THE STORM (acute coronary Syndrome in paTients end Of life and Risk assesMent) study Claudio Moretti

THE STORM (acute coronary Syndrome in paTients end Of life and Risk assesMent) study

Claudio Moretti, Giorgio Quadri, Fabrizio D'Ascenzo, Maurizio Bertaina, Federico Giusto, Sebastiano Marra, Corrado Moiraghi, Luca Scaglione, Mauro Torchio, Giuseppe Montrucchio, Mario Bo, Massimo Porta, Paolo Cavallo Perin, Carlo Marinone, Franco Riccardini, Javaid Iqbal, Pierluigi Omedè, Serena Bergerone, Franco Veglio, Fiorenzo Gaita

Abstract

Introduction. Elderly patients with coexisting frailty and multiple comorbidities frequently present to the emergency department (ED). Because non-cardiovascular comorbidities and declining health status may affect their life expectancy, management of these patients should start in the ED. This study evaluated the role of Gold Standards Framework (GSF) criteria for identifying patients with acute coronary syndromes (ACS) approaching end of life.

Methods. All consecutive patients admitted to the ED and hospitalised with a diagnosis of ACS between May 2012 and July 2012 were included. According to GSF criteria, patients were labelled as positive GSF status when they met at least one general criterion and two heart disease criteria; furthermore, traditional cardiovascular risk scores (the Global Registry for Acute Coronary Events (GRACE) score and the Age, Creatinine and Ejection Fraction (ACEF) score) were calculated and WHOQOL-BREF was assessed. Mortality and repeat hospitalisation due to cardiovascular and non-cardiovascular causes were evaluated at 3-month and 12-month follow-up.

Results. From a total of 156 patients with ACS enrolled, 22 (14%) had a positive GSF. A positive GSF was associated with higher rate of non-cardiovascular events (22.7% vs 6.7%; p=0.03) at 3 months and higher rates of both cardiovascular and non-cardiovascular events (36% vs 16.4%; p=0.04 and 27.3% vs 6.7%; p=0.009, respectively) at 12 months. In multivariate analysis, an in-hospital GRACE score was a predictor of cardiovascular events, while a positive GSF independently predicted non-cardiovascular events.

Conclusions. The GSF score independently predicts non-cardiovascular events in patients presenting with ACS and may be used along with traditional cardiovascular risk scores in choosing wisely the most appropriate treatment. The present results need to be externally validated on larger samples.

Introduction

Acute coronary syndromes (ACS) represent a frequent condition managed in emergency departments (EDs) daily.

They include unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI) and are associated with high rates of mortality and morbidity[1] often requiring angiography and percutaneous coronary intervention (PCI), with a favourable impact on prognosis.[2] These invasive approaches as well as the following elaborate medical therapy, have not negligible incidence of complications that must be accurately balanced according to clinical consideration and specific patient's risk-benefit ratio on one side and economical consideration on the other, in order to choose the most efficient pathway of treatment.[3,4]

Furthermore, patients with ACS represent a heterogeneous population and a sizeable proportion has significant comorbidities including pulmonary disease, renal dysfunction, neoplastic disorders, dementia or frailty. It is challenging for physicians, especially in a very acute setting such as that of EDs, to appropriately risk stratify these patients to select the most appropriate treatment modality whether it is PCI, coronary artery bypass grafting (CABG), medical therapy or palliative care. These patients are under-represented in randomised clinical trials as these comorbidities usually fall under the exclusion criteria, although they are increasingly encountered in everyday clinical practice.[5–7]

Clinical risk scores represent a potential solution to objectively risk stratify these patients and identify who may be approaching towards end of life (EoL) and may benefit from a holistic palliative approach.[8] The role of traditional cardiovascular risk scores, like GRACE[6] or ACEF.[9] is unknown in this field; moreover, these scores do not take into account the multisystem impairment, typical of many elderly patients who are frail and present with multicomorbidities.

The ‘Gold Standards Framework Prognostic Indicator Guide’ (GSF), originally developed for patients with cancer, recently demonstrated a good accuracy in determining risk stratification in unselected patients presenting with ACS; although it was a single centre experience and did not evaluate the difference between cardiovascular and non-cardiovascular adverse events at follow-up.[10,11] WHOQOL-BREF[12] represents another widely exploited score analysing physical, psycho-social, emotional and environmental issues, and has not yet been validated in ACS (see online supplementary appendix for details).

The main objective of this study was to compare the traditional cardiovascular risk scores (GRACE and ACEF) with scores dealing with EoL and quality of life (GSF and WHOQOL-BREF) and to assess their prognostic role in the setting of ACS.

Methods

Study design, setting and participants

This is a prospective, single centre study, reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[13]

All consecutive unselected patients admitted to the ED of a tertiary referral University hospital and discharged with an International Classification of Diseases (ICD) diagnosis of ACS (ICD number 410–414; 428 and 786.5) between May 2012 and July 2012 were included.

The diagnosis was independently verified by two cardiologists (GQ; FDA), according to the current guidelines on ACSs;[14,15] in case of disagreement, the opinion of a third cardiologist (CM) was obtained. Patients were divided according to positive or negative GSF scores. The treatment strategy was decided by the clinical team according to clinical assessment and current guidelines.[14,15] All enrolled patients consented to be interviewed by phone or during follow-up visits at 3 months and 12 months after their hospitalisation for the ACS index event.

Variables

The main clinical variables collected were cardiovascular risk factors, admission diagnosis (STEMI, NSTEMI and UA) type and timing of invasive treatment and presence of prognostic coronary lesions (multivessel, left main or proximal vessel disease).

GRACE scores and ACEF scores were completed by the investigators and treating physicians were aware of the results.

The GRACE score was calculated using online calculator as a raw score to define risk tertiles of intrahospital and 6-month mortality (see http://www.outcomes-unmassed.org/grace/). ACEF score was computed as follows: age (years)/ejection fraction (%) +1 (if serum creatinine value was >2 mg/dL).

The GSF was evaluated either at admission (coronary unit/ED ward, cardiology ward or internal medicine ward) or as soon as feasible if the patient was unstable at admission .The evaluation was performed by either the study investigators or the clinical team looking after the patient. Therefore, the medical staff were aware of the final GSF score.

According to GSF criteria,[10] (figure 1) patients were labelled as positive GSF status when they met at least one general criterion and two heart disease criteria.

GENERAL CRITERIA OF END-STAGE ILLNESS
1) Weight loss > 10% in last 6 months
2) General physical decline
3) Serum albumin < 25 g/l
4) Reducing performance status (Karnovsky score < 50%)
HEART DISEASE SPECIFIC CRITERIA
1) The Surprise Question (to be asked of a health care provider familiar with the patient): "Would you be surprised if the patients died in the next 6 to 12 months?"
2) New York Heart Association (NHYA). Stage III or IV heart failure
3) Repeated hospital admissions within the last year
4) Difficult physical or psychological symptoms despite optimised tolerated therapy
GSF Positive status: at least one general criterion and two heart disease specific criteria.

Figure 1 Gold Standards Framework criteria.[10]

The WHOQOL-BREF,[16] a simple multiple-choice questionnaire, was filled out by each participating patient (see online supplementary appendix for details).

Cardiovascular events (death and hospitalisation for cardiovascular cause) and non-cardiovascular events (death and hospitalisation for non-cardiovascular causes) at 1 year were the coprimary end points, while the same outcomes at 3 months were the co-secondary end points.

The study was approved by the local ethics committee.

Data source and measurement

Demographic, clinical and procedural data were collected from our institutional electronic database and individual patient charts. Follow-up data were collected at 3 months and 1 year from the discharge date of the index hospitalisation by phone calls, scheduled clinic visits or formal queries to primary care physicians.

Statistical analysis

Continuous variables are expressed as mean±SD and were compared by analysis of variance test and Student's t test. Categorical variables are presented as counts and percentages, and were compared by χ^2 test and with Fisher test. The p values unadjusted for multiplicity are reported throughout, with statistical significance set at the two-tailed 0.05 level.

Correlation analysis was performed through Pearson's test in a way to see the accordance between different scores to predict adverse events at follow-up.

Multivariate analysis was conducted performing linear regression logistic model and Cox regression, including each variable that was significant in the univariate analysis. Given number of events as dependent variable and number of covariates, propensity score was incorporated into the model.[17,18] For independent predictors in the multivariate analysis, area under curve (AUC) was calculated. Analysis was carried out using SPSS V.11.0 (SPSS, Chicago, Illinois, USA).

Results

Three hundred and thirty patients were evaluated for suspected ACS between May 2012 and July 2012 (figure 2), and a diagnosis of ACS was confirmed in 156 patients.

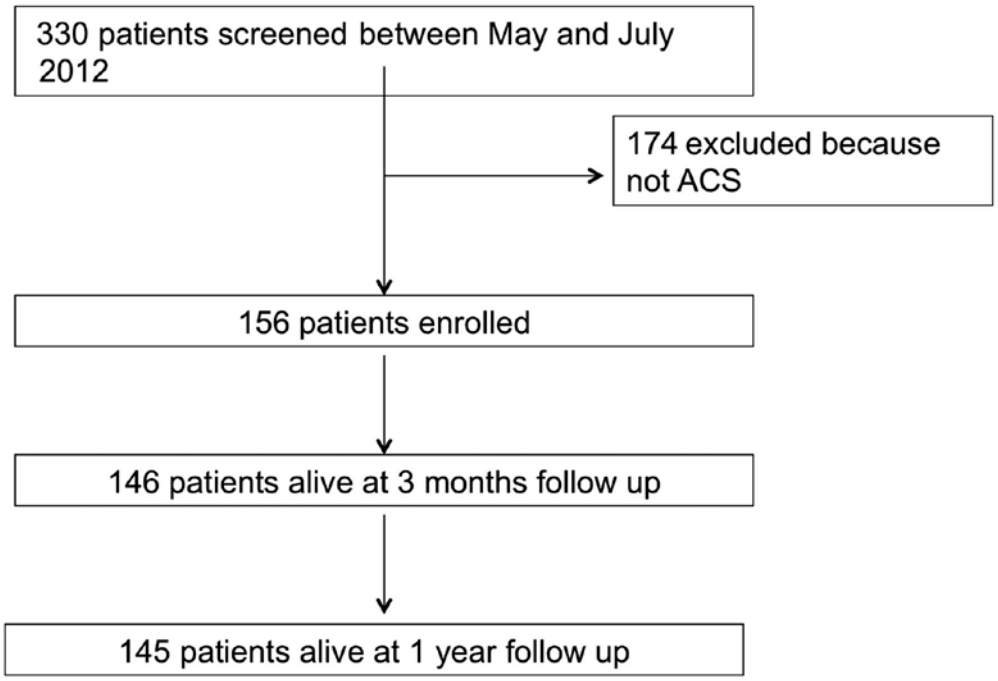

Figure 2 Flow chart of enrolled patients.

GSF was evaluated for every patient (100%) while ACEF and Grace scores were obtained for 130 (83.3%) and 152 (97.4%) patients, respectively; WHOQOL BREF was filled out by 106 patients (67.9%).

Twenty-two patients (14%) had a positive GSF and were older (77±11 vs 67±11 year; p=0.05) and with adverse cardiovascular profile than patients with negative GSF (table 1).

Table 1 Baseline features

Clinical feature	Patients with positive GSF (22: 14%)	Patients with negative GSF (134: 86%)	p Value	Overall (156)
Age (years)	77±11	67±11	0.05	71±11
Gender (female)	12 (54)	87 (65)	0.34	99 (63)
Hypertension	17 (77)	101 (75)	0.54	118 (76)
Previous smokers	5 (22)	43 (32)	0.048	48 (51)
Smokers	6 (26)	62 (28)	0.05	68 (44)
Non-insulin dependent diabetes	6 (27)	28 (21)	0.58	34 (22)
Insulin dependent diabetes	1 (4.5)	4 (3)	0.54	5 (3)
Hyperlipidaemia	9 (41)	70 (52)	0.36	79 (50)
Previous myocardial infarction	5 (23)	34 (25)	0.51	39 (25)
Previous percutaneous revascularisation	46 (29.5)	40 (29)	0.53	86 (55)
Previous surgical revascularisation	5 (23)	11 (8)	0.05	16 (10)
Hospitalisations for heart failure/acute coronary syndromes in the previous 6 months	8 (36)	22 (16)	0.03	30 (19)
GRACE for in-hospital risk of death	170±35	124±41	0.04	134 (49–263)
GRACE score for 6 months risk of death	141±28	106±34	<0.001	114 (39–210)
Patients with a GRACE score for in-hospital risk of death more than 140	18 (82)	45 (33)	<0.001	63 (40)
ACEF score	2.12±0.7	1.3±0.4	<0.001	1.3 (1.1–1.6)
QOL	48±42	61±42	0.18	89 (78–97)
Hospital ward:				
Coronary unit, emergency department ward	15 (68.2)	91(67.9)	0.92	106 (69)
Cardiology ward	4 (18.2)	28 (21)	0.67	32 (21)
Internal medicine ward	3 (14)	15 (11.2)	0.85	18 (10)

GSF, Gold Standards Framework; QOL, quality of life.

Moreover, they had higher GRACE (170±35 vs 124±41; p=0.04) and ACEF (2.12±0.7 vs 1.3±0.4; p<0.001) scores.

There were no differences in the angiographic features in terms of severity and extent of coronary artery disease (CAD). There was a trend for a less use of PCI among patients with positive GSF (77% vs 91%; p=0.06) Patients with two positive and one negative GSF scores died during index hospitalisation for cardiovascular causes (table 2).

Table 2 Management of included patients

Clinical feature	Patients with positive GSF (22: 14%)	Patients with negative GSF (134: 86%)	p Value	Overall (156)
Percutaneous coronary intervention (PCI)	17 (77)	122 (91)	0.06	139 (89)
Three vessel disease*	5 (23)	14 (11)	0.11	19 (12)
Left main disease*	3 (13)	6 (4.5)	0.11	9 (6)
Proximal descending anterior disease*	6 (27)	23 (17)	0.19	29 (19)
Proximal circumflex artery disease*	4 (18)	14 (11)	0.23	18 (11)
Proximal right coronary artery disease*	5 (22)	13 (17)	0.18	18 (11)
CABG as revascularisation strategy	3 (14)	4 (3)	0.06	7 (4)
Percutaneous transluminal coronary angioplasty (PTCA)	10 (45)	84 (63)	0.09	94 (60)
Primary PTCA	6 (27)	39 (31)	0.55	45 (29)
Number of implanted coronary stent	0.64±0.9	1.25±0.4	0.05	1 (0–2)
Number of implanted drug eluting stent)	0.41±0.7	1.04±1.33	0.03	1 (0–2)
Ejection fraction at discharge	44±11	46±22	0.5	55 (43–60)
Discharged alive:				
At home	14 (63.7)	124 (92.6)	0.03	134 (86)
Tertiary care	6 (27.3)	9 (6.7)	0.001	15 (10)
Death during hospitalisation (All for cardiovascular causes)	2 (9)	1 (0.7)	<0.001	3 (1.9)

*Thrombus at PCI. Stenosis >50% for left main and 70% for other vessels.
CABG, coronary artery bypass grafting; GSF, Gold Standards Framework.

Follow-up data were available for all patients at 3 and 12 months. Patients with positive GSF had more adverse events (63.6% vs 18.7%; p<0.001), more cardiovascular (36% vs 16.4%; p=0.04) and non-cardiovascular events (27.3% vs 6.7%; p≤0.009). There were three (14%) cardiovascular deaths and five (22.7%) non-cardiovascular deaths among the GSF positive group. The GSF negative group had a lower incidence of both cardiovascular (0.7%; p=0.009) and non-cardiovascular (1.5%; p=0.004) deaths. The large majority of these events occurred within the first 3 months of the index event (table 3).

Table 3 Events at follow-up

	Patients with positive GSF (22: 14%)	**Patients with negative GSF (134: 86%)**	**p Value**	**Overall (156)**
First follow-up 83 days (37–129)				
Adverse events (defined as all cause death and all cause rehospitalisations)	9 (41)	19 (14.2)	0.006	28 (18)
Cardiovascular events (defined as cardiovascular death, rehospitalisations for ACS, AHF and PTCA)	4 (18)	14 (10.5)	0.29	18 (11.5)
Non-cardiovascular events (non-cardiovascular death, rehospitalisation for non-cardiovascular diagnosis)	5 (22.7)	9 (6.7)	0.03	14 (9)
Cardiovascular death	3 (14)	1 (0.7)	0.009	4 (2.6)
Non-cardiovascular death	4 (18)	2 (1.5)	0.004	6 (3.8)
Rehospitalisations for:				
ACS	0 (0)	3 (2.2)	0.63	3 (2)
AHF	1 (4.5)	6 (4.5)	0.66	7 (4.5)
Non-cardiovascular diagnosis	1 (4.5)	7 (5.2)	0.64	8 (5.1)
PTCA	0 (0)	4 (3)	0.54	4 (2.5)
Follow-up at 370 days (285–440)				
Adverse events	14 (63.6)	25 (18.7)	<0.001	39 (25)
Cardiovascular events (defined as cardiovascular death, rehospitalisations for ACS, AHF and PTCA)	8 (36)	22 (16.4)	0.04	30 (19.2)
Non-cardiovascular events (non-cardiovascular death, rehospitalisation for non-cardiovascular diagnosis)	6 (27.3)	9 (6.7)	0.009	15 (9.6)
Alive at home at follow-up	15 (68.2)	131 (97.8)	<0.001	146 (93.6)
Cardiovascular death	3 (14)	1 (0.7)	0.009	4 (2.6)
Non-cardiovascular death	5 (22.7)	2 (1.5)	<0.001	7 (4.5)
Rehospitalisations for:				
ACS	1 (7)	7 (8)	0.63	8 (5.1)
AHF	4 (15)	8 (5)	0.66	12 (7.7)
Non-cardiovascular diagnosis	1 (4.5)	7 (5.2)	0.64	8 (5.1)
PTCA	0 (0)	6 (7)	0.4	6 (3.8)

ACS, Acute coronary syndromes; AHF, acute heart failure; GSF, Gold Standards Framework; PTCA, percutaneous transluminal coronary angioplasty.

There were no differences in outcomes among patients admitted to the coronary unit/ED ward and cardiology ward and internal medicine ward, both for cardiovascular events (10.4% vs 6.2% vs 16.7%; p=0.67) and for non-cardiovascular events (6.6% vs 9.4% vs 5.6%; p=0.83).

Table 4 shows Pearson's correlation coefficient for each comparison between scores considered in our work. Best concordance can be seen between GRACE (in-hospital mortality) and ACEF (0.63). The accordance between GSF and GRACE and between GSF and ACEF was very low (0.36 and 0.30, respectively).

Table 4 Correlations between risk scores (all are significative; p<0.001)

	ACEF (N=130)	**GSF (N=150)**	**Cardiac GSF (N=150)**	**QOL (N=110)**
GRACE IH (N=152)	0.63	0.36	0.51	0.38
ACEF (N=130)	–	0.3	0.54	0.36
GSF (N=150)	–	–	–	0.21
Cardiac GSF (N=150)	–	–	–	0.34

Pearson's correlation coefficient for each comparison between scores considered. 1 represents perfect concordance while 0 represents total discordance between those scores for a certain patient outcome prediction.
GSF, Gold Standards Framework; QOL, quality of life.

In multivariate analysis, in-hospital GRACE score was a significant predictor of cardiovascular events, while a positive GSF was independently related to non-cardiovascular adverse events both at 3 months (OR 4.8, 95% CI 2 to 15) and at 1 year follow-up (OR 4, 95% CI 2.1 to 8) (figures 3 and 4). AUC for positive GSF to predict non-cardiovascular events at 1 year was of 0.74 (0.67 to 0.78).

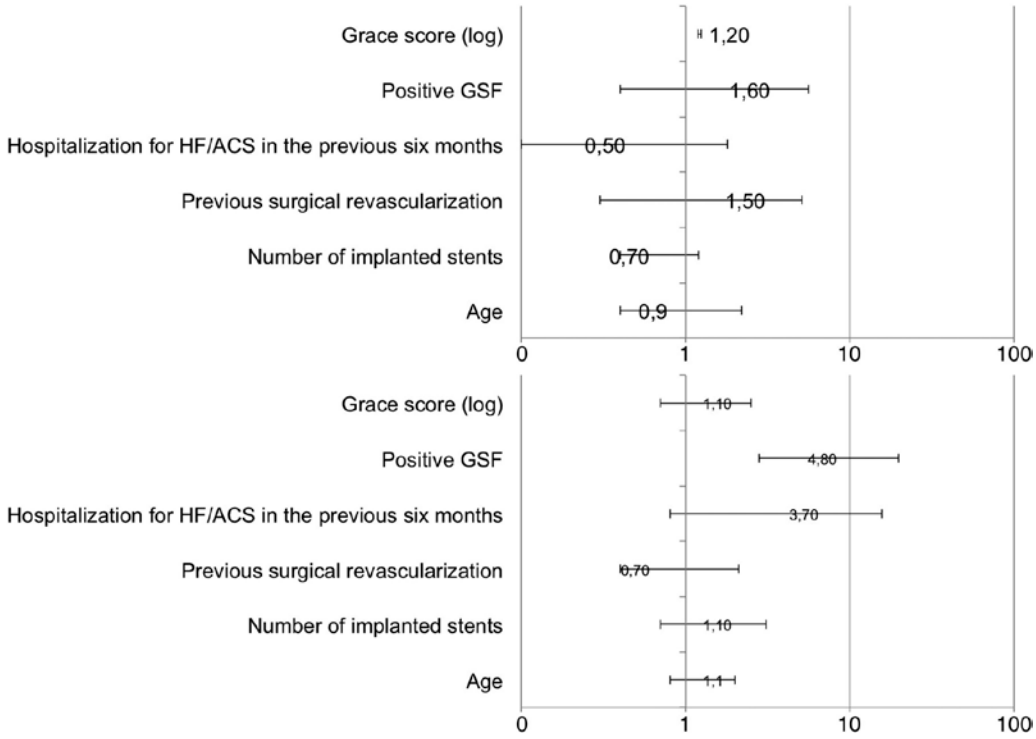

Figure 3 Independent predictors of cardiovascular (above) and non-cardiovascular (below) adverse events at 3 months.

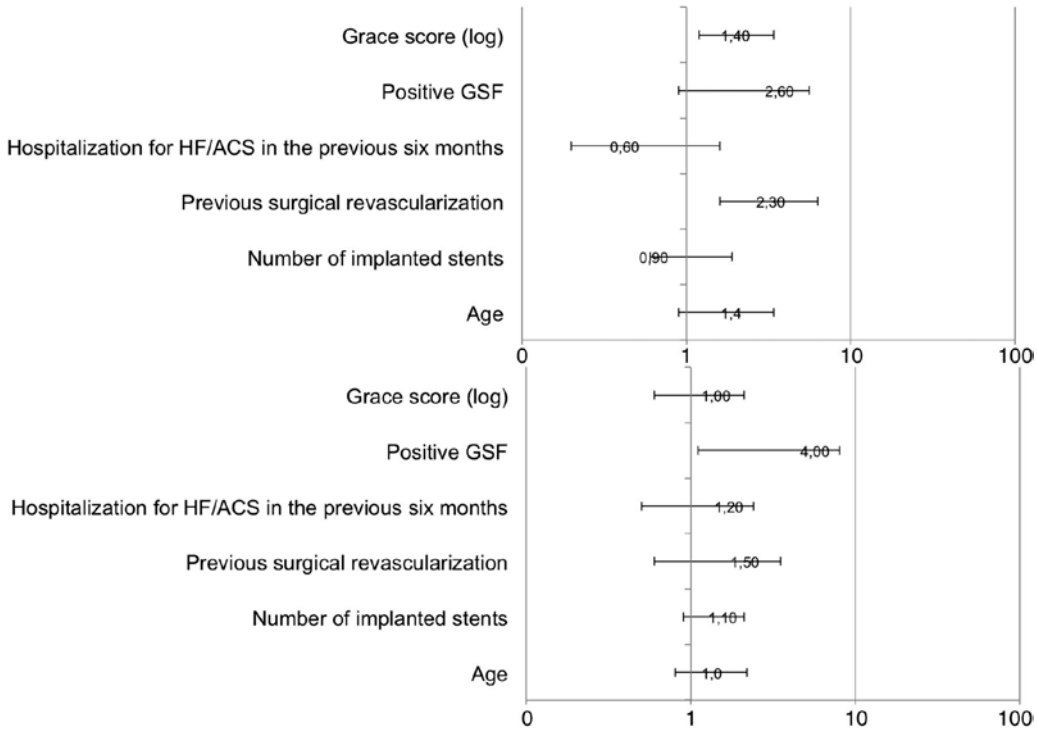

Figure 4 Independent predictors of cardiovascular (above) and non-cardiovascular (below) adverse events at 1 year.

Discussion

The main findings of the present study are: (a) prevalence of positive GSF in patients presenting with ACS to an ED in a metropolitan area is not negligible; (b) patients with positive GSF seem to be less frequently treated with PCI; (c) GSF scores independently predicted short-term and mid-term non-cardiovascular prognosis in patients with ACS, potentially allowing a more appropriate treatment strategy.

Management of patients approaching EoL presents a major challenge, involving clinical, economical and ethical questions. In addition to patients with cancer, most attention has been paid to patients with heart failure, severe chronic pulmonary obstructive disease and renal failure.[19–24]

The GSF, initially developed for patients with cancer, has recently been successfully applied to patients with chronic lung, kidney and neurological disease.[11–26] Fenning *et al*[10] were the first to analyse the impact of EoL among patients with ACS admitted to the cardiology department using GSF. In their study, 23% of patients had a positive score and 20% of these patients died at 1 year of follow-up. Incidence of ACS in these EoL and frail patients is likely to be high due to coexisting cardiovascular risk factors. Additionally, venous and arterial thromboembolism is increased by cancers, and coronary atherosclerosis is precipitated by end stage renal failure and diabetes.[23,27–29] Moreover, depression, a common clinical situation in these patients, dramatically impacts prognosis after a hospitalisation for ACS.[30]

Patients with positive GSF seem to be less frequently treated with PCI. This result is consistent with other similar studies on frailty in patients with ACS or CAD.[31,32] It is possible that a clinical bias, due to the awareness of GSF results as well as the focus on the EoL theme from the investigator, influenced treatment choices to a less aggressive approach. On the other hand, it is conceivable that important comorbidities of patients with positive GSF and consequently their worse interventional risk profile, prompt physicians to follow a more conservative strategy. Furthermore, other aspects of management in patients approaching EoL are also more difficult. Duration of dual antiplatelet therapy, for example, remains a challenging issue,[4,33] as frequently these patients are also at an increased risk of bleeding.[34] All these factors highlight the need for a dedicated tool to promptly and easily identify those patients with a poor negative non-cardiovascular prognosis, in order to offer them the more appropriate, possibly less invasive, therapeutic choice.

GSF provided accurate and independent prediction for non-cardiovascular events in patients with ACS. The GRACE score for cardiovascular death and hospitalisation was also accurate. However, risk assessment by a cardiovascular score alone may not help to identify patients approaching EoL, which may lead to inappropriate treatment decisions and delayed palliative care. By applying GSF criteria to every patient admitted to the ED for ACS, regardless of the ward of admission we provided a more holistic picture of the ACS population. On the contrary, the WHOQOL-BREF test failed to provide prognostic information in this

setting. The reason for this remains to be explored but may be related to brevity and self-reporting nature of this questionnaire.

Lack of good correlation between the calculated scores was found, thus stressing the need for dedicated tools (both cardiovascular and non-cardiovascular) to provide a global assessment of patient health in an acute cardiac setting.

Cardiologists and emergency physicians commonly face the difficult question of whether or not an older frail patient should be offered an interventional treatment strategy which could be beneficial but also has its hazards and expenses. GSF, together with an integrated evaluation of the patient also with other medical specialists, may represent a simple and intuitive tool. Patient's assessment with non-cardiovascular parameters such as GSF along with classical cardiovascular risk scores, can improve the accuracy of risk–benefit analysis. For example, it may be helpful first to decide if the patient needs to be hospitalised or not, if he/she needs intensive care support or a general ward and timing and appropriateness of interventional strategy (see the Key messages).

While in the European context the management of ‘end of life’ patients in an acute setting is reported only in few papers,[35–37] in the United States of America a closer collaboration between palliative care and emergency medicine contributed to the creation of the IPAL-EM (Improving Palliative Care in Emergency Medicine) project. It offers practical tools[38,39] and guidelines[40] that could be very useful for ED physicians to identify and manage patients who could benefit from a palliative strategy. It would be desirable that a standardised approach also be developed in Europe.

In conclusion, our study represents the first step towards this goal. The availability of an easy-to-use score to calculate the prognosis of EoL in patients with ACS could have a great impact in choosing wisely the most appropriate treatment: it is well known that in healthcare sometimes ‘less is more’.[41]

Limitations

The main limitation of the study is the single centre setting, with a relatively small number of patients and, consequently, high CIs in statistical data; however, multivariate analysis was powered enough to detect significant and reliable results. Furthermore, we were unable to complete the WHOQOL-BREF test in all patients due to their refusal or inability to fill out the questionnaire. Finally, absence of clinical variables and specific comorbidities other than cardiovascular ones may present a limitation, although many of them are captured in the GSF score.

Conclusions

A sizeable proportion of patients with ACS have a positive GSF score. GSF could represent a powerful and accurate tool to predict 3-month and 1-year non-cardiovascular adverse events and guide management in patients with ACS. These results need to be externally validated on a larger sample size (eg, multicentre studies) and finally by randomised trials.

References

1. D'Ascenzo F, Presutti DG, Picardi E, et al. Prevalence and non-invasive predictors of left main or three-vessel coronary disease: evidence from a collaborative international meta-analysis including 22 740 patients. Heart 2012;98:914–19.
2. McCarthy CL. Percutaneous Coronary Intervention: therapeutic intervention in the cardiac catheterization laboratory. Heart Lung 1982;11:499–504.
3. Authors/Task Force membersWindecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541–619.
4. D'Ascenzo F, Colombo F, Barbero U, et al. Discontinuation of dual antiplatelet therapy over 12 months after acute coronary syndromes increases risk for adverse events in patients treated with percutaneous coronary intervention: systematic review and meta-analysis. J Interv Cardiol. 2014;27:233–41.
5. Schoenenberger AW, Radovanovic D, Stauffer J-C, et al. Age-related differences in the use of guideline-recommended medical and interventional therapies for acute coronary syndromes: a cohort study. J Am Geriatr Soc 2008;56:510–16.
6. D'Ascenzo F, Biondi-Zoccai G, Moretti C, et al. TIMI, GRACE and alternative risk scores in Acute Coronary Syndromes: a meta-analysis of 40 derivation studies on 216,552 patients and of 42 validation studies on 31,625 patients. Contemp Clin Trials 2012;33:507–14.
7. Moretti C, D'Ascenzo F, Omedè P, et al. Thirty-day readmission rates after PCI in a metropolitan center in Europe: incidence and impact on prognosis. J Cardiovasc Med (Hagerstown) 2015;16:238–45. .
8. Iqbal, Denvir M, Gunn J. et al. Frailty assessment in elderly people. Lancet 2013;381:1985–6.
9. Wykrzykowska JJ, Garg S, Onuma Y, et al. Value of age, creatinine, and ejection fraction (ACEF score) in assessing risk in patients undergoing percutaneous coronary interventions in the "All-Comers" LEADERS trial. Circ Cardiovasc Interv 2011;4:47–56.
10. Fenning S, Woolcock R, Haga K, et al. Identifying acute coronary syndrome patients approaching end-of-life. PLoS ONE 2012;7:e35536.
11. National End of Life Care Programme. Gold Standards Framework Prognostic Indicator Guidance: to aid identification of adult patients with advanced disease, in the last months/years of life, who are in need of supportive and palliative care. [Internet]. 2011. http://www.goldstandardsframework.org.uk
12. Skevington SM, Lotfy M, O'Connell KA, WHOQOL Group. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res 2004;13:299–310.
13. http://www.strobe-statement.org/

14. Steg PG, James SK, Atar D, et al, Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569–619.
15. Hamm CW, Bassand J-P, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011;32:2999–3054.
16. http://www.who.int/substance_abuse/research_tools/en/english_whoqol.pdf
17. Biondi-Zoccai G, Romagnoli E, Agostoni P, et al. Are propensity scores really superior to standard multivariable analysis? Contemp Clin Trials 2011;32:731–40.
18. D'Ascenzo F, Cavallero E, Biondi-Zoccai G, et al. Use and misuse of multivariable approaches in interventional cardiology studies on drug-eluting stents: a systematic review. J Interv Cardiol 2012;25:611–21.
19. Murray SA, Boyd K, Sheikh A. Palliative care in chronic illness. BMJ 2005;330:611–12.
20. Stewart S, McMurray JJV. Palliative care for heart failure. BMJ 2002;325:915–16.
21. Boyd K, Murray SA, Kendall M, et al. Living with advanced heart failure: a prospective, community based study of patients and their carers. Eur J Heart Failure 2004;6:585–91.
22. Gore JM, Brophy CJGMA. How well do we care for patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. Thorax 2000;55:1000–6.
23. Van Bliesen W, Lameire N, Veys N, et al. From curing to caring: one character change can make a world of difference. Issues related withholding/withdrawing renal replacement therapy (RRT) from patients with important comorbidities. Nephron Dial Transplant 2004;19:536–40.
24. Kleinjan A, Aggarwal A, Van de Geer A, et al. A worldwide survey to assess the current approach to the treatment of patients with cancer and venous thromboembolism. Thromb Haemost 2013;110:959–65.
25. 25 Gardiner C, Gott M, Ingleton C, et al. Extent of palliative care need in the acute hospital setting: A survey of two acute hospitals in the UK. Palliat Med 2013;27:76–83.
26. Shaw KL, Clifford C, Thomas K, et al. Review: improving end-of-life care: a critical review of the gold standards framework in primary care. Palliat Med 2010;24:317–29.
27. D'Ascenzo F, Bollati M, Clementi F, et al. Incidence and predictors of coronary stent thrombosis: evidence from an international collaborative meta-analysis including 30 studies, 221,066 patients, and 4276 thromboses. Int J Cardiol 2013;167: 575–84.
28. Pullara A, Longo G, Gonella A, et al. Incidence and very long- term outcomes of stent thrombosis after bare-metal or drug-eluting stent implantation: a retrospective analysis. Minerva Cardioangiol 2013;61:1–9.

29. James MT, Tonelli M, Ghali WA, et al. Renal outcomes associated with invasive versus conservative management of acute coronary syndrome: propensity matched cohort study. BMJ 2013;347:f4151.

30. Rieckmann N, Kronish IM, Shapiro PA, et al. Serotonin reuptake inhibitor use, depression, and long-term outcomes after an acute coronary syndrome: a prospective cohort study. JAMA Intern Med 2013;173:1150–1.

31. Graham MM, Galbraith PD, O'Neill D, et al. Frailty and outcome in elderly patients with acute coronary syndrome. Can J Cardiol 2013;29:1610–15.

32. Purser JL, Kuchibhatla MN, Fillenbaum GG, et al. Identifying frailty in hospitalized older adults with significant coronary artery disease. J Am Geriatr Soc 2006;54:1674–81.

33. Killu AM, Wright RS, Kopecky SL. Questions and answers on proper peri-operative management of antiplatelet therapy after coronary stent implantation to prevent stent thrombosis. Am J Cardiol 2013;112:1046–50.

34. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial versus femoral randomized investigation in ST-segment elevation acute Coronary Syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. J Am Coll Cardiol 2012;;60:2481–9.

35. Van Tricht M, Riochet D, Batard E, et al. Palliative care for patients who died in emergency departments: analysis of a multicentre cross-sectional survey. Emerg Med J 2012;29:795–7.

36. Wallace EM, Cooney MC, Walsh J, et al. Why do palliative care patients present to the emergency department? Avoidable or unavoidable? Am J Hosp Palliat Care 2013;30:253–6.

37. Couilliot MF, Leboul D, Douguet F. Palliative care in emergency departments: an impossible challenge?. Eur J Emerg Med 2012;19:405–7.

38. http://www.capc.org/ipal/ipal-em/improvement-and-clinical-tools

39. Quest T, Herr S, IPAL-EM Advisory Board. Demonstrations of clinical initiatives to improve palliative care in the emergency department: a report from the IPAL-EM Initiative. Ann Emerg Med 2013;61:661–7.

40. Lamba S, DeSandre PL, Todd KH, et al. Integration of palliative care into emergency medicine: the Improving Palliative Care in Emergency Medicine (IPAL-EM) collaboration. J Emerg Med 2014;46:264–70.

41. Lipitz-Snyderman A, Bach PB. Overuse of health care services: when less is more … more or less. JAMA Intern Med 2013;173:1277–8.