Sex-Dependent Performance of the Neutrophil-to-Lymphocyte, Monocyte-to-Lymphocyte, Platelet-to-Lymphocyte and Mean Platelet Volume-to-Platelet Ratios in Predicting Covid-19 Severity.

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Research

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Abstract

Background

The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) and mean platelet volume-to-platelet ratio (MPR) are combined hematology tests useful for the assessment of COVID-19 severity, but different cut-off values have been reported. Sex can significantly impact immune responses and the course of COVID-19, so these combined hematology tests should be differentiated by gender.

Purpose

The aim of this study was to evaluate sex differences in the contribution of the NLR, PLR, MLR and MPR to severity and mortality using a sample of COVID-19 patients infected with SARS-CoV-2 from Quito (Ecuador).

Methods

This single center observational cross-sectional study included 3280 subjects with COVID-19 disease admitted in the IESS Hospital from Quito. Subjects over 18 years old having a positive result in the real time reverse transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2. Confirmed COVID-19 cases were categorized as Severe ($PaO_2 < 60$ mmHg) and Non-Severe ($PaO_2 \geq 60$ mmHg). Area under the curve, sensibility and specificity were calculated for these ratios to identify optimal cut-offs according to gender to predict severity and mortality in COVID-19 subjects.

Results

Covid-19 mortality rate among men was double that in women. Severe and non-surviving patients had a higher NLR and MLR, and a lower MPR. A higher PLR was also associated with severity, but not with mortality. The means of NLR, MLR, and PLR in men were significantly higher, yet MPR levels were lower than in women. In men, these ratios had lower cut-offs than in women (NLR: 2.42 vs. 3.31, MLR: 0.24 vs. 0.35 and PLR: 83.9 vs. 151.9). The sensitivity of NLR, MLR and PLR to predict severity was better in men (69%-77%), while their specificity enhanced in women compared to men (70%-76% vs. 23%-48%).

Conclusion

High NLR, MLR, PLR and low MPR levels were related to COVID-19 severity with different performance in men and women.

Introduction

Combined hematology tests like the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and monocyte to lymphocyte ratio (MLR), have become promising indicators of disease severity in COVID-19 patients [1–7]. In addition, the mean platelet volume (MPV), a hallmark of platelet activation and largely a high MPV/platelet count ratio (MPR), which predict long-term mortality in patients suffering from some cancers[8, 9], also constitute risk factors for severe pneumonia in patients suffering from COVID-19[10]. Their performance in predicting severity and mortality in patients with COVID-19 should then be secured in order to make medical care decisions[11]. A limitation of these ratios is that they show not only ethnic differences[12, 13]but also, they can deeply be influenced by sex[14], a relationship no yet explored in COVID-19 disease.

Current worldwide statistics show that Covid-19 severity is sex-dependent and that more men than women dye of SARS-CoV-2 infection[15–17]. Animal studies have confirmed the sex-dependent susceptibility to SARS-CoV-2 and severity of lung illness[18]. Estrogen and progesterone seem to provide protection to women against Covid-19[19, 20]. An intriguing hypothesis is that women express more toll-like receptor 7 (TLR7), which is encoded on the X chromosome. Because TLR7 detects viral single-strand RNAs, the innate immune response of women to SARS-CoV-2 seems to be more robust[21]. In addition, sex differences in platelet Toll-type receptors would also contribute to different COVID-19 severity [22]. Notifying hematological parameters meaningful to the innate immune response segregated by sex will undoubtedly help develop better treatment and prevention strategies against Covid-19.

Ecuador is among the top ten most affected countries in Latin America. As in February 2021, there were at least 260076 COVID-19 cases and 10413 deaths. The aim of this study was to evaluate sex differences in the contribution of the NLR, PLR, MLR and MPR parameters to severity and mortality using a sample of COVID-19 patients infected with SARS-CoV-2 from Quito (Ecuador). The role of applicable cut-offs of these ratios was investigated using the Receiver Operating Characteristic (ROC) Curve analysis for evaluating the prognostic ability of COVID-19 severity of these parameters.

Methods

Design

This observational retrospective study included 3280 patients over 18-years old, who were diagnosed with COVID-19 disease upon admission at the IESS Sur Hospital in Quito, Ecuador. A confirmed COVID-19 case was defined as a subject suffering from COVID-19-like symptoms and at the same time having a positive result in the real time reverse transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2. According to blood hypoxemia, confirmed COVID-19 cases were categorized as Severe ($PaO_2 < 60$ mmHg) and Non-Severe ($PaO_2 \geq 60$ mmHg).

Hematological tests

Hematological analyses were performed using a Sysmex XN-550™ Hematology Analyzer (Sysmex America Inc., USA). Arterial blood gasometry was conducted on a RAPIDPoint® 500 blood gas system (Siemens Healthcare GmbH; Germany). The calculation of the ratios was as follows: NLR, absolute neutrophil count divided by the absolute lymphocyte count; MLR, absolute monocyte count divided by absolute lymphocyte count; PLR: platelet count divided by absolute lymphocyte count; MPV, mean platelet volume divided by platelet count.

Statistics

Statistical analysis was performed using SPSS v24.0 for Windows (SPSS Inc., Chicago, IL, USA). Data were expressed as either means and standard deviations for continuous variables or as absolute counts and percentages for categorical variables. A Chi-Square test was run to challenge the association between severity, deaths, and sex. The Mann-Whitney U test was used to compare means of ratios between Non-Severe and Severe groups, between sex (women and men), as well as according to death (Yes or No). A two-sided p-value < 0.05 was statistically significant. The performance of the ratios in discriminating Severe from Non-Severe cases was assessed by areas under the curve (AUC) of Receiver Operating Characteristic (ROC) curves, which showed the relationship between sensitivity vs. 1-specificity. The point of the curves with both the maximum sensitivity and specificity was selected as the optimal cut-off point using the Youden Index. Parameters with AUC < 0.55 were not acceptable.

Ethics

Given the retrospective nature of the analysis, this study was performed in agreement to the STROBE guidelines for the dissemination of observational studies.

Results

Table 1 shows the nature and distribution (severity, mortality and sex) of a sample of 3280 COVID-19 patients. There were 389 severe cases (11.9%) and 2891 non-Severe cases. Mortality reached 3.1% of the subjects. Approximately two thirds of the deaths were men (69.9%). There were statistically significant differences in both severity and in the percentage of deceases as a function of the sex.

Table 1
Sex-dependent differences in severity and death

	Women **n = 1637**	**Men** **n = 1643**	**Total** **n = 3280**	
	n(%)	n(%)	n(%)	p-value*
Severity				
Severe	144(8.8)	245(14.9)	389(11.9)	0.00
Non-Severe	1493(91.2)	1398(85.1)	2891(88.1)	
Death				
Yes	34(2.1)	69(4.2)	103(3.1)	0.00
No	1603(97.9)	1574(95.8)	3177(96.9)	
*Chi square test				

Table 2 shows the mean levels of NLR, MLR and PLR in COVID-19 patients grouped by disease severity, sex and mortality. NLR, MLR and PLR levels were significantly higher in the Severe group, while MPR levels were significantly higher in the Non-Severe group. NLR, MLR and PLR levels were higher in men compared to women. In dead subjects from COVID-19, NLR and MLR levels were significantly higher compared to those who survived.

Table 2. Distribution of combined hematology tests in COVID-19 patients according to severity, sex and mortality

Ratio	Mean(SD)	Mean(SD)	p-value*
Severity	Severe	Non-Severe	
	n=635	n=2645	
Neutrophil-to-lymphocyte ratio (NLR)	5.03(5.90)	3.80(4.23)	< .001
Monocyte-to-lymphocyte ratio (MLR)	0.41(0.31)	0.34(0.24)	< .001
Platelet-to-lymphocyte ratio (PLR)	154.4(137.2)	130.0(113.6)	< .001
Mean platelet volume/platelet count ratio (MPR)	0.034(0.01)	0.037(0.01)	< .001
Sex	Women	Men	
	n=1637	n=1643	
Neutrophil-to-lymphocyte ratio (NLR)	3.58(3.89)	4.49(5.21)	< .001
Monocyte-to-lymphocyte ratio (MLR)	0.30(0.19)	0.40(0.30)	< .001
Platelet-to-lymphocyte ratio (PLR)	130.4(103.4)	143.4(131.9)	< .001
Mean platelet volume/platelet count ratio (MPR)	0.033(0.01)	0.014(0.01)	< .001
Death	Yes	No	
	n=103	n=3177	
Neutrophil-to-lymphocyte ratio (NLR)	10.85(7.69)	3.82(4.31)	< .001
Monocyte-to-lymphocyte ratio (MLR)	0.64(0.38)	0.34(0.24)	< .001
Platelet-to-lymphocyte ratio (PLR)	127.4(120.9)	132.8(111.9)	< .001
Mean platelet volume/platelet count ratio (MPR)	0.044(0.02)	0.034(0.01)	< .001

*Mann-Whitney U Test

Finally, data were submitted to the AUC-ROC analysis (Figure 1) to determine the sensitivity and specificity of the hematological ratios in predicting Severe cases of COVID-19 as well as their cut-offs. Most of the AUCs were above the acceptable threshold (0.55).

The AUCs for the combined hematology tests were low, ranging from 0.50 to 0.59 in the whole sample (Table 3). Nevertheless, the cut-offs of all the ratios except for MPR in women were higher than in men. Thus, NLR had a cut-off point of 2.42 in men versus 3.34 in women (38% higher), while the cut-off points of the MLR an PLR in women were 46% and 81% higher than in men respectively. The specificity of the NLR, MLR and PLR were higher in men, whereas their specificity was superior in women. For instance, the sensitivity of PLR in men was 71% versus 37% in women. The specificity of MLR in women was 61% against 23% in men. Unexpectedly, sex differences were not found in the cut-off point, sensitivity and specificity of MPR.

Table 3
AUC-ROC analysis for the combined hematology tests evaluation of COVID-19 severity.

	AUC (95% CI)	Cut-off	Sensitivity	Specificity	p value
General					
NLR	0.57(0.55–0.60)	2.28	0.66	0.48	0.00
MLR	0.57(0.54–0.59)	0.33	0.48	0.63	0.00
PLR	0.54(0.51–0.56)	196.7	0.58	0.49	0.00
MPR	0.55 (0.53–0.58)	0.03	0.43	0.64	0.00
Female					
NLR	0.55(0.51–0.58)	3.34	0.56	0.70	0.00
MLR	0.53(0.49–0.57)	0.35	0.52	0.61	0.00
PLR	0.52(0.48–0.55)	151.9	0.37	0.76	0.27
MPR	0.54(0.50–0.57)	0.03	0.54	0.56	0.03
Male					
NLR	0.59(0.56–0.63)	2.42	0.69	0.48	0.00
MLR	0.59(0.56–0.62)	0.24	0.77	0.23	0.05
PLR	0.56(0.52–0.59)	83.9	0.71	0.41	0.00
MPR	0.56(0.52–0.59)	0.03	0.60	0.49	0.00

Discussion

This observational retrospective investigation was the first to report the cut-off values of the NLR, LMR, PLR and MPR indices in COVID-19 patients segregated by sex, since most of the patients who died from COVID-19 were men. The performance of these biomarkers, which provide insight into COVID-19 progression as well as predictions of its severity, presented significant sex-based differences. In agreement with prior reports [23, 24], the percentage of mortality in our sample was of 3.1%. The analysis of the validity of these indicators as prognostic tools of COVID-19 severity was the first conducted in Ecuador. It revealed the influence of sex in these COVID-19 severity biomarkers.

Severe subjects had a higher NLR compared to Non-Severe patients, similar to the results obtained by others[25–27], and above the mean (3.27, 95% CI: 1.99–4.55) reported in a meta-analysis[28].The sensitivity (66%) and specificity (48%) were however fair for this indicator and below the levels reported for these parameters elsewhere[29, 30]. Despite this, neutrophilia is the hallmark of severe COVID-19.

whereas lymph cell percentage is inversely related to its progression[31], so a subject with NLR levels above 5.03 in our sample was very likely to be admitted to the intensive care unit[4, 5]. Indeed, there is evidence that high NLR levels are positively correlated with mortality by COVID-19[32–33]. A higher NLR value was still indicated in our sample to differentiate those subjects at risk of dying from COVID-19, especially if there were men (69% sensitivity).

The MLR biomarker was selected because of its prognostic value for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection[34]. A cut-off of 0.33 for MLR could discriminate severe COVID-19 patients from those non-severe with approximately of 50% of sensitivity and specificity values sin agreement with previous studies, yet with a higher cut-off[1]. Compared to the work of Peng and colleagues[35], our AUC for MLR was lower. Surprisingly, the sensitivity of MLR to discriminate severe COVID-19 subjects rose to 77% in men, yet with a specificity of 23% (61% in women). The PLR parameter reveals changes in platelet and lymphocyte counts because of acute inflammatory and pro-thrombotic conditions[36]. PLR levels associated with severe COVID-19 were within the range, since they were either higher[1, 25, 37] or lower [29] than the reference. PLR was higher in men, with a sensitivity of 71% (only 37% in women) and a specificity of 41%, (76% in women), which was suggestive of a different cytokine storm in COVID-19 patients[38] pending on the sex.

The MPR parameter has recently received attention as a prognostic marker in COVID-19 pneumonia[39]. MPV reflects the proliferation of megakaryocytes and platelet production in the bone marrow[40]. COVID-19 patients often have mild thrombocytopenia and appear to have increased platelet consumption, together with a corresponding increase in platelet production[41]. Although men showed a lower MPR level compared to women and it would then be thought a relationship with a higher risk of dying from COVID-19, the AUC-ROC did not detect any sex differences in predicting severity. Accordingly, the relationship between MPR and COVID-19 severity remains hazy and more research is needed to define the MLR cut-off point, sensitivity and specificity.

The AUC-ROC analysis revealed a fair performance of the combined hematology biomarkers in predicting COVID-19, which enhanced when the sample was split by sex. There is no doubt that patients with serious COVID-19 have dysregulated resistance reaction that permits viremia, thus ensuing hyper-inflammation and cytokine storm. Neutrophilia is the expression of the cytokine reaction and a hyper-immunity in this disease[42]. Sex-driven differences in COVID-19 immune response are not fully understood[43]. T cell activation at the early phase of SARS-CoV-2 infection is robust in older female COVID-19 patients, while it declines with age and has worse COVID-19 outcomes only in male COVID-19 patients[44]. Women have a more robust ability to control infectious agents[44]. Also, sex-biased expression of ACE2, coupled with the regulation of TMPRSS2 by androgens, increases SARS-CoV-2 susceptibility in men compared with women[45].To the best of our knowledge, this is the first report of the sex-dependent differences of biomarkers of a systemic inflammatory response such as NLR, MLR and PLR.

"Perspectives and Significance"

Severe and non-surviving patients had a higher NLR and MLR, and a lower MPR. The sensitivity of NLR, MLR and PLR to predict severity was better in men (69%-77%), while their specificity enhanced in women compared to men (70%-76% vs. 23%-48%). High NLR, MLR, PLR and low MPR levels were predictors of COVID-19 severity with different performance in men and women. Sex-dependent differences in immune responses related to COVID-19 disease would explain why current worldwide statistics show more men than women dying of SARS-CoV-2 infection.

Limitations

This study was a retrospective and single-center observational analysis.

Conclusions

NLR, MLR, and PLR levels were significantly higher, while the MPR value was lower in severe patients. The sensitivity of NLR, MLR, and PLR was higher in men, who were at a higher risk of dying by COVID-19, while in women these biomarkers had higher cut-offs and an enhanced specificity. Our findings confirm the validity of these parameters in predicting COVID-19 severity and encourages a hematological analysis stratified by sex.

Abbreviations

MLR
Monocyte-to-lymphocyte ratio
MPR
Mean platelet volume-to-platelet count ratio
NLR
Neutrophil-to-lymphocyte ratio
PLR
Platelet-to-lymphocyte ratio
AUC-ROC
Area under the curve-receiver operating characteristic
RT-PCT
Real-time reverse transcription polymerase chain reaction

Declarations

Consent for publication

Not applicable.

Availability of data

Data will be available on reasonable request.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author contributions

Conceived and designed the study: SB, MF, MP, KC, EF, HR. Collected data: JM, KS and FM. Analyzed the data: MP, SB, KC, SM, MF. Reviewed and approval of the manuscript: all the authors.

Ethical approval

This study was approved by the institutional ethics board of IESS Quito Sur. We followed STROBE guidelines for the reporting of results.

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Figures

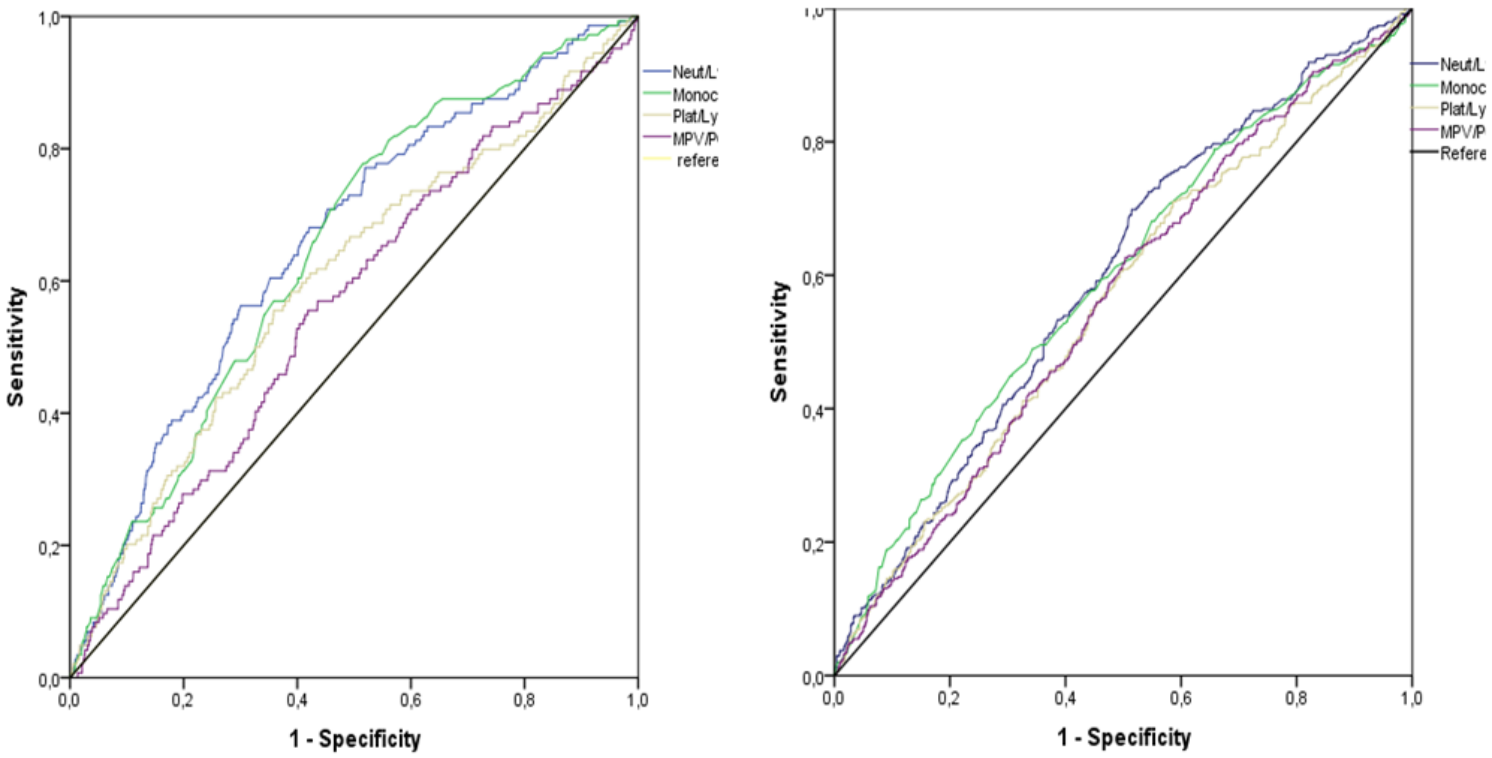

Figure 1

Receiver-operating characteristic (ROC) curves for the combined hematology tests evaluation of COVID-19 severity in men and women.