



Letter to the Editor

Additional predictive value of C-reactive protein to GRACE score in patients with acute coronary syndrome



The awareness that active inflammation plays a major role in the initiation and progression of atherosclerosis dates back to the seminal observations of Ross et al. [1]. Although this concept relies on extensive experimental and clinical evidences, it's not, at yet, defined if the inflammatory process has a causative role in or simply accompanies the development of atherosclerotic plaques and myocardial injury. Among the numerous biomarkers evaluated, C-reactive protein (CRP) has been the most intensely studied. Aims of the present study were to verify if CRP values obtained at admission using standard assay show an independent association with in-hospital and post discharge mortality (IHM and PDM) and if CRP is able to increase the prognostic performance of the GRACE score. This is a retrospective analysis of prospectively collected clinical data of patients admitted to the Coronary Care Unit (CCU) of the San Paolo Hospital in Milan between November 2012 and November 2014 and between June 2016 and June 2018 with a diagnosis of acute coronary syndrome (ACS). Medical history, clinical characteristics, biochemical findings at admission, angiographic data, treatments administered during hospitalization and incidence adverse events were collected on a custom electronic database (Microsoft Excel, Microsoft Office 2010). Patients were stratified in risk groups according to the GRACE values used for risk stratification in the original publications [2]. CRP values were measured from the first blood sample obtained upon admission in the emergency department or in the CCU (Ortho Clinical Diagnostics, Vitros 5600) and the analysis of the database allowed the determination of the incidence of IHM and PDM. The associations between clinical variables and events were evaluated using logistic regression analysis. Predictive capacities were assessed by the C-statistic, using Receiver Operating Characteristic (ROC) curves. In order to obtain new risk models incorporating CRP in the GRACE risk score these variables were entered in bivariate logistic regression models with GRACE score and new GRACE-CRP-CON and GRACE-CRP-CAT scores were derived by adding to the GRACE score the points obtained computing the ratio between the regression coefficients of both the continuous and categorical CRP variables. The capacity of the new risk models to correctly reclassify clinical endpoints risk in comparison to the GRACE model was evaluated using the net-reclassification index (NRI). MedCalc Statistical Software was used for the statistical analysis.

871 patients composed our population. Median age was 68 years (IQR 58–78), 26% being females. In 49% of patients the diagnosis was of NSTEMI-ACS and in 51% of STEMI. Of the 838 patients discharged from the hospital, 704 (84%) completed a post discharge follow up (duration 11.4 ± 1.6 months). 33 patients died during index hospitalization resulting in an IHM of 3.8%. Regarding the follow up period, 26 patients died resulting in a PDM of 3.7%. The GRACE score on admission showed a median value of 134 (IQR 111–160) in the total population and of 133 (IQR 110–156) in the follow up population. The events incidence significantly rises across the risk categories. GRACE score

showed a very good discriminatory capacity for IHM (C-statistic 0.93) and moderate for PDM (C-statistic 0.69). The CRP median value at admission was 9.6 mg/L (IQR 5.4–21.4) in the total population and 9.4 mg/L (IQR 5.4–19.7) in the follow-up group. CRP values at admission were significantly higher in patients with IHM (66.9 mg/L vs 9.4 mg/L, $p < .0001$) and in patients with PDM (16.1 mg/L vs 9.0 mg, $p = .001$). CRP values were independently significantly associated with IHM and PDM in multivariate analyses comprising GRACE score and most of the clinical variables collected. Admission CRP showed good discriminatory capacity for IHM (C-statistic 0.75) and moderate for PDM (C-statistic 0.68).

Regarding GRACE-CRP-CON and GRACE-CRP-CAT risk models, both demonstrated a good discriminative capacity both for IHM (C-statistic 0.94) and PDM (C-statistic 0.71 for GRACE-CRP-CON and 0.74 for GRACE-CRP-CAT). However, when compared to the original GRACE model they didn't show statistically significant differences. In Table 1 are summarized the results of the ROC curves and of the reclassification analysis. As far as IHM is concerned, GRACE-CRP-CON correctly reclassified 18 patients and GRACE-CRP-CAT 26 patients without events from high to low risk, while no patients were incorrectly reclassified. The NRI was 2.1 for GRACE-CRP-CON and 3.1 for GRACE-CRP-CAT ($p < .0001$). As concerns PDM, NRI were positive but not statistically significant.

The main results of the present study are that CRP values obtained with standard assay are positively and independently associated with IHM and PDM, showing a good predictive performance and that CRP added to the GRACE score enhances the discriminative accuracy of the risk model for IHM. These results are overall consistent with those of previous studies that showed an independent association between CRP values and acute and long-term adverse events in patients with ACS [3–6]. However, almost all previous studies concerned only the NSTEMI-ACS, the timing of CRP samplings was extremely variable, the follow up ranged from in-hospital period up to three years and the clinical endpoints considered varied from composite endpoints to all-cause mortality only [3]. Our study population was composed of both NSTEMI-ACS and STEMI patients, CRP values refer to the first blood sampling obtained at admission and IHM and PDM were both considered. In our population CRP values were significantly higher in patients with STEMI than in patients with NSTEMI-ACS, and, accordingly with previous observations [7], this is probably related with the presence of a larger myocardial injury. Unlike previous observations [8], in our population CRP showed good and significant predictive values for IHM and PDM both in NSTEMI-ACS and in STEMI patients. This fact suggests that the independent predictive capacity of CRP might be predominantly related to the extension of acute myocardial damage in association with the unknown basal inflammatory status of patients. Finally CRP was evaluated using the standard assay, obtaining equally predictive information with a less expensive test. As already stated by other authors, an

<https://doi.org/10.1016/j.ejim.2019.07.036>

Received 20 July 2019; Received in revised form 29 July 2019; Accepted 31 July 2019

Available online 06 August 2019

0953-6205/© 2019 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.

Table 1

Calibration and discrimination values of GRACE score, CRP and the new risk models obtained incorporating CRP into the GRACE model (upper). Results of the reclassification analysis concerning the new risk models in relation to the original GRACE score for the risk definition of in-hospital and post discharge mortality (lower).

ROC CURVES ANALYSIS					
	H-L test	p-value	C-statistic (95% CI)	Sens/Spec	p-value
IHM					
GRACE	5.09	0.74	0.93 (0.92–0.95)	94/81	< 0.0001
CRP	10.48	0.23	0.75 (0.72–0.77)	67/87	< 0.0001
GRACE-CRP-CON	7.81	0.45	0.94 (0.93–0.96)	94/83	< 0.0001
GRACE-CRP-CAT	5.99	0.65	0.94 (0.93–0.96)	94/84	< 0.0001
PDM					
GRACE	5.35	0.72	0.69 (0.66–0.73)	65/70	0.0007
CRP	10.20	0.25	0.68 (0.65–0.72)	73/61	0.0003
GRACE-CRP-CON	4.42	0.82	0.71 (0.68–0.75)	69/71	0.0002
GRACE-CRP-CAT	6.36	0.60	0.74 (0.70–0.77)	73/71	< 0.0001
RECLASSIFICATION ANALYSIS					
	n	RFM	RFL	NRI	z-value/p-value
GRACE-CRP-CON					
IHM					
Events	33	0	0		
Non events	838	0	18		
Total	871	0	18	2.1	4.2/ < 0.0001
PDM					
Events	26	1	0		
Non events	678	1	0		
Total	704	2	0	3.65	0.95/0.1
GRACE-CRP-CAT (CRP < or > of 34.8 mg/dL for IHM and of 11.7 mg/dL for PDM)					
IHM					
Events	33	0	0		
Non events	838	0	26		
Total	871	0	26	3.1	5.1/ < 0.0001
PDM					
Events	26	2	0		
Non events	678	0	5		
Total	704	2	5	8.4	1.54/0.06

Abbreviations: CI, confidence intervals; CRP, C-reactive protein; GRACE-CRP-CON, GRACE-CRP-Continuous; GRACE-CRP-CAT, GRACE-CRP-Categorical; H-L test, Hosmer-Lemeshow test; IHM, in-hospital mortality; PDM, post discharge mortality; RFL, reclassification for less; RFM, reclassification for more.

independent association with events occurrence is not enough to establish the clinical usefulness of a biomarker as a prognostic tool [9]. By means, an important proof that a new risk marker has incremental usefulness in clinical practice is given measuring the increase in predictive accuracy obtained by the incorporation of the new biomarker in a well-established prognostic model. Few studies have examined the incremental predictive effect of incorporation of inflammatory biomarkers in a known risk model in ACS patients. [9,10]. Our study differs for certain aspects from that of Correia et al. [9], the only one in which the predictive advantages of adding CRP to the GRACE score were selectively evaluated. Correia reported a significant predictive accuracy of CRP for in-hospital and not for post discharge adverse events. The reasons for this are probably related to the study small sample size in association with the clinical endpoint definition. Moreover, for each of the clinical endpoints, our new risk models were compared with GRACE risk score and both showed the ability to correctly reclassify a sensible number of patients without events from the high to the low risk group, without any incorrect reclassification,

resulting in a statistically highly significant NRI. These results correlate to an increase in sensitivity or specificity in comparison to the original risk model. The relatively limited sample size, although over three times larger than previous studies on this topic [9,10] is for sure one of the limitations of this study. However, we think that our population is well balanced, representing a contemporary ACS population, equally subdivided between STEMI and NSTEMI-ACS cases and managed according to current clinical practice, with the great majority of patients referred to coronary angiography, 76% to PCI, and 92% treated with new P2Y12 agents. In conclusion CRP values obtained at hospital admission using standard CRP assay are predictive of IHM and PDM. Although the incorporation of CRP does not increase the predictive power of the GRACE risk model, it determines a correct reclassification of patient risk.

Acknowledgements

The authors acknowledge the “Centro di Ricerca Aldo Ravelli” for supporting the study.

Funding

None.

Conflict of interest statement

The authors have no conflict of interest to declare.

References

- [1] Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med* 1999;340:115–26.
- [2] Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F et al for the GRACE investigators. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006;333:1091–6.
- [3] He L, Tang X, Ling W, Chen W, Chen Y. Early C-reactive protein in the prediction of long-term outcomes after acute coronary syndromes: a meta-analysis of longitudinal studies. *Heart* 2010;96:339–46.
- [4] Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, et al. The prognostic value of C-reactive protein and serum amyloid-a protein in severe unstable angina. *N Engl J Med* 1994;331:417–24.
- [5] Mueller C, Buetner HJ, Hodgson JM, Marsch S, Perruchoud AP, Roskamm H, et al. Inflammation and long-term mortality after non-ST elevation acute coronary syndrome treated with a very early invasive strategy in 1042 consecutive patients. *Circulation* 2002;105:1412–5.
- [6] Bursi F, Weston SA, Killian JM, Gabriel SE, Jacobsen SJ, Roger VL. C-reactive protein and heart failure after myocardial infarction in the community. *Am J Med* 2007;120:616–20.
- [7] Sanchez PL, Rodriguez MV, Villacort E, Albarran C, Cruz I, Moreiras JM, et al. Kinetics of C-reactive protein release in different forms of acute coronary syndrome. *Rev Esp Cardiol* 2006;59:441–7.
- [8] Roubin SR, Pardo CB, Roubin-Camina F, Sanchez RO, Castro EA, Dobarro BP, et al. High-sensitivity C-reactive protein predicts adverse outcomes after non-ST-segment elevation acute coronary syndrome regardless of GRACE risk score, but not after ST-segment elevation myocardial infarction. *Rev Port Cardiol* 2013;32:117–22.
- [9] Correia LCL, Vasconcelos I, Garcia G, Kalil F, Ferreira F, Silva A, et al. Does C-reactive protein add prognostic value to GRACE score in acute coronary syndromes? *Arq Bras Cardiol* 2014;102:449–55.
- [10] Lopez-Cuenca A, Manzano-Fernandez S, Lip GYH, Casas T, Sanchez-Martinez M, Mateo-Martinez A, et al. Interleukin-6 and high-sensitivity C-reactive protein for the prediction of outcomes in non-ST-segment elevation acute coronary syndromes. *Rev Esp Cardiol* 2013;66:185–92.

Simone Persampieri*, Diego Castini, Federica Valli, Ludovico Sabatelli, Stefano Carugo
 Division of Cardiology, San Paolo University Hospital, Department of Health Sciences, University of Milan, Italy
 E-mail address: simone.persampieri@gmail.com (S. Persampieri).

* Corresponding author at: Division of Cardiology, San Paolo University Hospital, Via Antonio di Rudinì 8, Milan, Italy.