ORIGINAL ARTICLE

Systemic immune-inflammation index (SII) as a prognostic marker of mortality in COVID-19 patients

Índice de inmunidad-inflamación sistémica (IIS) como marcador pronóstico de mortalidad en pacientes con COVID-19

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Abstract

Objective: *To determine if the systemic immune-inflammation index (SII) is a prognostic marker of mortality in COVID-19 patients.* **Method:** *Retrospective study that included patients admitted to a general hospital in Mexico City with diagnostic of COVID-19, confirmed by quantitative polymerase chain reaction from nasopharyngeal swab specimens in addition to characteristic symptomatology and computerized thoracic tomography imaging. Upon admission an hematic biometry was taken to calculate the SII (neutrophils x platelets/lymphocytes). The optimal cut-off point was determined from a ROC curve; the chi-square test was used to evaluate the association of SII with mortality, the strength of the association was estimated through the odds ratio (OR) and, finally, a multivariate binary logistic regression analysis was performed.* **Results:** *140 individuals were included, 86 (61.4%) men and 54 women (38.6%), the mean age of the patients was 52 (± 13.81) years old. The best prognostic cut-off point found was 2332.30 x 109 (area under the curve: 0.68; 95% confidence interval [95%CI]: 0.59-0.77; p < 0.05). The OR was 3.78 (95%CI: 1.83-7.82; p < 0.05).* **Conclusions:** *We demonstrated that the SII is an easily available tool, effective and a prognostic marker of mortality in hospitalized COVID-19 patients.*

Keywords: *SARS-CoV-2. Systemic immune-inflammation index. Mortality. Biomarkers.*

Resumen

Objetivo: *Determinar si el índice de inmunidad-inflamación sistémica (IIS) es un marcador pronóstico de mortalidad en pacientes con COVID-19.* **Método:** *Estudio retrospectivo que incluyó pacientes que ingresaron con diagnóstico de COVID-19 a un hospital general de la Ciudad de México, confirmado mediante prueba de reacción cuantitativa en cadena de la polimerasa con transcriptasa inversa de muestras de hisopado nasofaríngeo, además de la sintomatología característica y los hallazgos de la tomografía computarizada de tórax. A su ingreso se les realizó biometría hemática para el cálculo del IIS (neutrófilos x plaquetas/linfocitos). Mediante una curva ROC se determinó el punto de corte óptimo del IIS. Para evaluar la asociación del IIS con la mortalidad se utilizó la prueba de ji al cuadrado, la fuerza de la asociación con la razón de momios (OR, odds ratio) y se realizó un análisis multivariado de regresión logística binaria.* **Resultados:** *Se incluyeron 140 individuos, de los cuales 86 (61.4%) eran hombres y 54 (38.6%) mujeres, con una media de edad de 52 (± 13.81) años. El mejor punto de corte pronóstico fue 2332.30 x 109 (área bajo la curva: 0.68; intervalo de confianza del 95% [IC95%]: 0.59-0.77; p < 0.05). La OR fue de 3.78 (IC95%: 1.83-7.82; p < 0.05).* **Conclusiones:** *El IIS mostró ser una herramienta de fácil disponibilidad y un marcador pronóstico de mortalidad al ingreso en pacientes hospitalizados con COVID-19.*

Palabras clave: *SARS-CoV-2. Índice de inmunidad-inflamación sistémica. Mortalidad. Biomarcadores.*

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Date of reception: 09-01-2021
Date of acceptance: 03-08-2021
DOI: 10.24875/CIRUE.M21000529

Cir Cir (Eng). 2023;91(3):350-355
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

The new coronavirus was named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) due to its high homology (80%) with SARS-CoV, which caused severe acute respiratory syndrome with high mortality rates from 2002 through 2003[1]. The disease caused by this virus can range from asymptomatic cases to severe acute respiratory syndrome, which can be fatal.

Cases of moderate pneumonia often present with fever and cough, and hypoxemia is not usually evident. However, pulmonary lesions can be detected in chest imaging modalities. Severity criteria for SARS-CoV-2-induced pneumonia have been defined, being partial oxygen saturation of < 92% a prominent indicator[2].

In COVID-19-induced atypical pneumonia, the host inflammatory response plays a significant role in the pathogenesis of the disease, involving cells of the innate immune response, particularly lymphocytes, neutrophils, and to a lesser extent, platelets[3].

Once SARS-CoV-2 induces damage to lung cells, it activates the host immune response by recruiting macrophages and monocytes to respond to the infection. These immune cells release cytokines and activate adaptive immune responses of T and B cells[3,4]. However, a dysfunctional immune response can trigger severe lung and systemic disease.

The secretion of cytokines and chemokines attracts immune cells, especially monocytes and T lymphocytes but not neutrophils, from blood to the infected site. The pulmonary recruitment of immune cells from the blood and lymphocyte infiltration to the airways can explain the lymphopenia and increased neutrophil-lymphocyte ratio observed in nearly 80% of the patients with SARS-CoV-2 infection[5].

It has also been reported that during the cytokine storm, lymphopenia is closely related to the increase in proinflammatory cytokines such as interleukin-6. Other factors proposed to contribute to lymphopenia include CD4 and CD8 cells, which show increased expression of proapoptotic proteins, as well as the downregulation of some of the genes involved in T cell activation and function in patients infected with SARS-CoV-2[6].

Furthermore, T cells are more affected by SARS-CoV-2, as their count is nearly half of the lower reference limit and tends to be further hindered in severe cases[7]. Regarding platelet disorder, it was found that having high platelet levels at the beginning, which decreased during treatment, was correlated with disease progression and prognosis[8].

Cell counts and inflammation indices have proven useful in assessing the severity of various diseases since they are easy to perform, accessible, and cost-effective[9-11].

The Systemic Immune-Inflammatory Index (SII = neutrophils × platelets/lymphocytes) was proposed in 2014[12], and first used in cancer patients as a tool to determine prognosis by reflecting the balance of the host inflammatory and immune state[12-14]. It has subsequently been applied to other conditions, such as sepsis[15], as its elevation is primarily due to increased neutrophil and platelet levels with a low lymphocyte count due to a weak immune response. Given the importance of the cellular response in SARS-CoV-2 infection, the aim of this study was to determine if SII could be a mortality marker upon admission in patients with COVID-19.

Method

Ethical approval

The study was approved by Hospital General Ticomán Research Ethics Committee of the Ministry of Health of Mexico City (SEDESA), representing minimal risk. All participants, or their relatives signed an informed consent form.

Study design and population

This was a retrospective, observational, analytical, and cross-sectional study of 140 patients (54 women; 86 men) admitted to our center from May through August 2020, with confirmed COVID-19 through quantitative reverse transcription-polymerase chain reaction (qRT-PCR) testing of nasopharyngeal swab samples, along with characteristic symptoms and thoracic computed tomography findings. Patients undergoing treatment with immunomodulators, chemotherapy, or granulocyte colony-stimulating factor were excluded, as were those with rheumatological diseases, hematological disorders, or human immunodeficiency virus infection.

Analytical method

Hematological analysis at admission was performed using the Beckman Coulter DxH900 analyzer. All lab tests had completed the standardization and certification program.

We recorded the epidemiological and demographic characteristics, calculated the SII at admission, and determined the neutrophil-to-lymphocyte ratio (NLR),

D-dimer, C-reactive protein, and lactate dehydrogenase levels.

Hospitalized patients were classified based on their hospital discharge outcome, either improvement or death.

Statistical analysis

Descriptive tabulation was performed using data on age, sex, comorbidities, need for invasive mechanical ventilation, and mortality.

The Kolmogorov-Smirnov test was used to assess the normality of data distribution. Categorical variables were expressed as percentages, and continuous variables as mean with standard deviation or median with interquartile range, depending on the distribution. To compare continuous variable values between survivor and non-survivor groups, the independent samples t-test was used for normally distributed variables, and the Mann-Whitney U test for non-parametric distributed variables.

Cut-off values were calculated based on the Receiver Operating Characteristic (ROC) curves and the Youden index, selecting the maximum value of this index, which reflects the highest possible specificity and sensitivity. Once the cut-off point was determined, subjects were categorized into 2 groups based on whether they had an index higher or lower than the cut-off value. The association between mortality and categorical variables was assessed using the chi-square test in univariate analysis, and variables with statistical significance in the univariate analysis were included in a binary logistic regression multivariate analysis. Odds ratios (OR) were evaluated considering a 95% confidence interval (95%CI). Data were analyzed using IBM SPSS statistical software package, version 25. Statistical differences were considered significant with p values were < 0.05.

Results

We included a total of 140 patients in the study, 61.4% of which were men and 38.6%, women with a mean age of 52 (± 13.8) years. The most frequent comorbidity was diabetes in 28.6% and systemic arterial hypertension in 25.7% of the study participants (Table 1). Eighty-nine out of the 140 patients were discharged due to improvement, and 51 died. There was no statistically significant difference in terms of sex (p = 0.27), presence of diabetes (p = 0.86), hypertension (p = 0.44), and smoking (p = 0.25) between survivors and non-survivors. The mean age was 10 years higher in non-survivors compared to survivors (59 vs 49 years; p = 0.001).

Table 1. Comparison of clinical characteristics between discharged patients and those who died

Characteristics (n = 140)	Alive (n = 89)	Deceased (n = 51)	p
	n (%)	n (%)	
Sex			
Women	37 (41)	17 (33)	0.272
Men	52 (59)	34 (67)	
Age (years), mean ± SD*	49.37 ± 13.26	59.28 ± 12.54	0.001
Diabetes	25 (62.5)	15 (37.5)	0.868
Hypertension	21 (58.3)	15 (41.7)	0.449
Smoking	8 (8.9)	6 (11.7)	0.25
Invasive mechanical ventilation	9 (18)	41 (82%)	0.001
Markers, medians (p 25-75)			
CRP (mg/L)	14.82 (6.9-19.30)	14.89 (7.65-19.22)	0.836
SII (cell/L)	1930.81 × 10^9 (842.70-3204)	3239 × 10^9 (1906.45-5355)	0.001
NLR (cell/L)	7.5 (4.11-11.81)	14 (8.47-21)	0.001
D-dimer (µg/mL)	828 (379-1650)	1690 (602-3620)	0.005
LDH (IU/L)	380.89 (291.82-469)	474.5 (373.5-624.5)	0.001

CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; LDH: lactate dehydrogenase; SD: standard deviation; SII: systemic immunity-inflammation index.

Intubation during admission was performed in 41% of the patients who eventually died compared to only 18% of the patients discharged due to improvement were intubated (p= 0.001).

Using the ROC curve and the Youden index (0.32), we obtained the cut-off point for SII (2332.10 × 10^9/L) with a sensitivity of 0.673 and specificity of 0.352 (area under the curve [AUC]: 0.68; 95%CI, 0.59-0.77; p < 0.05) (Fig. 1). In patients who survived, the SII had a mean of 1930.81 × 10^9/L, which was lower compared to that from patients who died, with a mean of 3239 × 109/L (p = 0.001). Table 1 shows elements that had been previously reported as severity and prognosis markers in COVID-19-induced pneumonia[16-18], in both survivor and non-survivor groups. Through logistic regression, we obtained the OR for each of the variables predicting the outcome of death. As seen in table 2, the use of mechanical ventilatory support had the highest OR, with a value of 36.4 (95%CI, 13.73-96.72; p = 0.000). Age > 52 years had an OR of 4.27 (95%CI, 2.02-9.04; p = 0.001), and SII had an OR of 3.78 (95%CI, 1.83-7.82; p = 0.001).

We conducted a multivariate analysis using binary logistic regression of factors associated with mortality

in the univariate analysis (Table 3). Since SII shares variables with NLR, we built two models due to the risk of collinearity. In the first model (Table 3), not excluding NLR, SII had a P = 0.21 (95%CI, 0.68-5.41). In the second model, excluding NLR, SII had a p < 0.05 (95%CI, 1.49-7.55). In both models, age remained statistically significant (p = 0.006; 95%CI, 3.45-8.00) for mortality.

Table 4 shows performance in terms of AUC, sensitivity, and specificity of SII, and factors associated with mortality.

Discussion

In this study, we studied whether SII is a prognostic marker for mortality at admission in patients with COVID-19.

In Mexico, according to the epidemiological week 25 report, at the end of June 2021, a total of 2,478,551 confirmed cases of SARS-CoV-2 and 231 244 deaths were reported[19].

Similar to what has been reported in the Chinese population[20] regarding mortality, in our study, deaths accounted for almost 40% of all patients treated. Although reports indicate that men[21,22] have shown higher mortality, we did not find any statistically significant differences. Similar to other countries, we found that age is one of the factors determining mortality[22] because our results indicate that both in the univariate analysis and when performing logistic regression, age > 52 years is associated with mortality with an OR of 4.27 (p = 0.001).

Regarding comorbidities, the most common diseases reported in the studied patients were diabetes and systemic arterial hypertension. However, when the analysis was performed, we did not find any statistically significant differences between the compared groups. The most determining factor for the risk of death was the use of invasive mechanical ventilation. Patients who required mechanical ventilation, despite their clinical condition, could not be admitted to an intensive care unit and were monitored at our internal medicine ward.

The cut-off point we obtained for SII is 2332.10 × 10^9/L, with a sensitivity of 0.673 and a specificity of 0.352 (AUC, 0.68; 95%CI, 0.59-0.77; p < 0.05) (Fig. 1). Although the AUC shows relatively low performance, this value is not the best analysis in this case, as we are not talking about a diagnostic test but rather a prognostic marker whose strength of the association with the probability of an outcome is better evaluated by obtaining the OR.

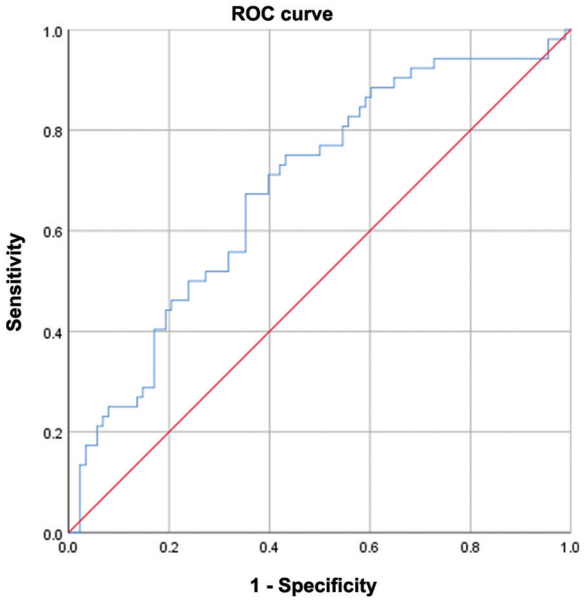

Figure 1. *Area under the curve of the systemic immunity-inflammation index (0.68; 95%CI, 0.59-0.77; p < 0.05).*

Table 2. Univariate analysis of different clinical factors associated with mortality outcomes

Factor	Cut-off value	OR*	95%CI	p
Sex		0.70	0.34-1.44	0.335
Age, years	52.5	4.27	2.02-9.04	0.001
Diabetes		1.06	0.49-2.27	0.657
Hypertension		1.34	0.62-2.93	0.981
Invasive mechanical ventilation		36.4	13.73-96.72	0.001
SII (cell/L)	2332.30 × 10^9	3.78	1.83-7.82	0.001
NLR (cell/L)	10.11	4.18	2.01-8.69	0.001
D-dimer (µg/mL)	934	2.42	1.15-5.05	0.018
LDH (IU/L)	421.5	2.7	1.19-6.3	0.016

95%CI: 95% confidence interval; NLR: neutrophil-to-lymphocyte ratio; LDH: lactate dehydrogenase; OR: odds ratio; SII: systemic immunity-inflammation index.
*Obtained through logistic regression.

A study conducted in Wuhan, China[23], obtained similar results compared to ours. In this research, they evaluated different inflammation indicators, including the SII, which correlates to predicting the severity of COVID-19. They found a sensitivity of 68.9%, specificity of 73.21%, an AUC of 0.72, and an OR of 1 (95%CI, 1.002-1.004; p = 0.006). They categorized patients into mild, moderate, or severe disease, with values of

Table 3. Multivariate analysis of clinical factors and their association with the risk of death

Factor	p	95%CI
Age	0.006	1.42-7.84
SII (cell/L)	0.21	0.68-5.41
NLR (cell/L)	0.088	0.88-6.88
D-dimer (µg/mL)	0.479	0.58-3.13
LDH (IU/L)	0.060	0.96-6.02
Best model		
Age	0.001	3.56-7.63
SII	0.006	1.34-6.15

LDH: lactate dehydrogenase; 95%CI: 95% confidence interval; SII: systemic immunity-inflammation index; NLR: neutrophil-to-lymphocyte ratio. Multivariate logistic regression.

Table 4. Reliability analysis of different markers

Marker	AUC	Sensitivity	Specificity	p	Youden Index
SII	0.684	0.67	0.65	0.001	0.32
NLR	0.745	0.67	0.67	0.001	0.34
D-dimer	0.649	0.63	0.58	0.018	0.21
LDH	0.692	0.62	0.62	0.016	0.24

AUC: area under the curve; LDH: lactate dehydrogenase; NLR: neutrophil-to-lymphocyte ratio; SII: systemic immunity-inflammation index.

1263.52 × 10^9/L (752.80-2094.42) for severe disease and 618.35 × 10^9/L (373.58-1123.39) for mild disease. In a different report from Germany[24], both younger patients and those with a lower SII at admission had higher survival rates than those > 70 years and a higher SII. In this study, the AUC was 0.82 (95%CI, 0.695-1; p = 0.0026), with a sensitivity of 0.875 and specificity of 0.571, concluding, as in our study, that an elevated SII is associated with mortality in patients with COVID-19.

In the univariate logistic regression, we obtained an OR of 3.78 (95%CI, 1.83-7.82; p = 0.001), so we consider that the SII can be a good prognostic marker. However, we observed that, compared to other markers, the OR is lower than both age (OR, 4.27) and NLR (OR, 4.18), but higher than D-dimer and C-reactive protein, markers that have also been used as disease severity predictors[16-18], but are not always available in our centers.

The host response to SARS-CoV-2 infection, involving both innate and adaptive immune system cells, mainly changes the production of lymphocytes, with more apoptosis, reflecting lymphopenia in most patients, as these types of cells are primarily affected[25].

Neutrophils, in addition to performing other immune functions, are responsible for producing cytokines to restrict virus replication. Regarding platelets, thrombocytopenia is detected in 5% to 41.7% of the patients with COVID-19 and is typically mild, occurring in 58% to 95% of severe cases. Severe thrombocytopenia is rarely reported in patients with COVID-19[26].

As far as we know, our study is the first in a sample of Mexican patients to explore the SII as a prognostic marker for mortality in patients with COVID-19, assuming it could be a marker of good performance due to its ability to quickly assess both the inflammatory and immune status of an individual.

Even with a slightly lower OR compared to the NLR, the authors believe that the performance of SII is largely similar to the latter and can be used along with other markers as a strategy to help identify the risk of mortality in these patients. One limitation could be the lack of an established laboratory cut-off point, but this can be standardized based on findings from studies like this.

Similarly, we also believe that one of the reasons the SII shows slightly lower performance compared to the NLR is that, as mentioned earlier, platelets can only be mildly altered during the course of the disease, and our measurement was performed at admission.

Our research may serve as a starting point to explore the prognostic capacity of SII in specific groups of patients in future studies, such as immunocompromised individuals, in whom, hypothetically and in accordance with pathophysiology, SII might better reflect the inflammatory state compared to the NLR.

Although various severity markers have been used, the clinical application of inflammation indices lies in their advantage of being cost-effective, reliable, and reproducible.

As limitations of our research, we found a small number of patients, a single measurement of SII at admission, and the fact that we did not associate SII with other clinical and biochemical severity variables.

Conclusions

In this study, it was determined that the SII, an index reflecting the homeostasis between inflammation and the host immune status, showed adequate sensitivity and specificity as a risk factor for mortality determined

at admission in patients with COVID-19. However, our results reveal that the AUC is lower than that for NLR.

Acknowledgments

The authors would like to express their gratitude to the laboratory staff at Hospital General Ticomán.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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