Validation of the GRACE Score (Global Registry of Acute Coronary Events) as Predictor of In-hospital Mortality in Acute Coronary Syndromes in Buenos Aires

Validación del score de GRACE (Global Registry of Acute Coronary Events) para predecir mortalidad intrahospitalaria en el síndrome coronario agudo en Buenos Aires

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ABSTRACT

Background: The GRACE score (GS) estimates the risk of in-hospital mortality (IHM) in patients with acute coronary syndromes (ACS). An external validation of the score is necessary due to the variability of patient characteristics, healthcare systems, socio-economic environment and changes in treatment. The recently published TRIPOD guideline standardizes the methodology used in these validation studies.
Objective: The objective of this study was to assess whether the GS adequately predicts IHM in patients with ACS treated at Hospital Dr. Juan A. Fernández [validation group (VG)].
Methods: A retrospective VG study was conducted between 2001 and 2016. Discrimination was evaluated using the area under the ROC curve (AUC) and calibration using the Hosmer-Lemeshow goodness of fit test, calibration-in-the-large, calibration slope, validation plot and calibration belt. A subgroup analysis was performed by type of ACS: ST-segment elevation or non-ST-segment elevation ACS (STE-ACS or NSTE-ACS, respectively).
Results: A total of 2,104 patients were analyzed. ST-segment elevation myocardial infarction (40.4%) and IHM (5.56%) were more prevalent in the VG than in the population from which the GS was derived (32% and 4.6%, respectively). Model calibration was poor, due to risk underestimation in the probabilities ranging between 3% and 13%. The calibration slope was adequate, indicating that the overall predictor effect on IHM was similar to the GS model. The AUC was 0.86. The model underestimated risk for probabilities ranging between 5% and 23% in patients with STE-ACS, with adequate discrimination. Calibration and discrimination had adequate performance in patients with NSTE-ACS.
Conclusions: Despite the lack of statistical validity in the overall population, the GS model variables were predictors of IHM in the VG. Therefore, the GS is clinically relevant, but should be recalibrated in our population.

Key words: Angina, Unstable, Myocardial Infarction, Validation Studies, Prognosis, Mortality.

RESUMEN

Introducción: El score de GRACE (G) estima el riesgo de mortalidad intrahospitalaria (MIH) al ingreso de los pacientes con síndrome coronario agudo (SCA). La validación externa es necesaria por variaciones en las características de los pacientes, sistemas de salud, diferencias socioeconómicas y cambios en el tratamiento. Recientemente se publicó la guía TRIPOD para estandarizar la metodología de estos estudios.
Objetivo: El objetivo del trabajo es determinar si G predice adecuadamente MIH en pacientes con SCA en el Hospital Juan A. Fernández (grupo Validación -V-).
Material y métodos: Estudio de validación retrospectivo de cohorte entre 2001 y 2016. Se evaluó discriminación con el área bajo la curva (ABC) y calibración con la prueba de Hosmer-Lemeshow, calibración general, pendiente de calibración, gráfico de validación y cinturón de calibración. Se analizaron subgrupos según tipo de SCA.
Resultados: Se analizaron 2104 pacientes. Se observó mayor proporción de infarto con supradesnivel del ST (40.4% y 32%) y MIH (5.56% y 4.6%) que en G. El modelo mostró falta de calibración por subestimación de riesgos entre probabilidades del 3 y 13%. La pendiente de calibración fue adecuada indicando que la magnitud del efecto de los predictores sobre la MIH fue similar a la de G. El ABC fue 0.86. En SCA ST se observó subestimación de riesgos en probabilidades entre 5% y 23%, con adecuada discriminación. En SCA no ST, tanto la calibración como la discriminación fueron adecuadas.
Conclusiones: A pesar de la falta de validez estadística en la población total, las variables del modelo fueron predictoras de MIH en la población de V. Se considera que el puntaje de G es clínicamente relevante, pero se sugiere su recalibración en nuestra población.

Palabras clave: Angina inestable, Infarto del Miocardio, Estudios de Validación, Pronóstico, Mortalidad

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INTRODUCTION

Acute coronary syndrome (ACS) includes a heterogeneous group of patients with different clinical outcomes. (1) Clinical guidelines recommend the Global Registry of Acute Coronary Events [GRACE (G)] score (GS) to stratify risk, (2, 3) as the presence of ST-segment elevation was not an additional predictor after considering the overall ST-segment deviation. (4)

The GS was developed between 1999 and 2991 in an international prospective cohort of 14 countries (two centers of Argentina), including 11,389 patients with ACS, to predict in-hospital mortality (IHM). A logistic regression model was developed with 8 predictive variables, using the Hosmer-Lemeshow goodness-of-fit test (H-L) to assess its calibration (p=0.77), and with an observed and predicted mortality plot in deciles of predicted risk. The model presented adequate discrimination with an area under the ROC curve (AUC) of 0.83. A score was built to estimate the individual risk of IHM, without establishing risk categories (1-372 points). It was validated in 3,972 patients enrolled a posteriori in the mentioned GS registry and in 12,142 patients of the GUSTO–IIb (Global Use of Strategies to Open Occluded Coronary Arteries IIb) trial, with no record of cardiopulmonary resuscitation (CPR) on admission. (4)

Geographical differences in patient characteristics, risk factors, therapeutic conducts and access to resources, as well as evolving changes in the treatment of ACS indicate the need to validate risk scores in the populations in which they will be used. In this sense, as more validation studies demonstrate the usefulness of the model, the greater the probability that it will be adequate even in populations in which it has not been evaluated. (1, 5, 6)

Given the heterogeneity and poor methodological quality observed in studies on the development and validation of predictive models, the TRIPOD guideline (Transparent Reporting of a multivariable prediction model for individual prognosis or diagnosis) was published in 2015, emphasizing the need of a more comprehensive approach in calibration assessment through different techniques providing complementary information. There are two fundamental tools that must be employed in risk prediction models: one is the AUC, that allows to discriminate among subjects presenting or not the event, and the other is calibration, which evaluates whether the estimated risks agree with the observed frequency of the event. However, it is common to observe in the literature risk predictive models assessed only through the AUC. (7-11)

The purpose of this work was thus to evaluate whether the GS adequately predicts IHM in patients with ACS admitted to the coronary care unit of Hospital de Agudos Dr. Juan A. Fernández [validation group (VG)], according to the methodology proposed by the TRIPOD guideline.

METHODS

An observational retrospective cohort study was performed to validate the ability of the multivariate GS model to predict IHM in patients diagnosed with ACS consecutively admitted to Hospital de Agudos Dr. Juan A. Fernández between January 1, 2001 and June 30, 2016. The data were obtained from the computed epicrisis reports and clinical histories. Patients presenting with diagnosis of secondary ACS, post-angioplasty or post coronary artery bypass graft surgery (CABGS) were excluded from the study. The third definition of infarction (12) and troponin I as diagnosis marker were used in all cases. There is limited and empirical evidence reported on validation studies about sample size calculation. A minimum of 100 events and 100 non-events is suggested. (7) A minimal sample size of 1,866 patients presenting 5.56% IHM was estimated.

The presence of missing data in the predictive variables and the event was quantified. A strategy of multiple imputation was implemented with multivariate normal regression (MCMC, Monte Carlo based on iterative Markov chains). To compare the derivation and validation cohort casuistry, the distribution of patient characteristics was reported in both populations.

The linear predictor of the GS model for IHM was calculated according to the equation published by Granger et al. (13) (original beta coefficients and intercept): logit(p) -7.7035 + age * 0.0531 + heart rate * 0.0087 – systolic blood pressure * 0.0168 + baseline creatinine * 0.1823 + KK class * 0.6931 + cardiopulmonary arrest on admission * 1.4586 + elevated cardiac markers on admission * 0.4700 + ST-segment deviation * 0.8755. The last three variables were assigned a value of 0 or 1 according to their presence or absence, respectively. The probability of IHM was calculated with the formula: 1/(1+e-linear predictor). The GS was computed according to the Granger nomogram. (13) A logistic regression model was used to assess its association with IHM in the VG.

Statistical analysis

The prognostic precision of the model (validation) was assessed through its components, calibration and discrimination. The original model coefficients or the linear predictor were used, as they provide more accurate information than the score derived from them. (5, 14)

Calibration: The H-L test was used (expected p value >0.05). (15) A calibration belt was performed, which plots the relationship between estimated probabilities and the observed proportion of the event with its 95% confidence interval, calculated through polynomial regression. The statistics is based on a likelihood ratio test (expected p value >0.05). (16) Moreover, a logistic recalibration method was implemented based on the development of a logistic regression model with the event and the original linear predictor as the only independent variable. The calibration slope b is thus obtained, whose ideal value is 1 and reflects the mean predictive factor effect on the result. If b is <1 (p<0.05) the estimated risks are very optimistic (very low for low risk patients and very high for high risk patients). If b is >1 the opposite occurs, the original coefficients are close to 0, indicating low variance and high bias (poor adjustment). The general calibration or intercept a (b=1) was evaluated, adding to the previous model the linear predictor set to one (offset) (assuming the predictors' optimal precision hypothesis). Thus, the systematic deviation of predictions (bias) is evaluated. If a (b=1) is >0, the average risk is overestimated and the contrary occurs if a (b=1) is <0. This type of lack of calibration usually implies differences in the incidence of the event between the derivation and validation populations, which is not explained by differences in the distribution of predictive variables. (9, 17-20)

A validation plot was built combining observed IHM versus estimated risk of IHM according to deciles of estimated

risk, the non-parametric Loess smooth curve (weighted polynomial regression) (5, 21) and the calibration slope. The discriminative capacity was evaluated through the AUC, and was considered adequate for values >0.70, poor between 0.51 and 0.70 and non-informative for values ≤0.50.

A subgroup analysis was performed according to type of ACS. STATA MP13 was used to analyze the data.

Ethical considerations

The study was approved by the institutional Research Ethics Committee and was conducted according to legal regulations in force to protect patients' privacy and confidentiality. No informed consent was requested as no identifiable data were reported.

RESULTS

Between January 2001 and June 2016, 2,138 patients with ACS were admitted to the coronary care unit of Hospital Dr. Juan A. Fernández. Thirty-five of these patients had secondary ACS and were excluded from the study. A total of 2,104 patients were analyzed with 5.56% IHM (n=11). Missing data were observed in the following predictors: heart rate (0.19%), systolic blood pressure (0.19%) and creatinine (1.28%), which prevented the calculation of the GS in 33 patients. It was assumed that missing data was at random (not completely at random). Multiple imputation was performed with Monte Carlo multivariate normal regression in iterative Markov chains (MCMC) with 5 imputations (convergence in imputation 4). The GS predictors, IHM and the variable associated to lack of data (date previous to 2010) were included in the imputation model. Diagnoses of the imputation model were performed.

Patient characteristics were compared between VG and GS populations (Table 1). In-hospital mortality was higher in the VG. No differences were observed in heart rate, systolic blood pressure, creatinine or age as predictive variables, although the prevalence of patients >75 years of age was greater in the G cohort (27.1% vs. 16.3%). The occurrence of ST-segment deviation was similar in both cohorts, though at the expense of ST-segment elevation in the VG, indicating a more severe final ACS diagnosis, consistent with greater incidence of elevated markers and CPR in this population.

Presence of heart failure on admission was the only predictor of severity, which was slightly higher in the G cohort. This population also had history of more coronary risk factors and known coronary heart disease, probably due to underreporting in our population. In-hospital outcome was worse in the G cohort, with more heart failure and ischemic recurrence, which could be attributed to lower use of percutaneous coronary intervention (PCI) (due to the moment in which the study was performed); nevertheless, IHM was lower in this cohort. The dominant diagnosis was unstable angina (UA) in the G cohort and ST-segment elevation acute myocardial infarction (STEMI) in the VG. The Grace Score (GS) presented statistically significant association with IHM in the univariate analy-

sis in the Validation Group (VG) with OR 1.03 (95% CI 1.027-1.036, p <0.001).

The calibration of the predictive model was assessed. The H-L test showed significant differences (p=0.014), indicating lack of agreement between the estimated probabilities of IHM in the GS and that observed in the VG. Figure 1 shows that the probability was mainly underestimated in intermediate and high risk deciles. The Loess smooth curve also showed risk underestimation for estimated probabilities >3%. Similarly, the calibration belt presented significant differences between estimated and observed results (p=0.004), with underestimated risk in the predicted probabilities ranging between 3% and 13% (Figure 2).

In the logistic recalibration model, the general calibration a (b=1) presented a statistically significant value >0 (0.36, p=0.0012), indicating an average of approximately 40% more cases than those predicted (MIH odds: $e^{0.36}=1.43$). The difference in the frequency of IHM could be the consequence of variables not included in the model or with different distribution; more severe casuistries generate lack of systematic calibration. The calibration slope b was 0.91 with non-significant Wald test (p=0.16), which denotes that the mean predictor effect was similar for the G cohort and VG. Therefore, an average underestimation of estimated risks was observed in the VG, specifically in the probabilities between 3% and 13%. The scale among estimated probabilities was adequate and without significant differences in the magnitude of predictor effect. The AUC was 0.87 (95% CI: 0.83-0.90, indicating good discrimination.

In the subgroup analysis, ST-segment elevation ACS (STE-ACS) presented greater primary PCI and lower use of thrombolytics in the VG (including a greater time period in our study than in the G cohort), with higher IHM. In non-ST-segment ACS (NSTE-ACS), the prevalence of PCI was also greater in the VG, although with similar IHM (Table 2).

In the STE-ACS subgroup (n=851), the H-L test and the calibration belt presented statistically significant differences between observed and predicted events (p=0.0003 and p=0.002, respectively). Both evidenced underestimation of risk. The calibration belt indicated underestimation of risk in probabilities ranging between 5% and 23% and coincided with the Loess smooth curve. Accordingly, the general calibration a (b=1) was >0 (0.45, p=0.001). The calibration slope b was 0.90 (p=0.26). The AUC was adequate (0.87, 95% CI 0.83-0.90). Therefore, this subgroup also showed lack of calibration with average IHM risk underestimated in the VG by the GS model, specifically in the probabilities between 5% and 23% (Figure 3).

In the NSTE-ACS subgroup (n=1,253), the H-L test and the calibration belt indicated significant differences between observed and predicted events (p=0.21 in both cases). It is possible that this is due to lack of sufficient power to discriminate, as there were only 35 events in this subgroup. The Loess smooth

Table 1. Patient characteristics included in the GRACE AND validation cohorts

Characteristics	Validation cohort		GRACE cohort	
	Total population n=2,104	IHM 5.56 (4.7-6.6)	Total population n=11,389	IHM 4.6
Demographics				
Age (years)	61 (54-70)	66 (60-77)	66.3 (56-75)	76.2 (67.8-82.6)
≥75 years, %	16.3	32.5	27.1	-
Women, %	24.55	30.77	33.5	41.7
Medical history				
Diabetes, %	19.3	20.5	23.3	30.1
Dyslipidemia %	35	26.5	43.6	27.5
Hypertension, %	57.6	50.4	57.8	62.8
Smoking, %	43.3	37.6	56.7	43.7
HF, %	4.7	9.4	11	23.1
Chronic stable angina, %	15.3	12.8	68.1	62
AMI, %	23.9	19.8	32	29.3
PCI, %	11.7	8.6	14	7.7
CABGS, %	5.9	3.4	12.6	8
Presentation characteristics				
HR (bpm)	74 (60-83)	92 (75-110)	76(65-90)	87 (70-100)
SBP (mmHg)	130 (117-150)	110 (90-140)	140 (120-160)	126 (100-148)
Killip and Kimbal 1, %	87.5	47.9	82.7	49.2
CPR on admission, %	3.5	25	1.5	9.2
Elevated markers, %	71.8	95.7	31.6	55.3
Creatinine (mg/dl)	0.98 (0.80-1.2)	1.17 (0.8-1.6)	1.0 (0.9-1.2)	1.3 (1.0-1.7)
Electrocardiographic changes				
ST-segment elevation, %	43	71.7	35.3	55.3
ST-segment depression, %	11.8	15	33.7	45
ST-segment deviation, %	55	84.6	54.1	78.8
Outcome				
HF, %	8.33	72.6	14.7	-
Recurrent ischemia, %	13.7	12.9	35.7	-
Treatment				
CA, %	61.7	49.6	49.3	-
PCI, %	41	35.9	28	-
CABGS, %	1.8	1.70	6	-
Final diagnosis				
STEMI, %	40.4	70	32	-
NSTEMI, %	31.2	25.6	27	-
UA, %	28.2	4.3	41	-

IHM: In-hospital mortality. HF: Heart failure. AMI: Acute myocardial infarction. PCI: Percutaneous coronary intervention. CABGS: Coronary artery by-pass graft surgery. HR: Heart rate. SBP: Systolic blood pressure. CPR: Cardiopulmonary resuscitation. CA: Coronary angiography. STEMI: ST-segment elevation myocardial infarction. NSTEMI: Non-ST-segment elevation myocardial infarction. UA: Unstable angina. Proportions are expressed as percentages (95% CI). Continuous variables are expressed as median (IQR 25%-75%) or mean (±SD), as appropriate.

curve was close to the bisector, changing direction in probabilities above the last risk decile. Both the general calibration as the calibration slope were not significant (a (b=1): 0.21; p=0.25 and b: 0.84; p=0.16). The discrimination was adequate, with AUC=0.81 (95% CI 0.74-0.88). In this subgroup, the GS model showed adequate calibration and discrimination in the VG. The drop in the discrimination capacity with respect to other groups may be attributed to the presence of less extreme risks (Figure 3).

DISCUSSION

In 14 previously published validation studies (8, 9, 14, 22-28), 3 indicated lack of calibration for IHM in ACS. One of them was conducted in a cohort from the GS model derivation population. (1) Another study presented an inadequate H-L test, considered irrelevant due to its excessive power. (29) An additional study with deficient sample size reported lack of calibration in patients with NSTE-ACS. (30) An Argentine multicenter study without adequate sample size due to

Fig. 1. Validation plot in the total population with ACS with frequency distribution of IHM probability with and without the event. H-L: Hosmer- Lemeshow test. AUC: Area under the curve.
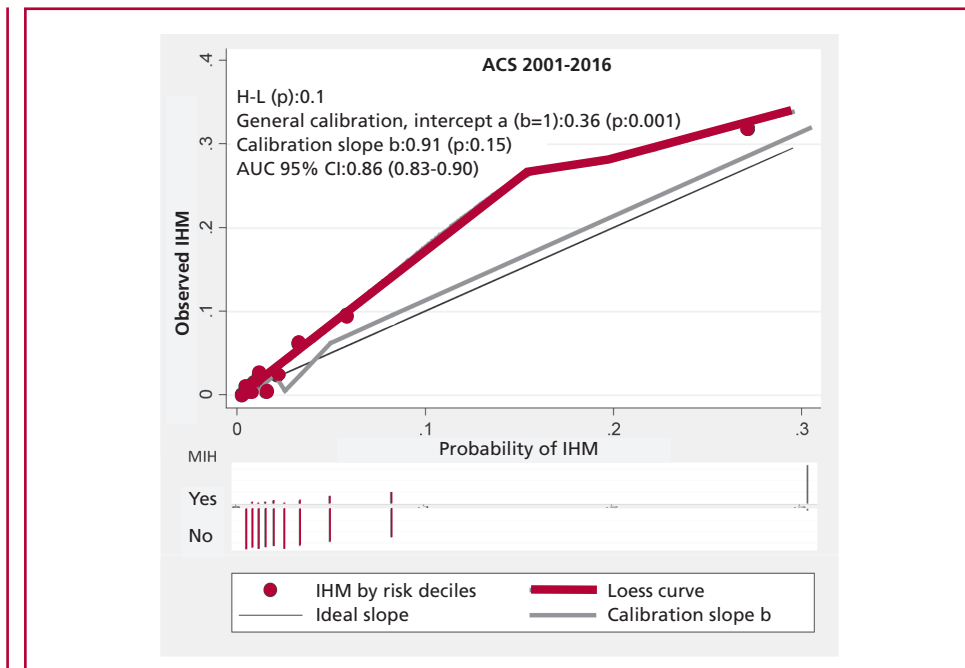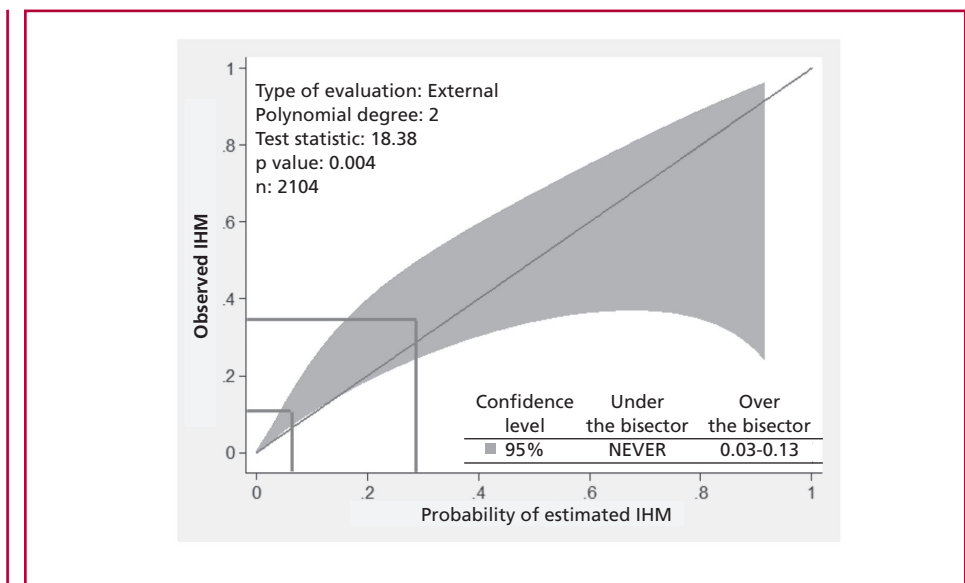

Fig. 2. Calibration belt in the total population with ACS. The curve indicates IHM risk underestimation between 3% and 13%. The first square includes 9 risk deciles, and the second square includes 10 risk deciles.

exclusion of patients with unstable angina, reported adequate calibration with a trend towards underestimation in intermediate risk deciles. (31) Furthermore, it is necessary to consider the possibility of publication bias in studies with lack of calibration.

The model supporting the GS presents poorly consistent prognostic precision in the VG to predict IHM in ACS at the expense of underestimating risk in the probabilities between 3% and 13%. It should be considered that the observed IHM was greater compared with the G cohort. The adequate calibration slope (b=0.91 , p:0.16) indicates there was no optimism in the results

and no significant differences were observed in the predictor effects between both populations.

Calibration issues are usually multifactorial. Our setting corresponds to a university public hospital in a developing country, where it is frequent to observe that patients have difficulties to access the healthcare system and to adhere to prevention treatments. This may determine that at the moment of being admitted due to an acute pathology, these patients present more unexpected comorbidities than in other populations. This study could not rule out a baseline risk difference between the G cohort and

Table 2. Patient characteristics according to the type of ACS in the GRACE and validation cohorts

Variable	Validation cohort		GRACE cohort	
	STEMI (n=851)	NSTE-ACS (n=1,253)	STEMI (n=3,410)	NSTE-ACS (n=7,290)
Age	60 (52-69)	61 (55-70)	64 (54-74)	69 (58-77)
CA, %	65	59.5	55	46.4
PCI, %	57	30.2	40	22
CABGS, %	0	3.0	4	7
Thrombolytics, %	29	-	47	4.3
Primary PCI, %	41.8	-	17.8	-
Rescue PCI, %	12	-	4.8	-
Reperfusion, %	70.9	-	62	-
Mortality, %	9.6	2.8	7	2.7

STEMI: ST-segment elevation myocardial infarction. NSTE-ACS: Non-ST-segment elevation acute coronary syndrome CA: Coronary angiography. PCI: Percutaneous coronary intervention. CABGS: Coronary artery bypass graft surgery. Information taken from references 4, 5 and 32. Data are expressed as percentages (95% CI) and median (IQR 25%-75%)
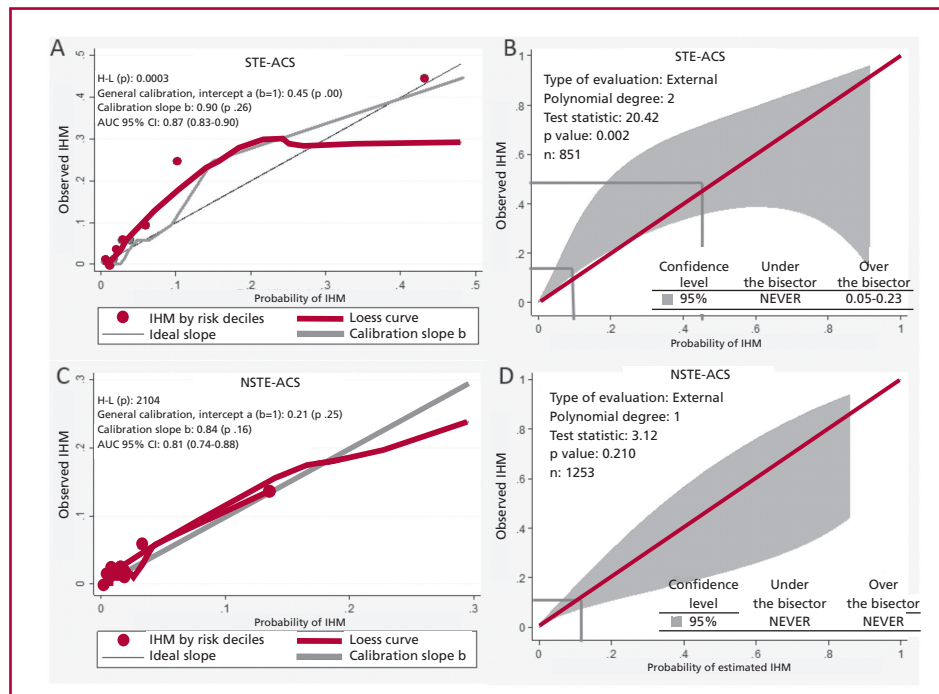

Fig. 3. Subgroup analysis. **A.** Validation plot in STE-ACS. **B.** Calibration belt in STE-ACS. The curve indicates underestimation between 5% and 23% risk of IHM. The first square includes 9 risk deciles, and the second includes 10 risk deciles. **C.** Validation plot in NSTE-ACS. **D.** Calibration belt in NSTE-ACS. A non-significant p value is observed, indicating adequate calibration. The square indicates 10 risk deciles. H-L: Hosmer-Lemeshow test AUC: Area under the curve

the VG based on predictors not included in the model. A more severe casuistry was observed in the VG, with higher prevalence of STEMI, positive markers, CPR and IHM.

It should be noted that during the development of the prognostic model in the G cohort, the presence of ST-segment elevation on admission did not add prognostic information to the overall ST-deviation. (4) Nevertheless, this study showed differences in the calibration of subgroups according to type of ACS. In the STEMI subgroup there was lack of calibration. Conversely, the NSTE-ACS subgroup presented adequate calibration in all the tests performed. In this last group, IHM was in agreement with that reported in the G cohort. In both subgroups, the calibration slope was adequate. The NSTE-ACS subgroup is particularly important due to its heterogeneity and to the need to adequately estimate the individual patient risk to define the use of more aggressive drugs an earlier invasive strategies.

Despite the GS underestimates risk in the VG, it is considered to provide relevant prognostic information, as the magnitude of predictor effect was consistent in both populations and their estimated IHM probabilities were within the same range. Therefore, the GS is thought to be clinically relevant, although it is sug-

gested to update it with the methodology proposed by the TRIPOD guidelines (logistic recalibration).

Limitations

The limitations of the study are its retrospective and single center nature. Moreover, it includes a period >10 years during which the treatment of ACS and the availability of resources underwent changes. The subgroup analysis does not have the adequate sample size and there is no information on the medical treatment implemented, hampering the comparison between both populations.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material).

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