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Original article

Derivation and validation of a simple inflammation-based risk score system for predicting in-hospital mortality in acute coronary syndrome patients



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ABSTRACT

Background: Accurate assessment of inflammatory status of patients during acute coronary syndrome (ACS) has become of great importance in their risk classification and in the research of new anti-inflammatory therapies.

Method: The study cohort included 7396 patients with ACS. We sought to derive and internally validate an inflammation-based score that included high-sensitivity C-reactive protein, white blood cell count, and serum albumin level at admission to evaluate the predictive role of systemic inflammation in the clinical outcome of these patients. We randomly assigned patients into derivation (66.6%) and validation (33.4%) cohorts. A total of four categories of systemic inflammation were defined.

Results: Assessed individually, the three biomarkers were associated with a higher rate of in-hospital mortality. When we combined them into an inflammation score, in-hospital mortality was significantly different across the four categories of inflammation in the derivation cohort (1.8%, 2.8%, 4.1%, and 13.8% for without, mild, moderate, and severe inflammation, respectively; $p < 0.0001$, C-statistic, 0.71). These results were similar in the validation cohort (1.1%, 2.9%, 5.2%, and 12.6%, respectively; $p < 0.0001$, C-statistic, 0.71). After multivariate adjustment, only the category of severe systemic inflammation was associated with a threefold increased risk of in-hospital mortality (odds ratios 3.02, $p < 0.0001$) and was the most powerful predictor of mortality. In the whole cohort, after subsetting patients based on GRACE risk score, the severe inflammation category was associated with a significant increase of in-hospital mortality across all sub-groups, mainly in patients with higher GRACE risk score. The inflammation-based risk score reclassified 25.3% of the population. The net reclassification index was 8.2% ($p = 0.001$).

Conclusion: A risk score system based on biomarkers of inflammation readily available at admission in patients with ACS, could better assess the inflammatory status and predict in-hospital mortality, as well as severe systemic inflammation that contributes to a worse outcome independently of clinical risk factors.

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Introduction

Nowadays, it is considered that inflammation is involved in many aspects of the acute coronary syndrome (ACS), not only in coronary plaque destabilization, but also in modulating the clinical consequences, systemic response, and resolution of ACS [1]. Therefore, it is unsurprising that different inflammation biomarkers have been used to identify ACS patient subgroups at increased risk of major cardiovascular events, independent of their degree of myocardial damage [2–4]. However, the clinical risk scores developed to date for ACS patient risk stratification at hospital admission have not considered the patient's inflammatory status [5,6]. Currently, high-sensitivity C-reactive protein (hs-CRP) has become the preferred inflammatory biomarker, when it is elevated at hospital admission it predicts poor outcome in patients with ACS [7]. However, interpreting the incremental predictive value of adding hs-CRP to well-established risk scoring systems to predict in-hospital mortality during ACS is complicated [8] and has only been partially investigated [9].

In this study, we developed and internally validated a simplified inflammation-based risk score based on a combination of three readily available inflammatory biomarkers [hs-CRP, white blood cell count (WBC), and serum albumin] at admission; these were used to categorize ACS patients based on their systemic inflammation severity. We postulated that simultaneous assessment of all three acute phase reactants would provide complementary information to stratify ACS patients better, based on their inflammatory status, compared with hs-CRP alone. In addition, we explored whether inflammatory status, as assessed by this novel score, could be used to identify additional subsets of at-risk groups when they are categorized according to the Global Registry of Acute Coronary Events (GRACE) scoring system.

Materials and methods

This was a retrospective cohort study using data from the Coronary Care Unit of the National Institute of Cardiology in Mexico City. We analyzed data from all patients with an ACS diagnosis who were admitted to the Coronary Care Unit from October 2005 to February 2015.

Inclusion criteria were: (i) ACS diagnosis, identified and classified as having either ST-elevation myocardial infarction (STEMI) or non-ST-elevation ACS (NSTEMI-ACS), according to standard definitions by the American College of Cardiology [10] and (ii) based on the available data, we included hs-CRP, WBC count, and serum albumin, as inflammatory biomarkers, all of which are known acute-phase reactants in inflammatory disorders [11]. These biomarkers were determined within the first 24 h of admission. Exclusion criteria were: (i) clear inflammatory pathologies at admission (e.g. infection established by clinical, laboratory, or imaging investigations, and patients with an autoimmune disease or cancer previously diagnosed or documented during their current hospitalization), (ii) significant hepatic failure, and (iii) no laboratory data for hs-CRP, WBC count, and serum albumin on the day of admission.

To develop an integer score that could be translated into a clinically relevant model, all eligible patients were randomly assigned to either a derivation or a validation cohort in a 2:1 manner, respectively. Mortality was defined as all-cause mortality during hospitalization.

Each patient's GRACE risk score for in-hospital mortality at admission was calculated [6]. In addition, three predefined categories were used for NSTEMI-ACS: low-risk (≤ 108 points), intermediate-risk (109–140 points), and high-risk (> 140 points) [12]; and for STEMI: low-risk (≤ 125 points), intermediate-risk (126–154 points), and high-risk (> 155 points) [13].

Statistical analyses

Categorical data were summarized as frequencies and percentages. Multiple Kolmogorov–Smirnov tests were applied and indicated that none of the quantitative variables were normally distributed. Continuous variables were reported as median and 25th and 75th percentiles (interquartile ranges, IQRs). Statistically significant differences between groups were assessed, using either chi-square or Fisher's exact probability tests for categorical variables, or Kruskal–Wallis or Mann–Whitney *U* tests, as appropriate, for continuous variables.

In the derivation cohort, a cubic splines transformation was used to assess non-linear relationships between each of the inflammatory biomarkers and the estimated probability of in-hospital mortality. To determine the optimal cut-off for each inflammatory biomarker for predicting in-hospital mortality, receiver operating characteristic (ROC) curve analysis was performed, and the exact value was determined using Youden's index (sensitivity [1 – specificity]), which is a discriminatory cut-off method for diverse biomarkers [14,15]. Continuous data from each biomarker level were categorized using the pertinent cut-off values.

In-hospital mortality rates were calculated according to inflammation-based risk score categories and were expressed as a percentage; group differences were evaluated by chi-square tests. The discriminatory capacity of the inflammation-based risk score categories for predicting in-hospital mortality was determined using the area under the ROC curve (C-statistic). Calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test and was satisfied when $p > 0.05$.

Initially, only data from the derivation cohort were used to estimate the risk of in-hospital mortality associated with each inflammation-based risk score category. Using the category “without systemic inflammation” as a reference, univariate analysis was performed to estimate the odds ratios (OR) for risk of in-hospital mortality associated with each inflammation-based risk score category. Each of the inflammatory biomarkers was subjected to further analysis of discrimination via iterative model building, assessing change in area under the curve (AUC) with the addition of biomarkers to the base model (age, gender, and ACS type), along with assessment of improvement in calibration from their addition through minimization of the Akaike (AIC) and Bayesian information criteria (BIC). A multivariable regression model with backward selection was then used to adjust for potential confounding on the basis of established associations between different inflammation-based risk score categories and in-hospital mortality. Candidate covariates included in the multivariate analysis were selected from clinical variables at the time of admission (Table 1), and that were associated with mortality in a univariate analysis with $p \leq 0.05$. OR with 95% confidence interval (CI) was calculated. Calibration of the model was evaluated using the Hosmer–Lemeshow goodness-of-fit test. The discriminative power of the final model was determined using C-statistic. Inflammation-based risk score categories were evaluated in terms of discrimination and calibration in the validation cohort.

We evaluated the interaction between inflammation-based risk score categories paired with respective GRACE score categories for in-hospital mortality. To get a sense of clinical usefulness, net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) were calculated as a measure to estimate any overall improvement in reclassification using the combination of our inflammation-based risk score with GRACE risk score instead of the GRACE risk score alone. We carried out the reclassification process using four groups of different risk level chosen in accordance with a previous study: $< 1\%$, 1 to $< 5\%$, 5% to

Table 1
Baseline characteristics of patients in the derivation cohort according to the inflammation-based score categories.

	Inflammatory status					p-Value
	Derivation (n=4932)	Without (n=1063)	Mild (n=1324)	Moderate (n=1473)	Severe (n=1072)	
Age median, (IQR) (years)	60 (52–69)	61 (53–69)	58 (51–67)	60 (52–69)	63 (56–71)	<0.0001
Men, n (%)	3906 (79.2)	812 (76.4)	1097 (82.9)	1157 (78.5)	840 (78.4)	0.001
Body mass index median, (IQR) (kg/m ²)	26.9 (24.8–29.4)	26.9 (24.8–29.3)	27.0 (24.9–29.4)	26.9 (24.9–29.4)	26.8 (24.5–29.3)	0.30
Current smoking, n (%)	1404 (28.5)	235 (19.3)	431 (32.6)	457 (31.0)	311 (29.0)	<0.0001
Hypertension, n (%)	2889 (58.6)	654 (61.5)	736 (55.6)	848 (57.6)	651 (60.7)	0.01
Dyslipidemia, n (%)	2152 (43.6)	546 (51.4)	587 (44.3)	607 (41.2)	412 (38.4)	<0.0001
Diabetes, n (%)	1931 (39.2)	388 (36.5)	444 (33.5)	554 (37.6)	545 (50.8)	<0.0001
Previous MI, n (%)	1468 (29.8)	444 (41.8)	377 (28.5)	388 (26.3)	259 (24.2)	<0.0001
Previous CABG, n (%)	235 (4.8)	81 (7.6)	60 (4.5)	53 (3.6)	41 (3.8)	<0.0001
Previous PCI, n (%)	739 (15.0)	241 (22.7)	187 (14.1)	195 (13.2)	116 (10.8)	<0.0001
Previous heart failure, n (%)	399 (8.1)	76 (7.1)	82 (6.2)	118 (8.0)	123 (11.5)	<0.0001
Previous stroke, n (%)	125 (2.5)	25 (2.4)	21 (1.6)	32 (2.2)	47 (4.4)	<0.0001
Family history of CAD, n (%)	365 (7.4)	102 (9.6)	104 (7.9)	115 (7.8)	44 (4.4)	<0.0001
Previous statin, n (%)	1497 (30.4)	450 (42.3)	398 (30.1)	385 (26.1)	264 (24.6)	<0.0001
Previous aspirin, n (%)	2008 (40.7)	616 (57.9)	525 (39.7)	499 (33.9)	368 (34.3)	<0.0001
Clinical features at admission						
Type of ACS (%)						<0.0001
STEMI	2256 (45.7)	189 (17.8)	627 (47.4)	794 (53.9)	646 (60.3)	
NSTE-ACS	2676 (54.3)	874 (82.2)	697 (52.6)	679 (46.1)	426 (39.7)	
Killip class ≥2 (%)	1158 (23.5)	119 (11.2)	201 (15.2)	363 (24.6)	475 (44.3)	<0.0001
Heart rate, median (IQR) (beats/min)	77 (68–89)	73 (65–80)	76.0 (68–86)	78 (70–90)	80 (70–97)	<0.0001
Systolic blood pressure, median (IQR) (mmHg)	130 (114–145)	130 (120–148)	130 (119–147)	130 (114–145)	120 (110–140)	<0.0001
LVEF, median (IQR) (%)	51 (43–60)	55 (49–60)	54 (45–60)	50 (43–58)	45 (36–55)	<0.0001
LVEF < 40% (%)	1105 (22.4)	156 (14.7)	228 (17.2)	326 (22.1)	395 (36.8)	<0.0001
C-reactive protein, median (IQR) (mg/L)	12.6 (5.3–36.2)	4.5 (2.4–7.6)	10.8 (5.4–21.4)	15.3 (7.0–38.3)	52.9 (24.0–120)	<0.0001
Albumin, median (IQR) (g/dL)	3.8 (3.5–4.0)	4.0 (3.8–4.2)	4.0 (3.8–4.1)	3.7 (3.4–3.9)	3.3 (3.0–3.5)	<0.0001
WBC, median (IQR) (×10 ³ /μL)	9.4 (7.6–12.0)	7.4 (6.3–8.2)	9.7 (8.1–11.8)	10.9 (9.3–13.0)	10.7 (8.3–13.4)	<0.0001
Hemoglobin, median (IQR) (g/dL)	14.7 (13.2–16.0)	14.7 (13.6–15.9)	15.1 (13.9–16.2)	14.8 (13.1–16.0)	13.8 (12.1–15.2)	<0.0001
Total cholesterol, median (IQR) (mg/dL)	163 (133–195)	166 (135–200)	170 (143–200)	166 (136–196)	144 (117–176)	<0.0001
HDL-C, median (IQR) (mg/dL)	36 (31–43)	37 (32–45)	37 (32–43)	36 (31–44)	35 (29–40)	<0.0001
LDL-C, median (IQR) (mg/dL)	98 (73–123)	101 (75–126)	104 (79–128)	101 (75–123)	85 (64–110)	<0.0001
Triglycerides, median, (IQR) (mg/dL)	144 (107–195)	149 (107–200)	153 (116–209)	149 (111–199)	128 (98–168)	<0.0001
Serum creatinine, median (IQR) (mg/dL)	1.0 (0.8–1.2)	0.9 (0.8–1.1)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.1 (0.9–1.6)	<0.0001
Renal dysfunction ^a (%)	1325 (26.9)	202 (19.0)	253 (19.1)	402 (27.3)	468 (43.7)	<0.0001
cTnI > 0.16 ng/mL (%)	3546 (71.9)	545 (51.3)	916 (69.2)	1151 (78.1)	934 (87.1)	<0.0001
Blood glucose level, median (IQR) (mg/dL)	130 (104–186)	112 (96–150)	128 (104–177)	134 (109–194)	151 (111–223)	<0.0001
GRACE score, median (IQR)	129 (103–155)	112 (89–133)	120 (97–143)	133 (109–156)	151 (128–180)	<0.0001
GRACE risk category (%) ^b						<0.0001
Low-risk	1846(37.4)	533 (50.1)	632 (47.7)	494 (33.5)	187 (17.4)	
Intermediate-risk	1586 (32.2)	358 (33.7)	405 (30.6)	501 (34.0)	322 (30.0)	
High-risk	1500 (30.4)	172 (16.2)	287 (21.7)	478 (32.5)	563 (52.5)	

^a Creatinine depuration ≤60 mL/min at the time of admission (according to the Cockcroft–Gault formula).

^b For NSTE-ACS, low-risk (≤108 points), intermediate-risk (109–140 points), and high-risk (>140 points). For STEMI, low-risk (≤125 points), intermediate-risk (126–154 points), and high-risk (>155 points).

MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; LVEF, left ventricular ejection fraction; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; cTnI, cardiac troponin I.

<10%, and >10% [9]. Unadjusted and adjusted multivariable Cox proportional hazards modeling was used to assess the relationship between each systemic inflammation category and time to in-hospital mortality. Variable candidates for best fit model were initially determined by univariate relationship with mortality, and only variables with $p \leq 0.05$ were retained for the final model.

All tests were two-sided, and $p \leq 0.05$ was considered to be statistically significant. SPSS software (version 20; SPSS, Chicago, IL, USA) and R software (version 3.1.0; The R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses.

Results

During the study period, 8286 patients were admitted with a final diagnosis of ACS, among whom 890 were excluded from the study. Thus, the final analyses were based on 7396 patients who met the inclusion criteria; 4932 patients were assigned to the derivation cohort and 2464 to the validation cohort (Fig. 1). With

the exception of lower levels of serum albumin, total cholesterol, low-density lipoprotein cholesterol, and triglycerides in the validation cohort, there were no significant differences in either baseline characteristics or presenting clinical features between the derivation and validation cohorts (Supplementary Table 1).

Derivation cohort analyses

The relationship between each of the inflammatory biomarkers and the probability of in-hospital mortality was modeled using logistic regression and was found to be non-linear. ROC curve analysis in the derivation cohort identified the cut-off values for each of the inflammatory biomarkers that best discriminated between survivors and non-survivors: WBC $\geq 9.3 \times 10^3/\mu\text{L}$ (C statistic = 0.63); hs-CRP ≥ 13.0 mg/L (C statistic = 0.68); and serum albumin ≤ 3.6 g/dL (C statistic = 0.71) (Supplementary Fig. S1).

An in-hospital mortality risk score was created by assigning weighted values to each of the inflammation biomarkers, based on the OR for in-hospital mortality. Point values were: 1 point for WBC

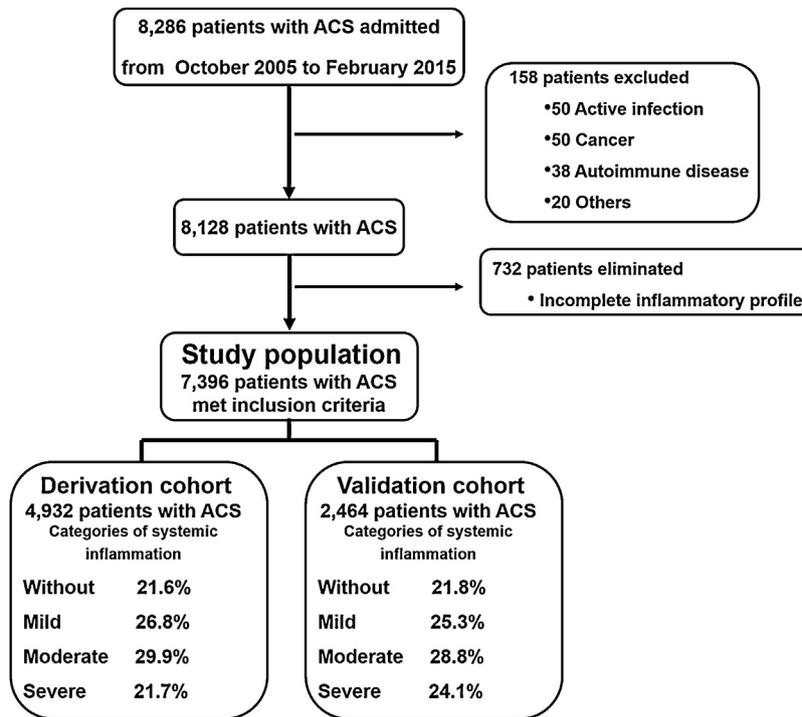


Fig. 1. Flow chart illustrating the study sample selection. ACS, acute coronary syndrome.

$\geq 9.3 \times 10^3/\mu\text{L}$, 2 points for $\text{hs-CRP} \geq 13.0 \text{ mg/L}$, and 3 points for albumin $\leq 3.6 \text{ g/dL}$ (Supplementary Table 2). The observed rates of in-hospital mortality according to this scoring system are shown in Fig. 2. Among the 4932 patients, four categories of systemic inflammation were created based on the point totals: without inflammation, 0 points (21.6% of the patients); mild inflammation, 1–2 points (26.8%); moderate inflammation, 3–4 points (29.9%); and severe inflammation, 5–6 points (21.7%) (Table 2).

Patients with severe inflammation were older and significantly more likely to have a history of diabetes, heart failure, and stroke compared with patients without inflammation. In addition, levels of hemoglobin, lipoproteins, and triglycerides were lower among patients with severe inflammation. In contrast, patients without inflammation were more likely to have multiple risk factors, such as a history of hypertension, dyslipidemia, myocardial infarction, percutaneous coronary intervention, and coronary bypass surgery. A history of previous aspirin and statin use at admission was more frequent in patients in the without-inflammation category (Table 1).

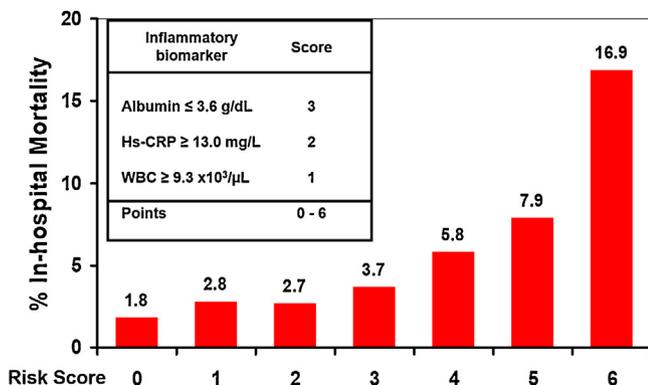


Fig. 2. Integer scoring system and corresponding in-hospital mortality rates. Hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell count.

At presentation, patients in higher-inflammation categories were more likely to have STEMI and high-risk clinical features, as reflected by an overall higher GRACE risk score ($p < 0.0001$) (Table 1). During hospitalization, patients in higher-inflammation categories were less likely to be taking beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists. Among patients with STEMI, those with higher scores were less likely to receive reperfusion therapy (Supplementary Table 3).

Predictors of in-hospital mortality

In the derivation cohort, in-hospital all-cause mortality occurred in 265 patients (5.4%). In these patients, median age was 62 years, 31.7% were women and the 65.1% of the patients had STEMI. Of all deaths, 256 (96.6%) were cardiovascular causes during hospitalization, mainly because of cardiogenic shock, heart failure, ventricular arrhythmias, and stroke.

Elevated concentrations of $\text{hs-CRP} (\geq 13.0 \text{ mg/dL})$ and WBC count ($\geq 9.3 \times 10^3/\mu\text{L}$), and low levels of albumin ($\leq 3.6 \text{ g/dL}$) were individually associated with a higher rate of mortality (hs-CRP 2.7% vs 8.1%; WBC count 3.1% vs 7.4%; and albumin 2.8% vs 10.1%; $p < 0.0001$).

The unadjusted rate of in-hospital mortality was significantly higher among patients with severe inflammation (1.8%, 2.8%, 4.1%, and 13.8% for without, mild, moderate, and severe inflammation, respectively; $p < 0.0001$). The area under the ROC curve was 0.71, indicating good discriminatory power, with a Hosmer–Lemeshow statistic ($p > 0.99$), suggesting appropriate goodness-of-fit (Fig. 3A). Model fitting performed on the derivation cohort showed that the addition of each individual biomarker to age, gender, and type of ACS improved mortality discrimination, as evidenced by minimization of the Akaike or Bayesian information criteria and the increase of the AUC (Table 3).

Statistically significant univariate predictors of in-hospital mortality in the derivation cohort are listed in Supplementary Table 4. Patients in the moderate and severe inflammation-based

Table 2
Inflammation-based risk score categories.

Biomarker combination	Total of points	Category of systemic inflammation
All 3 biomarkers beyond threshold	0	No signs of systemic inflammation
WBC ≥ 9.3 or hs-CRP ≥ 13.0	1–2	Mild
Albumin ≤ 3.6 or WBC ≥ 9.3 and hs-CRP ≥ 13.0 or WBC ≥ 9.3 and albumin ≤ 3.6	3–4	Moderate
hs-CRP ≥ 13.0 and albumin ≤ 3.6 or All 3 biomarkers	5–6	Severe

hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell.

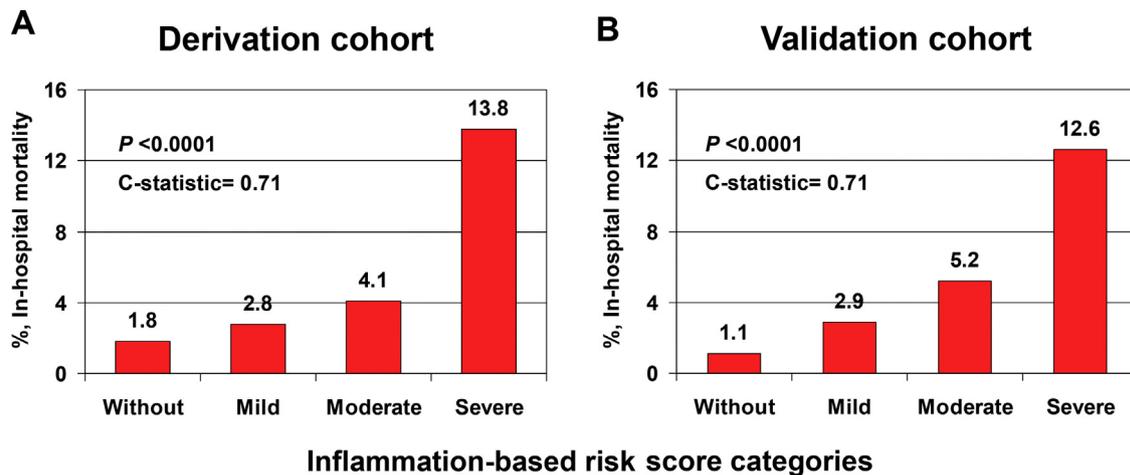


Fig. 3. Inflammation-based risk score categories with corresponding in-hospital mortality rate and discriminatory performance in the derivation (A) and validation (B) cohorts.

Table 3
Model discrimination for univariate biomarker models compared to inflammation-based classification for derivation cohort.

	Log likelihood ratio test	χ^2	BIC	AIC	AUC	p-Value
Model 1						
Age + gender (male as reference)	37.69	38.79	3858	3851	0.63	<0.0001
Model 2						
Age + gender + ACS type	84.81	87.59	3816	3806	0.67	<0.0001
Model 3						
Age + gender + ACS type + WBC ≥ 9.3 ($\times 10^3/\mu\text{L}$) alone	109.3	109.7	3798	3783	0.69	<0.0001
Model 4						
Age + gender + ACS type + hs-CRP ≥ 13 (mg/L) alone	117.5	117.9	3789	3775	0.70	<0.0001
Model 5						
Age + gender + ACS type + albumin ≤ 3.6 (g/dL) alone	128.5	133.1	3778	3764	0.71	<0.0001
Model 6						
Age + gender + ACS type + inflammation-based risk score categories	157.5	169.9	3760	3739	0.73	<0.0001

BIC, Bayesian information criterion; AIC, Akaike information criterion; AUC, area under the curve; ACS, acute coronary syndrome; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein.

risk score categories had an increased risk of in-hospital mortality. After adjusting for potential confounders in the multivariate analysis, only the severe inflammation category was associated with a threefold increased risk of in-hospital mortality (OR 3.02; 95% CI 1.79–5.09, $p < 0.0001$), and it was the most powerful predictor of mortality (Fig. 4). The C-statistic for the fully adjusted model was 0.84 (95% CI 0.81–0.86, $p < 0.0001$), suggesting good model discrimination. The Hosmer–Lemeshow goodness-of-fit test indicated good calibration for the model ($p = 0.25$) (Table 4).

Internal validation of inflammation-based risk score

In-hospital mortality occurred for 139 (5.6%) of the 2464 patients in the validation cohort. In addition, the rates of in-hospital mortality were close to the results in the derivation

cohort of the four risk groups. The predictive accuracy of this scoring system for mortality was good (C-statistic = 0.71), as well as calibration ($p > 0.99$) when applied to the validation cohort (Fig. 3B).

Impact of the inflammatory status on the in-hospital mortality in each category of GRACE risk score

We applied the GRACE risk score in the overall study cohort. The patients in the high-risk group based on their GRACE score had significantly higher rates of in-hospital mortality (1.5%, 2.8%, and 13.3% for low-, intermediate-, and high-risk patients, respectively; $p < 0.0001$) (Fig. 5A). Fig. 5B shows the in-hospital mortality rate for each of the 12 subgroups obtained by combining both scores. The inflammation-based risk score had an impact in all categories

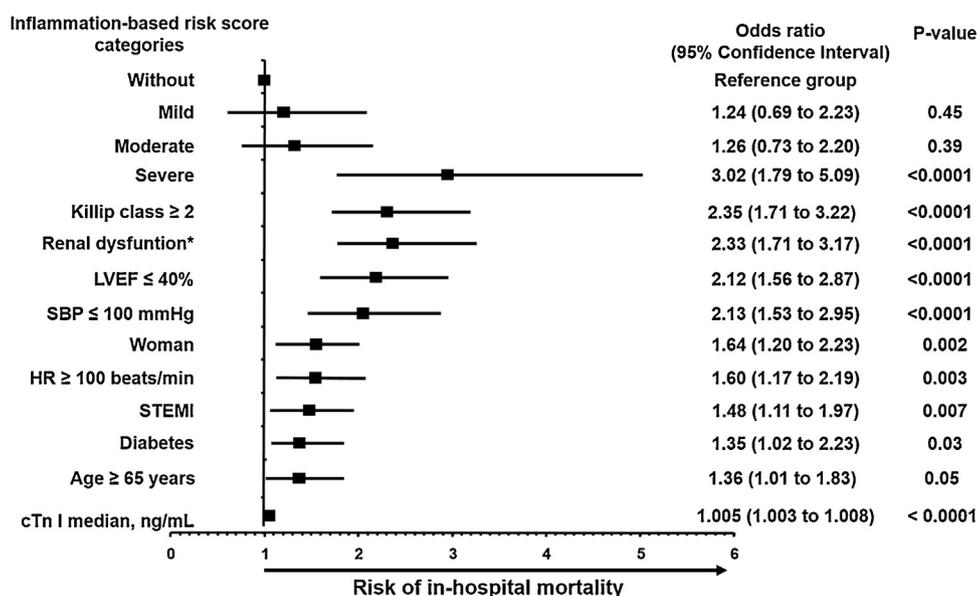


Fig. 4. Independent predictors of in-hospital mortality in the multiple logistic regression model. *Creatinine deputation ≤ 60 mL/min at hospital admission (according to the Cockcroft–Gault formula). SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; HR, heart rate; STEMI, ST-elevation myocardial infarction; cTn I, cardiac troponin I.

Table 4
Hazard ratios for in-hospital mortality by subtype of acute coronary syndrome.

	Overall (n = 7396)			STEMI (n = 3408)			NSTE-ACS (n = 3988)		
	Hazard ratio	95% confidence interval	p-Value	Hazard ratio	95% confidence interval	p-Value	Hazard ratio	95% confidence interval	p-Value
Inflammation-based risk score categories									
Without inflammation		Reference group			Reference group			Reference group	
Mild	1.32	0.81–2.14	0.25	1.86	0.55–6.23	0.31	1.51	0.87–2.63	0.14
Moderate	1.44	0.91–2.27	0.11	2.76	0.86–8.84	0.08	1.09	0.62–1.91	0.75
Severe	2.13	1.36–3.32	0.001	3.53	1.11–11.23	0.03	2.16	1.29–3.62	0.003
Age ≥ 65 years	1.40	1.12–1.75	0.003	1.31	0.99–1.73	0.054	1.72	1.19–2.50	0.004
Gender (female)	1.50	1.19–1.88	<0.0001	–	–	–	2.04	1.45–2.88	<0.0001
Diabetes	1.22	0.99–1.50	0.056	1.39	1.07–1.80	0.01	–	–	–
STEMI	1.23	0.96–1.57	0.09	–	–	–	–	–	–
Killip class ≥ 2	2.08	1.61–2.69	<0.0001	2.13	1.51–3.02	<0.0001	2.10	1.45–3.05	<0.0001
Heart rate > 100 beats/min	1.31	1.04–1.65	0.01	1.40	1.06–1.85	0.01	–	–	–
Systolic blood pressure < 100 mmHg	1.50	1.18–1.89	0.001	1.84	1.40–2.42	<0.0001	–	–	–
LVEF $< 40\%$	1.84	1.46–2.32	<0.0001	1.75	1.30–2.36	<0.0001	1.93	1.34–2.78	<0.0001
Renal dysfunction ^a	2.00	1.58–2.53	<0.0001	2.17	1.62–2.91	<0.0001	1.71	1.17–2.50	0.005
cTn I (by ng/mL increments)	1.005	1.003–1.007	<0.0001	1.004	1.001–1.006	0.002	1.009	1.004–1.015	0.001

^a Creatinine deputation ≤ 60 mL/min at the time of admission (according to the Cockcroft–Gault formula); STEMI, ST-elevation myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; LVEF, left ventricular ejection fraction; cTn I, cardiac troponin I.

of GRACE risk score, perhaps the most dramatic finding was among patients with high GRACE risk scores, a severe systemic inflammation was associated with a mortality of 20.2% compared with 4.1% in the category without inflammation. Indeed, it appears that systemic inflammation may contribute to a worse outcome in spite of having similar clinical risk factors.

In the whole cohort, adding the inflammation-based risk score to the GRACE score had a better discrimination, compared with the GRACE risk score alone (C-statistic 0.78, vs 0.74; $p = 0.005$). The combination of both scores reclassified 25.3% of the study population (1877/7396) into higher- or lower-risk categories. The NRI associated with the addition of inflammation-based risk score was 8.2% ($p = 0.001$). This corresponded to 3.4% rate of correctly reclassifying events and 4.8% rate of correctly reclassifying nonevents. The IDI was also significant ($p < 0.0001$) (Supplementary Table 5).

Finally, we performed Cox proportional hazard regression model adjusted for key baseline characteristics to determine the

association between inflammation categories and in-hospital outcome. In this model, only patients with severe inflammation remained at higher risk for death (hazard ratio 2.13, CI 1.36–3.32, $p = 0.001$). Cox regression models were also estimated separately for STEMI and NSTE-ACS. As before, in both cases only the score related to severe inflammation remained as a higher risk for death (hazard ratio 3.53, CI 1.11–11.23, $p = 0.03$ and hazard ratio 2.16, CI 1.29–3.62, $p = 0.003$, respectively) (Supplementary Table 6).

Discussion

Using a retrospective cohort of ACS patients, we derived and internally validated inflammation-based risk score categories that include readily available biomarkers of inflammation, including hs-CRP, serum albumin levels, and WB, at hospital admission. Our results demonstrated, first, that the inflammation-based risk score has good discriminative ability to predict in-hospital mortality in both derivation and validation patient cohorts with ACS. Second, a

Overall cohort 7396 patients with ACS

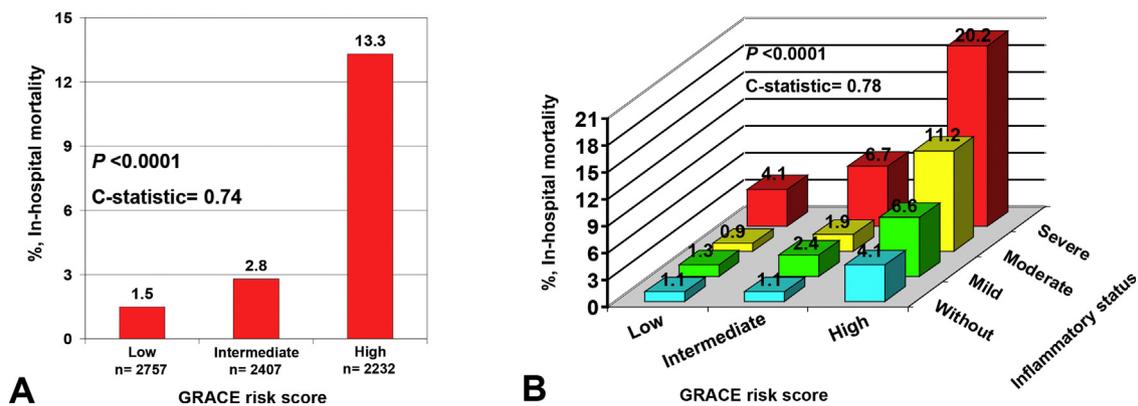


Fig. 5. (A) Distribution of the in-hospital mortality rates in the different risk groups for the GRACE score in the overall study cohort. (B) This 3-dimensional plot shows the relationship of in-hospital mortality (%) between the inflammation-based risk score and GRACE risk score. ACS, acute coronary syndrome.

severe systemic inflammation is a strong independent predictor for in-hospital mortality, even after adjusting for common cardiovascular risk factors. Third, approximately one-fifth of patients had severe systemic inflammation. Fourth, a severe inflammation was associated with increased in-hospital mortality across all GRACE risk score categories.

It has been considered that the sources of inflammation in the setting of ACS are: (i) the inflammatory process at the site of the culprit plaque; (ii) the iatrogenic myocardial injury; and (iii) resulting from myocardial ischemia and necrosis. The latter is an additional source for a local and systemic inflammatory response [16]. Currently, the optimal inflammatory biomarker for assessing a patient's inflammatory status does not exist, and the evaluation of the inflammatory state is based mainly on CRP. We integrated a score comprising three inflammatory biomarkers, each of which has been associated with worse prognosis in ACS patients [7,17–20]. Our results show that this combination of biomarkers had stronger discriminative power than any of the biomarkers alone. Indeed, the derived inflammation-based risk score categorization had great power to discriminate survivors from non-survivors. We postulated that selecting multiple biomarkers representing distinct components of systemic inflammation would improve discriminative power and reduce prediction error compared with using each biomarker in isolation. CRP is synthesized and released from hepatocytes in response to several inflammatory cytokines mainly interleukin-6 [21]. The decrease in albumin synthesis during inflammation is mediated by interleukin-6, interleukin-1 β , and tumor necrosis factor [22–24], while leukocytes can exacerbate inflammatory signaling and establish chemotactic gradients to guide other leukocyte populations to the injury site [25]. Indeed, in addition to its simplicity, the inflammation-based risk score categories were found to have good predictive capacity for in-hospital mortality, and calibration was satisfactory for both derivation and validation cohorts.

The multivariate analyses showed that factors associated with in-hospital mortality in ACS patients consistent with those recently reported by McNamara: age, heart rate, systolic blood pressure, presentation after cardiac arrest, presentation in cardiogenic shock, presentation in heart failure, presentation with STEMI, creatinine clearance, and troponin ratio [26]. However, we have also highlighted here that the highest inflammation-based risk score category was the strongest independent predictor of in-hospital mortality even after adjusting for variables recognized as prognostic factors. It has been described that the systemic

inflammatory response syndrome can develop in 25% of patients with acute myocardial infarction, and was independently associated with a poor outcome. The excessive inflammatory response could be caused by a deregulated immune system due to infarct tissue, deteriorated hemodynamics, and adrenergic activation [27,28].

The addition of inflammatory biomarkers to different clinical risk scores is considered to improve their prognostic strength only moderately [9,29]. Schiele et al. reported that the combination of GRACE risk score with high CRP concentration improves risk classification [9]. We demonstrated that the addition of inflammation-based risk score category to GRACE risk score significantly improved discrimination of in-hospital mortality over GRACE risk score, as evidenced by improvement in the C-statistic and NRI. However, we believe that assessing inflammatory status in the context of well-established clinical risk scores, such as GRACE, allows identification of subgroups – those with severe inflammation – at higher risk of death and highlights the absence of inflammation as a low mortality risk, regardless of GRACE risk score values.

This observation is consistent with the proposal by Crea and Libby [30,31], who suggested a pathogenetic classification of ACS based on inflammation. They recommend to distinguish coronary artery thrombosis caused by plaque rupture between cases with or without signs of concomitant inflammation, so this differentiation may have substantial therapeutic implications as direct anti-inflammatory interventions for patients in a more personalized and precise manner. In addition, they point out that the identification of patients without systemic inflammation can be a great opportunity for future investigations.

We also found that patients without inflammation had lower mortality despite having more risk factors and prior evidence of coronary artery disease, however, these patients had more frequently prior use of aspirin and statins. These findings are in accordance with observations that prior use of aspirin and/or statins in patients with ACS is associated with more comorbidities and coronary disease and lower in-hospital mortality [32,33]. We expect that the absence of detectable inflammation in these patients might be partially explained by their use of aspirin and statin because both, beyond their anti-thrombotic and low-density lipoprotein cholesterol lowering effects, have direct anti-inflammatory actions (i.e. decreased hs-CRP concentration) in patients with stable coronary artery disease [34,35].

Our study shows that the intensity of systemic inflammation measured with three different biomarkers included in a single

score could better assess the inflammatory status in patients with ACS at admission, therefore providing a rationale for precision medicine in anti-inflammatory therapies [16,36,37].

Study limitations

First, our study was retrospective and reflected the experiences of a single tertiary center specializing in cardiovascular diseases. The second limitation relates to the study design; the inflammation-based risk score was internally validated, but external validation in an independent sample is required to confirm prognostic value. Finally, our database did not provide information about prior use of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists, which have been associated with anti-inflammatory effects. Thus, larger prospective studies will need to be performed to confirm these results.

Conclusions

The inflammation-based risk score for in-hospital mortality is a useful tool for risk stratification when admitting patients across the full spectrum of ACS. It has the advantage of being simple to measure, routinely available, and well standardized. Our results demonstrate an additive value of each individual marker on top of the clinical assessment and that the simultaneous examination of multiple inflammatory biomarkers helps to reclassify the individuals into a different risk stratum. These findings provide strong support for concepts of inflammation biology in clinical practice as well as evidence of utility regarding inflammation measures in the ACS setting and may also supplement the clinical risk scores. If this is corroborated by other studies, these findings may have profound clinical implications for contemporary stratification and management of ACS.

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Conflict of interest

The authors state that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jcc.2018.11.010.

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