)[f,j]	95 (77–98)[m,q]	89.5 (82–95)[f,m,r]	82 (45–95)[j,q,r]	0.001

Abbreviation: BP, blood pressure.

Values are given as median (minimum and maximum).

Kruskal-Wallis analysis.

Healthy vs mild: [a]$P < 0.031$, [b]$P < 0.51$.

Healthy vs moderate: [c]$P < 0.018$, [d]$P < 0.005$, [e]$P < 0.001$, [f]$P < 0.001$.

Healthy vs severe: [g]$P < 0.001$, [h]$P < 0.001$, [i]$P < 0.001$, [j]$P < 0.001$.

Mild vs moderate: [k]$P < 0.012$, [l]$P < 0.001$, [m]$P < 0.001$.

Mild vs severe: [n]$P < 0.01$, [o]$P < 0.001$, [p]$P < 0.001$, [q]$P < 0.001$.

Moderate vs severe: [r]$P < 0.015$.

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

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

	Healthy (n = 24)	Mild (n = 33)	Moderate (n = 10)	Severe (n = 10)	P value
Fever	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	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

	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,i]	1350 (600–2530)[m,p]	855 (370–1200)[d,m,t]	568.5 (112–1120)[i,p,t]	0.001
Neutrophils per mm^3	6495 (2440–16 920)[b,e,j]	4790 (2700–9640)[b]	5080.5 (270–9500)[e]	4196 (1420–9266)[j]	0.043
Platelets 10^3 per µl	247.5 (35–386)[f]	227 (146–346)[n]	182.5 (149–452)[f,n]	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]	0.169
PLR	166.25 (23.6–638.5)[g,k]	195.6 (79.8–465)[r]	226.93 (148.6–567.6)[g]	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
D-dimer (ng/ml)	450 (74–949)[h,l]	411.5 (197–831)[o,s]	705 (367–1935)[h,o]	973 (404–1402)[l,s]	0.001

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: [a]$P < 0.004$, [b]$P < 0.013$.

Healthy vs moderate: [c]$P < 0.021$, [d]$P < 0.001$, [e]$P < 0.049$, [f]$P < 0.047$, [g]$P < 0.034$, [h]$P < 0.045$.

Healthy vs severe: [i]$P < 0.001$, [j]$P < 0.054$, [k]$P < 0.001$, [l]$P < 0.001$.

Mild vs moderate: [m]$P < 0.006$, [n]$P < 0.021$, [o]$P < 0.011$.

Mild vs severe: [p]$P < 0.001$, [q]$P < 0.041$, [r]$P < 0.001$, [s]$P < 0.001$.

Moderate vs severe: [t]$P < 0.034$, [u]$P < 0.041$.

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 7 Sensitivity, specificity, positive predictive value, and negative predictive value of NLR and PLR with different cutoff points between patients with and without COVID-19

	Cutoff point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	OR	95% CI
NLR	2.65	79	25	70	35	1.27	0.41–3.97
NLR	5.1	38	63	69	31	1.01	0.37–2.73
PLR	193.5	60	67	80	43	3.05	1.11–8.38
PLR	221	47	83	86	42	4.46	1.34–14.84

Abbreviations: CI, confidence interval; NLR, neutrophil/lymphocyte ratio; NPV, negative predictive value; OR, odds ratio; PLR, platelet/lymphocyte ratio; PPV, positive predictive value.

TABLE 8 Sensitivity, specificity, positive predictive value, and negative predictive value of NLR and PLR at different cutoff points and according to the severity of the COVID-19 disease

	NLR 2.65			NLR 5.1			PLR 193.5			PLR 221		
Cutoff point	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev
Sensitivity (%)	76	80	90	24	50	70	52	60	90	33	50	90
Specificity (%)	25	25	25	63	63	63	67	67	67	83	83	83
PPV (%)	58	25	33	47	36	44	68	43	53	58	56	69
NPV (%)	43	63	86	38	75	83	50	80	94	73	80	95
Odds ratio	1.04	1.33	3.0	0.53	1.67	3.89	2.12	3.0	18.0	2.5	5.0	45
95% CI	0.31–3.52	0.22–8.10	0.31–28.84	0.17–1.68	0.38–7.40	0.80–19.0	0.71–6.30	0.65–13.80	1.93–168.0	0.68–9.12	0.97–26.80	4.40–461.7

Abbreviations: CI, confidence interval; Mod, moderate; NLR, neutrophil/lymphocyte ratio; NPV, negative predictive value; PLR, platelet/lymphocyte ratio; PPV, positive predictive value; Sev, severe.

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.

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