Hemogram as marker of in-hospital mortality in COVID-19

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The main results are in the manuscript. The rest of the data are available on reasonable request.

Abstract (247 words)

The clinical impact of COVID-19 disease calls for the identification of routine variables to identify patients at increased risk of death. Current understanding of moderate to severe COVID-19 pathophysiology points toward an underlying cytokine release driving a hyperinflammatory and procoagulant state. In this scenario, white blood cells and platelets play a direct role as effectors of such inflammation and thrombotic response. We investigate whether hemogram-derived ratios such as neutrophil-to-lymphocyte-ratio (NLR), platelet-to-lymphocyte-ratio (PLR), and the systemic immune-inflammation-index (SII) may help to identify patients at risk of fatal outcomes. Activated platelets and neutrophils may be playing a decisive role during the thromboinflammatory phase of COVID-19 so, in addition, we introduce and validate a novel marker, the neutrophil-to-platelet-ratio (NPR).

Two thousand and eighty-eight hospitalized COVID-19 patients admitted at any of the hospitals of HM Hospitales group in Spain, from March 1 to June 10, 2020, were categorized according to the primary outcome of in-hospital death.

Baseline values, as well as the rate of increase of the four ratios analyzed were significantly higher at hospital admission in patients who died than in those who were discharged ($p<0.0001$). In multivariable logistic regression models, NLR ([OR]:1.05; 95% IC: 1.02-1.08, $p=0.00035$) and NPR ([OR]: 1.23; 95% IC: 1.12-1.36, $p<0.0001$) were significantly and independently associated with in-hospital mortality.

According to our results, hemogram-derived ratios obtained at hospital admission, as well as the rate of change during hospitalization, may easily detect, primarily using NLR and the novel NPR, COVID-19 patients at high risk of in-hospital mortality.

What is already known about this subject?

The current pathophysiological understanding of moderate to severe COVID-19 cases points toward a cytokine release that follows endothelial injury. Such cytokine storm would in turn be the driver of a hyperinflammatory and procoagulant state. White blood cells and platelets directly mediate such inflammation and thrombotic events.

What are the new findings?

Hemogram-derived ratios obtained at hospital admission, as well as the rate of change during hospitalization, may easily detect, primarily using NLR and the novel NPR, patients at high risk of in-hospital mortality due to COVID-19.

How might these results change the focus of research or clinical practice?

Hemogram is easily measurable, available, cost-effective and reliable test that could be very useful in establishing the risk of mortality at hospital admission and guiding therapeutic decisions in patients with COVID-19. In this sense, the hemogram is a tool within the reach of all hospitals and doctors who do not have the technical and material means to carry out complex immunological studies

Introduction

The current global pandemic of coronavirus disease 2019 (COVID-19), has posed a major threat to global public health (1). Despite the fact that the majority of patients are asymptomatic or present mild symptoms (1), due to the high proportion of people affected, the number of deaths has exceeded 1.4 million people worldwide as of December 2020 (2). Given the rapid spread and profound clinical consequences of COVID-19, it is imperative to continuously improve and advance appropriate, scalable, and efficient clinical diagnostic and therapeutic innovations (3).

In this context, several studies have attempted to establish a series of epidemiological, analytical, and clinical risk factors in order to identify patients at risk of mechanical ventilation or death. These studies have included outcomes of severity (3,7), ICU transfer (8) and factors most associated with in-hospital mortality (4-6, 9,10).

Some of the variables that have shown significant correlation with poor outcomes include several analytical parameters, male sex, older age, smoking status, and the coexistence of comorbidities such as obesity, hypertension, diabetes, cardiovascular

disease, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, hepatitis B infections and malignancy (3,7,8).

The pathophysiology of severe COVID 19 appears to be closely related to a hyperinflammatory state and endothelial damage, therefore circulating biomarkers that can represent inflammation and immune status could potentially predict the clinical outcomes of COVID-19 patients (3, 11).

Based on these pathophysiological plausibility and clinical observations (1,8) several systematic inflammatory response markers have been evaluated and found to correlate with poor outcomes, including peripheral white blood cell (WBC) count, neutrophil-lymphocyte ratio (NLR), derived NLR ratio (neutrophil count divided by the result of WBC count minus neutrophil count), platelet-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (3,12).

NLR and PLR have been proposed as inflammatory markers in a variety of diseases, including COVID-19 (1,3,4,13-15). NLR appears to be an indicator of endothelial dysfunction and an important predictor of cardiovascular mortality (16,17). Different publications have shown the use of PLR as an informative marker in acute inflammatory and prothrombotic states. PLR appears to be a better predictor of clinical outcomes in patients with systemic inflammation than isolated platelet or lymphocyte counts (3) but the relationship between PLR and mortality has been less explored. It has been postulated (15) that PLR may reflect the degree of cytokine release, which might provide a useful indicator the clinical evolution of COVID-19 patients. Systemic immune-inflammation-index (SII) has been recently proposed as a prognostic indicator in the follow-up of sepsis (18) and in cancer patients (19,20) as an index defining the instability in the inflammatory response.

To date, few articles have been published investigating the relationship between the hemogram and all its inflammatory indices and the COVID-19. (21,22)

According previous results (12) and expanding on the current understanding of the pathophysiology of severe COVID-19, we hypothesized that specific hemogram-derived ratios at hospital admission and their respective rates of change during hospitalization may help identify patients at high risk of in-hospital mortality.

Material and Methods

A retrospective observational study was performed at HM Hospitales including 2453 hospitalized COVID-19 patients due to confirmed or suspected infection by SARS-CoV-2 who were admitted to any of the 10 hospitals of the HM Hospitales group across different regions (including Madrid, Barcelona, and Galicia) from March 1 to June 10, 2020. Clinical and laboratory data measurements were available up to and including June 24, 2020.

Diagnostic criteria set forth by the Spanish Ministry of Health changed during the study period, due to the dramatic pandemic situation with overwhelming numbers of admissions and shortage of PCR tests. For several weeks, the diagnosis of COVID-19 was based solely on clinical characteristics and radiological criteria.

Data from 2453 patients were collected. Patients under 18 years old (n=5), missing laboratory data (n=216) or being transferred to other designated hospitals during hospitalization (n=144) were excluded from the analysis. Twenty six patients died in the emergency room and 10 patients died during the first 24 hours after admission. These patients were excluded due to insufficient data for analysis. In total, of the 2453 patients screened for the current study, 2088 (85.1%) were included in the final analysis (figure S5).

The study protocol was approved by the HM Hospitales ethics committee on March 25, 2020 (approval number 20.03.1573-GHM).

Information from each patient was collected form the electronic health report system at hospital admission including demographic data, comorbidities, epidemiological characteristics and laboratory results and up to discharge of in-hospital death.

Laboratory assessments include complete blood count (including white blood cell count, leukocyte subtypes, hemoglobin count and platelet count), biochemical parameters (aspartate aminotransferase (AST), lactate aminotransferase (ALT), creatinine; lactate dehydrogenase (LDH), C-reactive protein (CRP), urea and glucose), and various blood coagulation tests (including D-dimer, prothrombin time and activated partial prothrombin time).

Three distinct ratios derived from routine hemogram parameters signal inflammation. These include NLR, which is the ratio between the count of neutrophils (x 10^9 cells/L) and the count of lymphocytes (x 10^9 cells/L), PLR is the ratio between the count of platelets (x 10^{11} cells/L) and the count of lymphocytes (x 10^9 cells/L), and the systemic immune-inflammation index (SII) defined as the counts of neutrophils (x 10^9 cells/L) multiplied by the counts of platelets (x 10^{11} cells/L) and divided by the count of lymphocytes (x 10^9 cells/L).

Additionally, we have investigated the utility of a novel parameter, the neutrophil-platelet ratio (NPR), in its capacity to identify high risk COVID-19 patients. NPR is the ratio between the count of neutrophils (x 10^9 cells/L) and the count of platelets (x 10^{11} cells/L), and may be useful in signaling a combination of hyperinflammatory response and microvascular occlusion that has been identified in moderate to severe COVID-19 cases (23,24).

Baseline measurements as well as the rate of change (defined as the change of up to four consecutive results during hospital admission) of the different inflammation ratios were included for analysis. Based on these measurements, the rate of change was defined as the slope of the linear fit of the relative rates versus time from hospital entry in days. A rate of change higher than 10% per day was considered as positive, lower than -10% per day as negative and between -10% and 10% per day as null.

The primary outcome of the present study was to evaluate the use of hemogram-derived ratios as inflammation markers and prognostic indicators of in-hospital mortality in moderate to severe COVID-19 patients.

Continuous variables were summarized as median (interquartile range) and categorical variables as absolute frequency (relative frequency, %). Summary statistics were performed for the whole cohort and grouping patients in survivors and non-survivors. Differences between those groups were evaluated using Mann-Whitney U test for quantitative variables and X^2 test or Fisher's exact test for categorical variables.

Correlations between continuous variables were evaluated by Spearman's rho test under rho equals 0 null hypothesis. Correlation plots between pairs of variables were obtained using the R package *GGally*. Variables with p value < 0.2 for difference between survivors and non-survivors were selected for univariable logistic regression. Bivariable logistic regression models were performed combining one of the inflammatory ratios, NLR, PLR, NPR or SII, with other variables. Those variables that changed the inflammatory ratios estimate by at least 10 per cent when added to the model were considered to build the multivariable adjusted models. Model A included age, diastolic blood pressure, NLR rate of change > 10 % per day, creatinine, blood urea and glucose. Model B-D included previous model and oxygen saturation (> 94, 90 – 94 or < 90 %), LDH and CRP respectively.

Interaction and stratified analyses were performed for each inflammatory ratio adjusted to model A and conducted for age (< 75 and > 75 years), sex, cardiovascular disease, diabetes mellitus, oxygen saturation (< 90 and > 90 %) and LDH and CRP both categorized through their respective median values (Figures 1A, 1B, S1C, S1D).

Statistical inference was performed using two-tailed test and with type I error rate of 0.05. All statistical analyses were done using R (version 4.0.0).

Results

Clinical, epidemiological, and laboratory data for 2088 patients admitted to Group HM Hospitales due to COVID-19 infection from March 1 to June 10, 2020, were included for analysis. Clinical characteristics are summarized in Table 1 and laboratory results are presented in Tables 2 and 3. The median age of patients was 69 [57–80] and 59.6% were men. All patients were initially assessed in the emergency department where a blood sample was drawn. Infection by SARS-CoV-2 was confirmed by PCR in 1954 (93.6%) patients. The remaining 134 patients included presented clinical and/or radiological signs compatible with COVID-19, as per protocol.

Three hundred and twenty one (15.3%) patients died. At the time of hospital admission, baseline clinical differences were observed between patients who died and those who did not, including age (83 [75-89] vs 66 [55-77], odds ratio [OR]: 1.09; 95% CI: 1.08-1.11; $p < 0.0001$), sex (66.4% vs 58.4% males, odds ratio [OR]: 1.4; 95% CI: 1.10-1.81; $p = 0.0091$), and SaO2 (SaO2 < 90% 37.4% vs 10.9%, odds ratio [OR]: 6.21; 95% CI: 4.57-8.47; $p < 0.0001$) (Table 1).

Comorbidities were significantly more prevalent among patients who died, specifically hypertension (45.5% vs 34.4%, odds ratio [OR]: 1.59; 95%IC: 1.25-2.02; $p = 0.00018$) , diabetes mellitus (23.7% vs 16.7%, odds ratio [OR]: 1.55; 95%IC: 1.16-2.05; p =

0.0034), chronic obstructive pulmonary disease (10% vs 4.8%, odds ratio [OR]: 2.19; 95%IC: 1.41-3.32; p = 0.00036) and previous cardiovascular disease, (20.9% vs 9.3%, odds ratio [OR]: 2.58; 95%IC: 1.88-3.51; p < 0.0001) (Table 1).

Patients who died presented significantly higher baseline values of NLR (8.7 [4.3 - 14.3] vs 3.8 [2.5 - 6.7], p < 0.0001), PLR (2.4 [1.5 - 3.7] vs 1.9 [1.3 - 2.8], p < 0.0001), NPR (3.5 [2.4 - 5.0] vs 2.1 [1.5 - 3.0], p < 0.0001) and SII (16.4 [7.5 - 31.5] vs 8.5 [4.7 - 15.5], p < 0.0001) than those who were discharged (Table 3). These hemogram rates shew independent mortality prediction ability as can be seen in the ROC curves (Figure S2) and their optimal cut-off values are shown in table 4. Furthermore, these patients presented a significantly higher rate of ascent in the velocity of NLR (39.3% vs 17.3% odds ratio [OR]: 4.79; 95% CI: 3.47-6.66, p < 0.0001), PLR (36.1% vs 25.6% odds ratio [OR]: 3.05; 95% CI: 2.24-4.17, p < 0.0001), NPR (49.5% vs 41.1% odds ratio [OR]: 2.58; 95% CI: 1.90-3.53, p < 0.0001) and SII (42.4% vs 27.4% odds ratio [OR]: 3.68; 95% CI: 2.64-5.21, p < 0.0001) (Table 3).

The results of multivariable logistic regression models assessing the relation of the different hemogram-derived ratios and mortality are shown in Table 5. Model A adjusted the hemogram-derived ratios OR for age, diastolic blood pressure, positive NLR rate of change, creatinine, blood urea and glucose. This adjustment did not weaken the association between each ratio and mortality. However, a weak decrease in OR can be observed when oxygen saturation < 90% was added to the adjustment variables and PLR lost its association with mortality as did SII in model D which included the addition of CRP to the adjusted variables. Conversely, NLR and NPR remained predictors of in-hospital mortality when adjusted for the more complex model D (Table 5).

Stratified analysis showed that increasing values of NLR associates with mortality for both males (OR: 1.09, $p < 0.001$) and females (OR: 1.07, $p < 0.001$), age > 75 years (OR: 1.08, $p < 0.001$) and age < 75 years (OR: 1.09, $p < 0.001$) and LDH above median (> 517 U/L) (OR: 1.07, $p < 0.001$) and LDH below median (< 517 U/L) (OR: 1.12, $p < 0.001$), with no significant interaction. Interaction with NLR was observed for presence of cardiovascular disease (OR: 1.04, $p = 0.15$) and absence of cardiovascular disease (OR: 1.11, $p < 0.001$) (p of interaction < 0.001), for the presence of diabetes (OR: 1.06, $p = 0.0077$) and absence of diabetes (OR: 1.09, $p < 0.001$) (p of interaction = 0.005), and a borderline significant interaction ($p = 0.05$) was found for oxygen saturation > 90% (OR: 1.05, $p = 0.0027$) and < 90% (OR: 1.11, $p < 0.001$) (Figure 1A).

Regarding stratified analysis for increasing values of NPR, interaction with NPR was observed for presence of diabetes (OR: 1.15, $p = 0.049$) and absence of diabetes (OR: 1.40, $p < 0.001$) (p for interaction = 0.003) and for CRP > 64 mg/L (median value) (OR: 1.21, $p < 0.001$) and CRP < 64 mg/L (OR: 1.65, $p < 0.001$) (p for interaction = 0.029). For the remaining variables, analyzed NPR did not show significant interaction with mortality independently of the stratification (Figure 1B).

Interactions and stratified analyses for PLR and SII are shown in Figures S1C and S1D.

Correlation analysis between the four hemogram-derived ratios (Figure S3) shows that NLR correlated with all other hemogram-derived ratios independently from mortality (NLR vs PLR, $\rho = 0.7$, $p < 0.001$; NLR vs NPR, $\rho = 0.667$, $p < 0.001$; NLR vs SII, $\rho = 0.89$, $p < 0.001$). However, PLR is correlated with SII ($\rho = 0.814$, $p < 0.001$) but not with NPR ($\rho = 0.003$, $p = 0.88$). Finally, NPR and SII showed a significant but weak correlation ($\rho = 0.417$, $p < 0.001$).

Figures S3A y S3B show the correlation analysis between NLR, NPR, PLR and SII and those variables that were significantly associated with mortality. As expected, the ratios

were correlated with the hemogram parameters including neutrophils (NLR: $\rho = 0.744$, $p < 0.001$; NPR, $\rho = 0.720$, $p < 0.001$; SII, $\rho = 0.792$, $p < 0.001$) and lymphocytes (NLR: $\rho = -0.694$, $p < 0.001$; PLR, $\rho = -0.719$, $p < 0.001$; SII, $\rho = -0.493$, $p < 0.001$) or platelets (NPR, $\rho = -0.323$, $p < 0.001$; PLR, $\rho = 0.470$, $p < 0.001$; SII, $\rho = 0.517$, $p < 0.001$). All the hemogram-derived ratios were significantly but weakly correlated with most of the different laboratory and demographic variables but NLR and CRP ($\rho = 0.56$, $p < 0.001$) which was the only case with a correlation higher than 0.5.

Discussion

At the time of analysis there had been, to the best of our knowledge, no reports on the potential use of various hemogram-derived ratios that signal inflammation and coagulation as prognostic markers of in-hospital mortality in COVID-19. Very recently, two studies including small cohorts have been published exploring the usefulness of known hemogram-derived ratios. One describes laboratory and radiological findings in a small group of patients (21) and another compares blood inflammatory markers in SARS-CoV-2 virus infection to influenza A (22).

In most clinical care settings, the first encounter with a moderate to severe COVID-19 patients takes place in the Emergency Department, where it is routine clinical practice to carry out a full blood panel. According to our results, in predisposed COVID-19 patients, SARS-CoV-2 causes a hyperinflammatory/hypercoagulable response. This response can be measured, quantified, and its evolution during admission may help identify patients at high risk of in-hospital mortality (Tables 1 and 2). Importantly, some of these parameters may fall within their normal range at admission, hence the significance in the evolution for a prognostic use.

Several studies have reported laboratory characteristics of severe COVID-19 patients, and have found low lymphocytes, high leukocytes and high NLR, as well as lower percentages of monocytes, eosinophils, and basophils (1,3,4,13-15).

Following alveolar viral damage by SARS-CoV-2, the host´s inflammatory response to SARS-CoV-2 infection appears critical in clinical evolution of COVID-19 as a hyperinflammatory response has been identified in moderate to severe cases (23). Blood cell interactions are essential in the pathophysiology of inflammation, immune responses and hemostasis and endothelial cells may be playing an important role as a driver of inflammation mediating the release of cytokines. In this context, activated platelets and neutrophils play a determining role in microvascular occlusion during the thromboinflammatory phase of the disease and could be useful counts and have prognostic value in patients with severe course by COVID-19 (24). Our study emphasizes not only the utility of the total number of white cell, lymphocyte neutrophil or platelet recruited but the utility of hemogram-derived ratios in evolution of hospitalized patient reflecting the complexity and heterogeneity of SARS-CoV-2 infection response.

According to our results, consistent with previous data (12,15), NLR is associated with in-hospital mortality as it is higher at baseline hospital admission and maintains significance after multivariable adjustment.

We observed that patients who died presented significantly higher PLR and SII at admission compared to patients who survived, but they did not maintain significance after more complex model of multivariable adjustment.

The modulatory interaction between neutrophils and platelets has been previously described (25)**.** We included the blood cell proportion NPR based on the biological

plausibility of higher total neutrophils count and lower total platelets count observed among the most severe COVID-19 cases compared to more mild ones. Interestingly, NPR levels were significantly associated with mortality and its association remained significant even after multivariable adjustment. This represents a novel finding which merits further investigation.

Overall, the use of four hemogram-derived ratios from routine blood counts may help identify severe cases of COVID-19 at higher risk of in-hospital mortality. Of these, NLR and NPR appear to be independently associated with mortality in multivariable adjusted models. This relationship would be explained by the capacity of these measures to signal cell activation, endothelial dysfunction following a hyperinflammatory state along with other, more established markers including LDH, CRP and markers of coagulation.

The velocity of increase in the value of these ratios has shown to be a useful marker of severity and associates with mortality in the current study. Undoubtedly, these rates of change could be affected not only by COVID-19 but also by treatments applied, but we hypothesize that some of these rates could be a parameter of value in the surveillance of patients without additional risk factors that support a possible benefit of changing the therapeutic decision.

We are aware the current study presents several limitations. COVID-19 was not confirmed in all patients of both groups, but during the period of the study, as a consequence of the changes in the diagnostic protocol by the Spanish Ministry of Health due to the dramatic pandemic situation, and following instructions in the diagnostic protocols, the diagnosis of COVID-19 in some cases was based solely on clinical characteristics and radiological criteria. We realize that the change rates could be

modified by concomitants treatment such as corticosteroids or tocilizumab, so the rates and their utility have to be proven in more cohorts but we found significant differences of blood cells proportions at hospital admission prior to any treatment. Finally, the in-hospital mortality shown in our results does not correspond to the overall mortality as during first wave, population's fear led to late hospital care, which resulted in a high percentage of deaths in the first 24 hours of admission and those patients were not included in the analysis even though they had blood tests, since the research team understood that the deterioration of the patient had taken place several days earlier and therefore the analytical control in the emergency room could bias the analysis. On the other hand, patients in an unfavorable social situation or with longer expected admissions discharged to medicalized hotels and therefore with unexpected deaths, were not taken into account since, although they presumably did not die, there was no reliable proof of this.

Conclusions

Hemogram-derived ratios at hospital admission and rates of ascent during first days of hospital stay have shown their usefulness as prognostic markers of inflammation in patients who ultimately died, especially NLR and novelty NPR.

Hemogram is easily measurable, available, cost-effective and reliable test that could be very useful in establishing the risk of mortality at hospital admission and guiding therapeutic decisions in patients with COVID-19. In this sense, the hemogram is a tool within the reach of all hospitals and doctors who do not have the technical and material means to carry out complex immunological studies, which often produce late results. The analysis of the blood cells proportions obtained from the hemogram would provide much more information than could be extracted a priori by evaluating the parameters in

isolation. We now know that it is crucial to initiate early anti-inflammatory treatment when the patient deteriorates and the hemogram could be an indicator of that signal that could indicate which patients could potentially benefit from earlier anti-inflammatory therapy. Further comprehensive studies are needed to determine how useful are these blood tests and future prognostic scores will demonstrate their usefulness in guiding treatment decisions.

Conflict of Interest

The authors have indicated they have no potential conflicts of interest to disclose.

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NA

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	Total (n = 2088)	Non-survivors (n = 321)	Survivors (n = 1767)	*P* value	Univariable análisis	
					OR (95%CI)	*P* value
Demographics characteristics						
Age (years)	69 (57 – 80)	83 (75 – 89)	66 (55 – 77)	**< 0.0001**	**1.09 (1.08 - 1.11)***	**< 0.0001**
Male (%)	59.6%	66.4%	58.4%	**0.0091**	**1.40 (1.10 - 1.81)**	**0.0078**
Comorbidities						
HT	36.1%	45.5%	34.4%	**0.00018**	**1.59 (1.25 - 2.02)**	**0.0002**
DM	17.8%	23.7%	16.7%	**0.0034**	**1.55 (1.16 - 2.05)**	**0.0028**
COPD	5.6%	10%	4.8%	**0.00036**	**2.19 (1.41 - 3.32)**	**0.0003**
CD	11.1%	20.9%	9.3%	**< 0.0001**	**2.58 (1.88 - 3.51)**	**< 0.0001**
Clinical Characteristics						
Temperature >38ºC (%)	6.8%	7.2%	6.8%	0.92	NA	NA
Heart rate (bpm)	89 (78-101)	87 (78 - 102)	89 (78 - 101)	0.86	NA	NA
BP max (mm Hg)	131 (117 - 146)	131 (114 - 146)	131 (118 - 146)	0.35	NA	NA
BP min (mm Hg)	76 (67 - 84)	72 (62 - 80)	76 (68 - 85)	**< 0.0001**	**0.98 (0.97 - 0.99)***	**< 0.0001**
Sat O2 (%) > 94%	51.9%	30.8%	55.7%	**< 0.0001**	NA	NA
Sat O2 (%) 90- 94%	20.6%	16.8%	21.3%	**< 0.0001**	**1.43 (1.00 - 2.02)**	**0.048**
Sat O2 (%) < 90%	14.9%	37.4%	10.9%	**< 0.0001**	**6.21 (4.57 - 8.47)**	**< 0.0001**

Table 1. Baseline Demographics and Clinical characteristics (% and median value (interquartile range)). * The variable is continuous, the OR is for each increment in a unit. Non-survivors vs Survivors. Abbreviations: HT, hypertension; DM, Diabetes; COPD: Chronic obstructive pulmonary disease; CD, cardiovascular disease; Bpm, beats per minute; $SatO_2$, oxygen saturation; BP, Blood Pressure.

	Total (n = 2088)	Non-survivors (n = 321)	Survivors (n = 1767)	p value	Univariable analysis	
					OR (95%CI)	*P* value
Laboratory findings						
White blood cells (10^9/L)	6.6 (5.0 - 8.8)	8.4 (5.8 - 12.0)	6.4 (4.9 - 8.4)	**< 0.0001**	**1.13 (1.10 - 1.16)***	**< 0.0001**
Red blood cells (10^12/L)	4.7 (4.3 - 5.1)	4.5 (4.0 - 4.9)	4.7 (4.3 - 5.1)	**< 0.0001**	**0.67 (0.56 - 0.81)***	**< 0.0001**
Neutrophils (10^9/L)	4.7 (3.3 - 6.8)	7.0 (4.4 - 10.1)	4.5 (3.2 - 6.3)	**< 0.0001**	**1.17 (1.14 - 1.21)***	**< 0.0001**
Lymphocytes (10^9/L)	1.1 (0.8 - 1.5)	0.8 (0.5 - 1.2)	1.1 (0.8 - 1.5)	**< 0.0001**	**0.58 (0.46 - 0.73)***	**< 0.0001**
Monocytes (10^9/L)	0.5 (0.3 - 0.7)	0.5 (0.3 - 0.7)	0.5 (0.3 - 0.7)	0.14	NA	NA
Platelets (10^9/L)	207 (160 - 267)	186 (151 - 249)	210 (163 - 270)	**< 0.0001**	**0.998 (0.996 - 0.999)***	**< 0.0001**
Hemoglobin (g/dL)	13.9 (12.6 - 15.0)	13.5 (11.9 - 14.8)	13.9 (12.8 - 15.0)	**0.00034**	**0.88 (0.83 - 0.94)***	**< 0.0001**
MCHC (g/dL)	33.7 (32.8 - 34.5)	33.2 (32.1 - 34.1)	33.7 (32.9 - 34.5)	**< 0.0001**	**0.70 (0.64 - 0.76)***	**< 0.0001**
MCV (fL)	88.2 (85.1 - 91.4)	90.3 (86.8 - 94.0)	87.9 (84.9 - 90.9)	**< 0.0001**	**1.07 (1.05 - 1.10)***	**< 0.0001**
MPV (fL)	10.3 (9.6 - 11.0)	10.5 (9.9 - 11.3)	10.2 (9.6 - 11.0)	**< 0.0001**	**1.37 (1.22 - 1.54)***	**< 0.0001**
AST (U/L)	31.6 (22.5 - 49.2)	37.7 (26.2 - 58.1)	30.6 (21.7 - 46.9)	**< 0.0001**	**1.01 (1.00 - 1.01)***	**0.0003**
ALT (U/L)	25.8 (16.1 - 42.6)	22.3 (14.2 - 37.9)	26.0 (16.6 - 43.6)	**0.0014**	1.00 (0.99 - 1.00)	0.3189
Creatinine (mg/dL)	0.9 (0.7 - 1.1)	1.1 (0.9 - 1.6)	0.9 (0.7 - 1.0)	**< 0.0001**	**4.28 (3.36 - 5.50)***	**< 0.0001**
LDH (U/L)	517 (394 - 673)	658 (509 - 935)	500 (383 - 639)	**< 0.0001**	**1.02 (1.02 - 1.03)***	**< 0.0001**
C-reactive protein (mg/L)	64 (24 - 131)	120 (68 - 229)	55 (21 - 115)	**< 0.0001**	**1.01 (1.01 - 1.01)***	**< 0.0001**
Urea (mg/dL)	34.1 (26.0 - 49.0)	56.0 (42.3 - 92.0)	32.4 (24.7 - 44.4)	**< 0.0001**	**1.03 (1.03 - 1.04)***	**< 0.0001**
Glucose (mg/dL)	114 (101 - 136)	126 (110 - 163)	112 (99 - 132)	**< 0.0001**	**1.01 (1.01 - 1.01)***	**< 0.0001**

Partial thromboplastin time (s)	32 (30 - 35)	32 (30 - 36)	32 (30 - 35)	0.076	**1.03 (1.01 - 1.04)***	**0.0010**
D-dimer (mg/L)	0.7 (0.4 - 1.4)	1.3 (0.7 - 2.7)	0.7 (0.4 - 1.2)	**< 0.0001**	**1.04 (1.02 - 1.06)***	**< 0.0001**
Prothrombine time (s)	13.2 (12.3 - 14.5)	14.1 (12.8 - 16.1)	13.1 (12.3 - 14.2)	**< 0.0001**	**1.01 (1.01 - 1.02)***	**0.0003**

Table 2. Laboratory findings at admission. Median value (interquartile range). *The variable is continuous, the OR is for each increment in a unit. Non-survivors vs Survivors. Abbreviations: MCHC, mean corpuscular hemoglobin concentration; MCV, Medium corpuscular volume; MPV, Medium platelet volume; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; NPR, neutrophil-platelets ratio; SII, systemic immune-inflammation index; AST, Aspartate aminotransferase; ALT; lactate aminotransferase; LDH, lactate dehydrogenase.

	Total (n = 2088)	**Non-survivors (n = 321)**	**Survivors (n = 1767)**	**p value**	**Univariable analysis**	
					OR (95%CI)	***P* value**
Hemogram rates at admission						
NLR	4.2 (2.7 - 7.8)	8.7 (4.3 - 14.3)	3.8 (2.5 - 6.7)	**< 0.0001**	**1.10 (1.08 - 1.12)***	**< 0.0001**
PLR	1.9 (1.3 - 2.9)	2.4 (1.5 - 3.7)	1.9 (1.3 - 2.8)	**< 0.0001**	**1.21 (1.14 - 1.29)***	**< 0.0001**
NPR	2.3 (1.6 - 3.3)	3.5 (2.4 - 5.0)	2.1 (1.5 - 3.0)	**< 0.0001**	**1.46 (1.37 - 1.56)***	**< 0.0001**
SII	9.1 (4.9 - 17.7)	16.4 (7.5 - 31.5)	8.5 (4.7 - 15.5)	**< 0.0001**	**1.03 (1.02 - 1.03)***	**< 0.0001**
Positive rate of change (> 10 % · day^-1)						
NLR	20.7%	39.3%	17.3%	**< 0.0001**	**4.79 (3.47 - 6.66)**	**< 0.0001**
PLR	27.3%	36.1%	25.6%	**< 0.0001**	**3.05 (2.24 - 4.17)**	**< 0.0001**
NPR	42.4%	49.5%	41.1%	**< 0.0001**	**2.58 (1.90 - 3.53)**	**< 0.0001**
SII	29.7%	42.4%	27.4%	**< 0.0001**	**3.68 (2.64 - 5.21)**	**< 0.0001**

Table 3. Hemogram rates findings. Median value. (interquartile range). * The variable is continuous, the OR is for each increment in a unit. Non-survivors vs Survivors. The rate of change of the different inflammation rates was obtained with up to four consecutive blood cells measurements since hospital entry. The rate of change was defined as the slope of the linear fit of the relative rates versus time from hospital entry in days. A rate of change higher than 10% per day was considered as positive. Abbreviations: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; NPR, neutrophil-platelets ratio; SII, systemic immune-inflammation index.

Variable	Cut-off	Sensitivity	Specificity
NLR	6.63	0.62 (0.52 - 0.70)	0.74 (0.69 - 0.83)
PLR	2.98	0.44 (0.35 - 0.69)	0.78 (0.51 - 0.83)
NPR	2.98	0.65 (0.56 - 0.79)	0.72 (0.57 - 0.79)
SII	13.87	0.57 (0.46 - 0.66)	0.71 (0.63 - 0.82)

Table 4. Optimal cut-off values for the different immunoinflammatory ratios with their sensitivities and specificities and their corresponding 95% confidence interval.

Model		NLR	PLR	NPR	SII
Unadjusted	OR (95% CI)	1.1 (1.08 - 1.12)	1.21 (1.14 - 1.29)	1.46 (1.37 - 1.56)	1.03 (1.02 - 1.03)
	p value	**< 0.0001**	**< 0.0001**	**< 0.0001**	**< 0.0001**
Model A	OR (95% CI)	1.08 (1.05 - 1.11)	1.13 (1.03 - 1.24)	1.33 (1.22 - 1.47)	1.02 (1.01 - 1.03)
	p value	**< 0.0001**	**0.011**	**< 0.0001**	**< 0.0001**
Model A + SatO2	OR (95% CI)	1.06 (1.04 - 1.09)	1.06 (0.955 - 1.18)	1.3 (1.18 - 1.43)	1.02 (1 - 1.03)
	p value	**< 0.0001**	0.24	**< 0.0001**	**0.0039**
Model B + LDH	OR (95% CI)	1.06 (1.03 - 1.09)	1.06 (0.945 - 1.17)	1.27 (1.15 - 1.4)	1.01 (1 - 1.02)
	p value	**< 0.0001**	0.32	**< 0.0001**	**0.015**
Model C + CRP	OR (95% CI)	1.05 (1.02 - 1.08)	1.01 (0.901 - 1.13)	1.23 (1.12 - 1.36)	1.01 (0.995 - 1.02)
	p value	**0.00035**	0.81	**< 0.0001**	0.27

Table 5. Multivariable adjusted models. Model A: Age, Dyastolic BP, NLR rate of change > 10% per day, creatinine, urea and glucose. Model B: Model A + Saturation O2. Model C: Model B + LDH. Model D: Model C + CRP. Abbreviations: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; NPR, neutrophil-platelets ratio; SII, systemic immune-inflammation index; BP, blood pressure; LDH, lactate dehydrogenase; CRP, C-reactive protein.

Figure 1A. Interactions and stratified analyses for NLR (neutrophil-lymphocyte ratio) adjusted to model A (Table 5) and conducted for age (< 75 and > 75 years), sex, cardiovascular disease (CD), diabetes mellitus (DM), oxygen saturation (< 90 and > 90 %) ($SatO_2$), and lactate dehydrogenase (LDH) and C-reactive protein (CRP) both categorized through their respective median values.

Figure 1B. Interactions and stratified analyses for NPR (neutrophil-platelets ratio) adjusted to model A (Table 5) and conducted for age (< 75 and > 75 years), sex, cardiovascular disease (CD), diabetes mellitus (DM), oxygen saturation (< 90 and > 90 %) ($SatO_2$), and lactate dehydrogenase (LDH) and C-reactive protein (CRP) both categorized through their respective median values.

Supplementary Figure S1C. Interactions and stratified analyses for PLR (platelet-lymphocyte ratio) adjusted to model A (Table 5) and conducted for age (< 75 and > 75 years), sex, cardiovascular disease (CD), diabetes mellitus (DM), oxygen saturation (< 90 and > 90 %) ($SatO_2$), and lactate dehydrogenase (LDH) and C-reactive protein (CRP) both categorized through their respective median values.

Supplementary Figure S1D. Interactions and stratified analyses for SII (systemic immune-inflammation index) adjusted to model A (Table 5) and conducted for age (< 75 and > 75 years), sex, cardiovascular disease (CD), diabetes mellitus (DM), oxygen saturation (< 90 and > 90 %) ($SatO_2$), and lactate dehydrogenase (LDH) and C-reactive protein (CRP) both categorized through their respective median values.

Supplementary Figure S2. ROC curves for the different immunoinflammatory ratios and their respective areas under the curves (AUC).

Supplementary Figure S3. Correlation analysis between the four hemogram ratios. Abbreviations: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; NPR, neutrophil-platelet ratio; SII, systemic immune-inflammation index.

Supplementary Figure S4A. Correlation analysis between NLR and NPR and those variables that were significantly associated with mortality. Abbreviations: NLR, neutrophil-to-lymphocyte ratio; NPR, neutrophil-to-platelet ratio; BP min, minimum blood pressure; HGB, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; WBC, white blood cells; RBC, red blood cells; NEU, neutrophils; LYM, lymphocytes;

EOS , eosinophils; PLAT, platelets; AST, aspartate aminotransferase; CREA, creatinine; LDH, lactate dehydrogenase; CRP, C-reactive protein; DD, D-dimer; PT, prothrombin time; GLU, glucose.

Supplementary Figure S4B. Correlation analysis between PLR and SII and those variables that were significantly associated with mortality. Abbreviations: PLR (platelet-to-lymphocyte ratio); SII (systemic immune-inflammation index); BP min (minimum blood pressure), HGB (mean corpuscular hemoglobin); MCHC (mean corpuscular hemoglobin concentration); MCV (mean corpuscular volume); MPV (mean platelet volume); WBC (white blood cells); RBC (red blood cells); NEU (neutrophils); LYM (lymphocytes); EOS (eosinophils); PLAT (platelets); AST (aspartate aminotransferase); CREA (creatinine); LDH (lactate dehydrogenase); CRP (C-reactive protein); DD (D-dimer); PT (prothrombin time); GLU (glucose).

Supplementary Figure S5. Patients Flowchart