Prognostic Performance of GRACE and TIMI Risk Scores in Critically ill Patients with Sepsis and a Concomitant Myocardial Infarction

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Performance pronostique des score de risque GRACE et TIMI chez les patients hospitalisés en réanimation pour un sepsis et présentant un infarctus du myocarde concomitant

Abbreviated title: Prognostic value of GRACE and TIMI risk scores for AMI during sepsis

Tweet: Acute myocardial infarction in critically ill patients with sepsis is a common situation at high risk of cardiovascular events, including severe ischaemic events, bleeding events and death. Neither the GRACE risk score nor the TIMI risk score predicted poor prognosis

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Summary

Background. – Identifying which patients with acute myocardial infarction (AMI) during sepsis are at risk of poor outcome is a clinical challenge.

Aim. – To evaluate Global Registry of Acute Coronary Events (GRACE) and Thrombolysis In Myocardial Infarction (TIMI) risk scores to predict in-hospital mortality and severe ischaemic events in this setting.

Methods. – In this single-centre retrospective study conducted from 2012 to 2016, all consecutive adults hospitalized in the intensive care unit for sepsis who had a concomitant AMI (within 72 hours of admission) were enrolled. AMI was defined by an elevated cardiac troponin I value associated with at least one sign (clinical, electrocardiographic or echocardiographic) suggestive of myocardial ischaemia. The primary outcome was in-hospital mortality from any cause. Secondary outcomes were in-hospital occurrence of severe ischaemic events (cardiac arrest with resuscitation, ischaemic stroke and myocardial reinfarction) and major bleeding events.

Results. – Among 856 patients hospitalized for sepsis, 120 (14.5%) had a concomitant AMI (37.5% women; median age 65 years; median Sequential Organ Failure Assessment [SOFA] score 8). Severe ischaemic events occurred in 15 patients (12.5%), and 39 (33%) died in hospital. Neither the GRACE score (median 192, interquartile range 154–223) nor the TIMI score (median 3, interquartile range 2–4) was associated with occurrence of severe ischaemic events. Only the GRACE score was associated with in-hospital mortality (odds ratio 1.01, 95% confidence interval 1.00–1.02 per 1 point increase). Multivariable analysis identified previous aspirin use and SOFA score as independent factors associated with in-hospital mortality.

Conclusions. – GRACE and TIMI scores did not predict in-hospital severe ischaemic events and mortality in patients with AMI during sepsis. Among individual components of both scores, previous aspirin use was associated with poor prognosis. However, because of lack of statistical power, we cannot formally rule out the usefulness of these scores in this setting.

Résumé

Contexte. – Parmi les patients ayant un infarctus du myocarde (IDM) au décours d'un sepsis, identifier ceux à risque de mauvais pronostic est un défi clinique.

Objectif. – Notre objectif est d'évaluer les scores de risque GRACE et TIMI afin de prédire la mortalité intra-hospitalière et les évènements ischémiques sévères dans ce contexte.

Méthodes. – Dans cette étude mono-centrique rétrospective conduite de 2012 à 2016, tous les patients adultes hospitalisés en unité de soins intensifs pour un sepsis et présentant un IDM concomitant (dans les 72 heures de l'admission) ont été consécutivement inclus. L'IDM était défini par une élévation de la troponine cardiaque I associée à la présence d'au moins un signe clinique, électrocardiographique ou échocardiographique suggérant une ischémie myocardique. Le critère de jugement principal était la mortalité intra-hospitalière toute cause. Les critères de jugement secondaires intra-hospitalier étaient les évènements ischémiques sévère (arrêt cardiaque avec réanimation cardio-pulmonaire, accident vasculaire cérébral ischémique, infarctus du myocarde récidivant) et les évènements hémorragiques sévère.

Résultats. – Parmi 856 patients hospitalisés pour sepsis, 120 patients (14,5 %) ont présenté un AMI concomitant (femme, 37,5 % ; âge médian, 65 ans, score SOFA médian 8). Un évènement ischémique sévère est survenu chez 15 patients (12,5 %) and 39 patients (33 %) sont décédés à l'hôpital. Ni le score GRACE (médiane 192, IQR 154–223), ni le score TIMI (médiane 3, IQR 2–4) n'étaient associés à la survenue d'un évènement ischémique sévère. Seul le score GRACE était significativement associé à la mortalité (OR 1,01, IC95 % 1,00–1,02 par point). En analyse multivariée, la prise d'aspirine au long court et le score SOFA étaient indépendamment associés à la mortalité intra-hospitalière.

Conclusions. – Ni le score GRACE, ni le score TIMI ne prédisent la survenue d'évènement ischémique sévère intra-hospitalier et la mortalité intra-hospitalière chez les patients présentant un IDM au cours d'un sepsis. Parmi les composants individuels des deux scores, la prise d'aspirine au long court était associée à un plus mauvais pronostic. Cependant, en raison du manque de puissance statistique, notre étude ne peut exclure formellement l'utilité de ces scores dans ce contexte.

KEYWORDS

TIMI risk score;

GRACE risk score;

Myocardial infarction;

Sepsis;

Prognosis

MOTS CLÉS

Score de risqué TIMI ;

Score de risque GRACE ;

Infarctus du myocarde ;

Sepsis ;

Pronostique

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; GRACE, Global Registry of Acute Coronary Events; ICU, intensive care unit; IQR, interquartile range; ROC, receiver operating characteristic; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; TIMI, Thrombolysis In Myocardial Infarction; TnI, troponin I.

Background

Cardiovascular complications are common in patients admitted to intensive care units (ICUs) for sepsis [1]. In particular, acute myocardial infarction (AMI), reported in 4.5% of critically ill patients with sepsis, is independently associated with increased mortality in this setting [1]. However, the characteristics of AMI during sepsis, and their significance in predicting the risk of death and severe ischaemic events are uncertain. Hence, identifying which patients are most likely to benefit from specific cardiac management is a major clinical challenge [2]. To date, in cardiology wards, both the Global Registry of Acute Coronary Events (GRACE) and Thrombolysis In Myocardial Infarction (TIMI) risk scores are used to evaluate the risk of death and severe ischaemic events associated with an AMI [3-6] (Table 1); to our knowledge, neither has been tested in patients in ICUs with AMI during sepsis. Thus, we sought to characterize AMI, and to investigate its consequences in a cohort of patients admitted to the ICU, aiming to evaluate the prognostic performance of the GRACE and TIMI scores.

Methods

This retrospective observational cohort study was conducted in a 20-bed ICU from June 2012 to August 2016 in a French university teaching hospital in Paris, France. All consecutive adult patients (aged ≥ 18 years) with sepsis/septic shock, according to the Sepsis-3 definition [7], and who had a concomitant AMI (within 72 hours of ICU admission) were included. AMI was defined by an elevated cardiac troponin I (TnI) value above the 99th percentile upper reference limit, with a variation (rise and/or fall) of 20% in cardiac TnI values (myocardial injury [8]), associated with at least one sign suggestive of myocardial ischaemia, including clinical symptoms or electrocardiogram modifications or transthoracic echocardiography abnormalities (detailed definition in Table A.1) [9]. Non-inclusion criteria were cardiac surgery, percutaneous coronary intervention or coronary artery bypass grafting during the preceding month, moribund patients and patients with limitation of life-sustaining therapy. This study was conducted in accordance with the amended Declaration of Helsinki, and was approved by the ethical board of the French Intensive Care Society institutional review board (CE SRLF 20-77).

Selection of patients

As part of routine assessment in patients with sepsis, the occurrence of AMI was diagnosed prospectively by the intensivist in charge of the patient. Clinical and electrocardiogram signs

suggestive of myocardial ischaemia were systematically sought on admission, and whenever clinically appropriate during the ICU stay. Electrocardiogram signs were compared with the baseline electrocardiogram, when available, and were classified using standard definitions [9]. At admission and during the ICU stay, measurement of cardiac TnI was left at the discretion of physicians in charge. When elevation of cardiac TnI was observed, physicians were encouraged to obtain additional cardiac TnI measurements to determine the cardiac TnI peak value. Transthoracic echocardiography studies were systematically performed within 72 hours of ICU admission by trained operators (competence in advanced critical care echocardiography [10]) using a CX50 system (Philips Ultrasound, Bothell, WA, USA). Left ventricular ejection fraction was assessed using the biplane Simpson's method, or was visually estimated in case of inadequate identification of the endocardium. Transthoracic echocardiography sign suggestive of myocardial ischaemia was defined as left ventricular ejection fraction ≤ 45% or wall motion abnormality [11]. Electrocardiograms were reviewed by two cardiologists (V. L. and S. E.) in a blinded fashion, and discordance was resolved by consensual agreement between the two reviewers. All AMI diagnoses were adjudicated by two experts in cardiology (V. L. and C. D.).

Clinical and biological data, and management

Demographics, medical history, previous antithrombotic use, admission category, Simplified Acute Physiology Score II (SAPS II) [12] and infection sites were recorded on ICU admission. At the time of AMI onset, SOFA (Sequential Organ Failure Assessment) [13], Killip [14], GRACE [6] and TIMI [3] scores (Table 1), standard biological data and medical treatments for AMI were collected. Norepinephrine was the first-line vasopressor therapy (used to target a mean arterial pressure of 65 mmHg or more); dobutamine was added in the presence of decreased left ventricular ejection fraction (< 45%) with ongoing signs of hypoperfusion despite adequate mean arterial pressure (epinephrine could be considered if the latter condition was not met). Data on coronary angiography with or without reperfusion during the index hospitalization were also collected. Early reperfusion therapy was defined as coronary reperfusion within the first 72 hours after AMI onset (by percutaneous coronary intervention or coronary artery bypass graft surgery).

Outcomes

All the patients were followed from the day of the AMI until hospital discharge, based on the analysis of medical records, including medical observations and hospitalization reports, as well as biological and radiological examinations. The primary outcome was in-hospital mortality from any cause. Secondary outcomes were the occurrence of in-hospital severe ischaemic events (cardiac arrest with resuscitation, ischaemic stroke and myocardial reinfarction) and in-hospital major bleeding events (detailed definition in Table A.1).

Statistical analysis

Data are reported as medians (interquartile ranges [IQRs]) for quantitative variables, and as frequencies (percentages) for categorical variables. Distributions of patient characteristics were compared according to in-hospital mortality, using the Mann-Whitney-Wilcoxon test for quantitative variables, and Fisher's exact test for categorical variables. Distributions of patient characteristics were compared according to severe ischaemic events, using univariate cause-specific Cox models for the first occurrence of a severe ischaemic event (accounting for the competing risk of death). Performances of the GRACE, TIMI and SOFA risk scores in predicting in-hospital mortality were evaluated according to their discriminations (areas under the receiver operating characteristic [ROC] curve) and calibrations (Hosmer-Lemeshow tests and calibration plots). Two multivariable models for the outcomes were built from the GRACE and TIMI risk scores (logistic regression for in-hospital mortality and cause-specific Cox regression for severe ischaemic events), with additional adjustment on variables associated with outcomes in the univariate analysis, and deemed to be the most clinically relevant. To avoid overfitting, we considered that we could enter a maximum number of four variables in the mortality model (in view of the 39 events observed) and two variables in the severe ischaemic event model (in view of the 15 events observed) [15]. Odds ratios and hazard ratios were estimated and reported with their 95% confidence intervals (CIs). All tests were two-tailed, and *P* values < 0.05 were considered significant. Statistical analysis was conducted with R, version 3.6.3 (R Core Team 2019; R foundation for Statistical Computing, Vienna, Austria).

Results

Description of patients

Among 856 patients with sepsis during the study period, 461 (54%) had a myocardial injury, and 121 (14%) experienced a concomitant AMI. One moribund patient was excluded (Fig. 1). Therefore, 120 patients were analysed (45 women), with a median (IQR) age of 65 (56–75) years (Table 2). The AMI occurred on ICU admission in 96 patients (80%). The median value of the cardiac TnI peak was 1280 (IQR 539–3725) ng/mL at the time of the AMI. Clinical symptoms, electrocardiogram modifications and transthoracic echocardiography abnormalities consistent with myocardial ischaemia were observed in 14 (12%), 101 (84%) and 89 (74%) patients, respectively, at the time of the AMI (Table 3). Details regarding conditions of echocardiographic examinations are given in Table A.2. The median GRACE and TIMI risk scores were 192 (IQR 154–223) and 3 (IQR 2–4), respectively, at the time of the AMI.

Antiplatelet and therapeutic anticoagulation were administered to 79 (66%) and 49 (41%) patients, respectively (Table 2). Among 32 patients (27%) who underwent a coronary angiography, 20 patients were diagnosed with an obstructive coronary artery disease, and 10 patients were treated by an early reperfusion therapy with percutaneous coronary intervention. AMI characteristics and organ dysfunction management on the day of the AMI, according to performance of coronary angiography, are displayed in Table A.3. Patients who underwent a coronary angiography had higher troponin concentrations, lower plasma creatinine concentrations, a higher left ventricular ejection fraction and more frequent wall motion abnormalities, whereas GRACE and TIMI scores and electrocardiogram abnormalities were similar between the two groups. Patients for whom coronary angiography was considered had lower SOFA scores and less often required catecholamines and invasive mechanical ventilation on the day of the AMI compared with patients who did not undergo coronary angiography. No major complication related to the coronary angiography occurred.

Outcomes

Thirty-nine patients (33%) died in the hospital. The causes of death were multiple organ failure (*n* = 20), refractory cardiogenic shock (*n* = 5), acute respiratory distress syndrome-related refractory hypoxaemia (*n* = 4), cardiac arrest of suspected cardiogenic origin (*n* = 3), mesenteric ischaemia (*n* = 3), gastrointestinal haemorrhage (*n* = 1) and end-of-life decision (*n* = 3).

Fifteen patients (12.5%) presented at least one severe ischaemic event, occurring after a median (IQR) of 3 (2–18) days from AMI onset. Severe ischaemic events included four ischaemic strokes, 10 cardiac arrests with resuscitation and three myocardial reinfarctions. Thirteen patients (11%)

presented at least one bleeding event, occurring after a median (IQR) of 3 (1–11) days from AMI onset. Major bleeding events occurred in 13 patients (11%), after a median (IQR) of 3 (1–11) days from AMI onset, including 12 extracranial major bleedings (gastrointestinal, *n* = 5; pulmonary, *n* = 3; urological, *n* = 2; vascular, *n* = 1; pericardial, *n* = 1) and one intracranial bleeding. The median (IQR) packed red blood cell transfusion was 2 (1–3) units. Three patients presented a major bleeding event, categorized as life-threatening in three patients, including fatal gastrointestinal bleeding in two cases.

Patient factors associated with in-hospital mortality

Compared with survivors, non-survivors were more likely to be receiving long-term aspirin, and more frequently had septic shock and a higher SAPS II score on ICU admission (Table 2). On the day of the AMI, non-survivors had higher SOFA and GRACE scores, lower systolic arterial blood pressure and more frequent left ventricular systolic dysfunction (Table 3). The TIMI score was similar between survivors and non-survivors. After adjustment on previous aspirin use, SOFA score and left ventricular dysfunction at the time of the AMI, neither the GRACE score nor the TIMI score was associated with in-hospital mortality (Table 4). The multivariable analysis for GRACE score identified aspirin use and SOFA score as independent factors associated with in-hospital mortality (respectively, odds ratio 5.29, 95% CI 1.66–18.77; and odds ratio 1.30, 95% CI 1.15–1.49; Table 4). In a multivariable model excluding GRACE and TIMI scores, previous aspirin use and SOFA score remained independently associated with mortality (Table A.4). The areas under the ROC curves (95% CI) for the GRACE, TIMI and SOFA risk scores were 0.62 (0.51–0.73), 0.57 (0.46–0.68) and 0.78 (0.70–0.87), respectively (Fig. 2). No calibration issue was identified for these scores (Hosmer-Lemeshow tests: *P* = 0.49, 0.99 and 0.82, respectively; Fig. A.1).

Patient factors associated with in-hospital severe ischaemic events

Patients who had a severe ischaemic event were more frequently treated with aspirin, had septic shock and a higher SAPS II score on ICU admission (Table 2). On the day of the AMI, patients who had a severe ischaemic event had a higher SOFA score, lower systolic arterial blood pressure and a higher cardiac TnI concentration, and more frequently had left ventricular systolic dysfunction (Table 3). Neither the GRACE score nor the TIMI score was associated with the occurrence of severe

ischaemic events in the univariate analysis (Table 3) or the multivariable analysis after adjustment on SOFA score (Table A.5).

Discussion

To our knowledge, this is the first study assessing the prognostic performance of GRACE and TIMI risk scores in patients with sepsis and a concomitant AMI. The main findings are as follows: (1) AMI occurred in 14% of patients with sepsis; (2) the incidence of adverse events was high, including major ischaemic events (12%), major bleeding events (11%) and in-hospital mortality (33%); and (3) neither the GRACE score nor the TIMI score predicted in-hospital mortality. Among individual components of scores, previous aspirin use was associated with a poor prognosis.

Consistent with our results, Smilowitz et al. reported that myocardial infarction was diagnosed in 4.5% of patients in a contemporary nationwide retrospective cohort of more than 2.6 million patients with sepsis. Previous series support the concept that acute infections are associated with an increased risk of myocardial infarction [16]. Smeeth et al. showed that the risk of myocardial event was higher after a lower respiratory tract infection, especially during the first 3 days [16]. Even so, these data suggest a substantial burden of concomitant myocardial infarction and sepsis that warrants renewed attention.

Cardiovascular risk in patients with AMI during sepsis should be a major concern. In the large retrospective cohort of patients with sepsis reported by Smilowitz et al., AMI was independently associated with increased mortality [1]. Tachycardia and blood pressure perturbations may lead to plaque rupture and coronary thrombosis [9], and proinflammatory cytokines contribute to a prothrombotic state [17]. Thus, ischaemic and bleeding events seem to be more common in critically ill patients with sepsis than in patients in cardiology wards. In the cardiology setting, a recent randomized clinical trial comparing prehospital (experimental group) versus in-hospital (control group) treatment with ticagrelor in 1862 patients with ST-segment elevation myocardial infarction reported 30-day severe ischaemic events and major bleeding events in 4.4% and 1.2% of patients, respectively, in the control group [18].

Observational data suggest that invasive management with revascularization is associated with lower in-hospital mortality among propensity score-matched patients with sepsis and myocardial infarction [1]. However, the authors reported that revascularization was performed in a minority of

patients (4%), in line with our findings (8%) [1]. In this setting, the relatively low rate of coronary angiography and percutaneous coronary intervention could be explained by the initial severity of the sepsis. We found that patients who did not undergo coronary angiography had higher organ dysfunction scores, with more frequent haemodynamic, renal and respiratory failure than patients who did undergo coronary angiography. Moreover, Del Pace et al. showed that the occurrence of an infective or inflammatory event may facilitate the development of coronary stent thrombosis [19]. These data suggest the urgent need to find risk stratification bedside tools to determine who may derive the greatest benefit from invasive management in this setting.

Several hypotheses may explain the poor predictive values of both the GRACE and TIMI scores within our cohort. First, the GRACE and TIMI scores were modestly predictive of all-cause in-hospital mortality among patients with myocardial infarction type 2 [20]. In our cohort, one third of our patients who underwent coronary angiography had no obstructive coronary artery disease, suggesting a myocardial infarction type 2. Second, previous coronary artery disease was more frequent in the myocardial infarction cohorts from which the GRACE and TIMI scores were derived (32% and 26%, respectively) than in our present cohort (17%) [3, 6]. Third, the GRACE and TIMI risk scores may not be valid in patients in whom the use of percutaneous coronary intervention and antiplatelet agents is very low compared with in the cardiology wards. Fourth, in our study, the diagnosis of myocardial ischaemia was uncertain, with other potential physiopathological mechanisms of myocardial injury during sepsis, such as stress cardiomyopathy or myocarditis [9]. However, among individual components of GRACE and TIMI scores, previous aspirin use was a marker of cardiovascular risk, as already reported in large cardiology cohorts [3, 21].

Study limitations

Our study has several limitations. First, the retrospective nature of the analysis is a weakness, and the single-centre design reduces its external validation. Second, because of the relatively small number of patients and the low absolute rate of in-hospital events, our findings cannot rule out a role for these scores in cardiovascular risk estimation. Third, the incidence of AMI could have been underestimated because troponin was not systematically measured in patients in the ICU with sepsis. However, the dosage of troponin was guided by the pretest probability of myocardial injury estimated by the physician in charge. Fourth, as mentioned above, the diagnosis of myocardial infarction was uncertain.

In particular, in the context of septic shock, left ventricular systolic dysfunction on echocardiography is not specific to myocardial ischaemia. However, AMI was based on current assessment tools readily available at bedside in the ICU. Finally, the present study was an observational study. The treatment of co-morbid conditions, revascularization, and antiplatelet and therapeutic anticoagulation could have influenced the occurrence of ischaemic and bleeding events.

Conclusions

AMI in patients with sepsis is a common situation at high risk of cardiovascular events, including severe ischaemic events, bleeding events and death. Neither the GRACE risk score nor the TIMI risk score predicted poor prognosis. Consequently, a GRACE or TIMI score-guided strategy for ischaemic therapies in this context appears inaccurate. Among individual components of scores, previous aspirin use was independently associated with mortality. However, because of the lack of statistical power as a result of the limited sample size, our findings cannot formally rule out the usefulness of these scores for cardiovascular risk estimation in this setting. Further studies are needed to develop bedside cardiovascular risk stratification tools, which may guide direct anti-ischaemic therapies and invasive management.

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None.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this manuscript.

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Figure legends

Figure 1. Patient flow chart. cTnI: cardiac troponin I; ICU: intensive care unit.

Figure 2. Receiver operating characteristic curves for Global Registry of Acute Coronary Events (GRACE), Thrombolysis In Myocardial Infarction (TIMI) and Sequential Organ Failure Assessment (SOFA) scores to predict in-hospital mortality. AUC: area under the curve.

Table 1 Global Registry of Acute Coronary Events (GRACE) and Thrombolysis In Myocardial Infarction (TIMI) risk scores in patients with myocardial infarction in cardiology wards.

GRACE score[a]	Points 1–372	TIMI score[b]	Points 0–7
Age (years)[c]	0–100	Age ≥ 65 years	1
Heart rate (beats/min)[d]	0–46	At least three coronary artery disease risk factors	1
Systolic blood pressure (mmHg)[e]	0–58	Known coronary artery disease	1
Creatinine (mg/dL)[f]	1–28	Previous aspirin use (in the past 7 days)	1
Killip class[g,h]	0–59	Severe angina (at least two episodes in the last 24 hours)	1
Elevated cardiac troponin	14	Elevated cardiac troponin	1
ST-segment modification	28	Electrocardiogram changes ≥ 0.5 mm	1
Cardiac arrest	39		

[a] Derived to estimate the probability of in-hospital mortality in a cardiology population with a high probability of myocardial infarction on admission to the wards [6].

[b] Derived in patients with non-ST-segment elevation myocardial infarction to predict 14-day outcomes, including all-cause mortality, new or recurrent myocardial infarction or severe recurrent ischaemia requiring urgent revascularization [3].

[c] ≤ 30 years: 0 points; 30–39 years: 8 points; 40–49 years: 25 points; 50–59 years: 41 points; 60–69 years: 58 points; 70–79 years: 75 points; 80–89 years: 91 points; ≥ 90 years: 100 points.

[d] ≤ 50 beats/min: 0 points; 50–69 beats/min: 3 points; 70–89 beats/min: 9 points; 90–109 beats/min: 15 points; 110–149 beats/min: 24 points; 150–199

beats/min: 38 points; ≥ 200 beats/min: 46 points.

[e] < 80 mmHg: 58 points; 80–99 mmHg: 53 points; 100–119 mmHg: 43 points: 120–139 mmHg: 34 points; 140–159 mmHg: 24 points; 160–199 mmHg: 10 points; ≥ 200 mmHg: 0 points.

[f] 0–0.39 mg/dL: 1 point; 0.4–0.79 mg/dL: 4 points; 0.8–1.19 mg/dL: 7 points; 1.2–1.59 mg/dL: 10 points; 1.6–1.99 mg/dL: 13 points; 2–3.99 mg/dL: 21 points; > 4 mg/dL: 28 points.

[g] Relies on the clinical level of heart failure after a myocardial infarction to stratify the patients in one out of four risk classes, as follows: class I: no sign of heart failure; class II: crackles in the lungs; class III: frank acute pulmonary oedema; and class IV: cardiogenic shock; it was developed to predict and stratify the risk of mortality [14].

[h] I: 0 points; II: 20 points; III: 39 points; IV: 59 points.

Table 2 Baseline patient characteristics and initial management, according to in-hospital severe ischaemic event and all-cause death.

Variables	Total	Severe ischaemic event			All-cause death		
		No	Yes	*P*	No	Yes	*P*
	(*n* = 120)	(*n* = 105)	(*n* = 15)		(*n* = 81)	(*n* = 39)	
Baseline characteristics							
Age (years)[a,b]	65 (56–75)	66 (56–74)	64 (58–78)	0.46	65 (53–72)	69 (60–77)	0.11
Female sex	45 (38)	40 (38)	5 (33)	0.89	31 (38)	14 (36)	0.84
Coronary artery disease[a]	20 (17)	15 (14)	5 (33)	0.14	13 (16)	7 (18)	0.80
Smoking	80 (67)	70 (66)	10 (66)	0.39	57 (70)	23 (59)	0.29
Diabetes mellitus	33 (28)	29 (28)	4 (27)	0.85	23 (28)	10 (26)	> 0.99
Dyslipidaemia	44 (37)	40 (38)	4 (29)	0.69	29 (36)	15 (38)	0.84
Hypertension	60 (50)	52 (50)	8 (53)	0.30	38 (47)	22 (56)	0.44
Previous aspirin use[a]	30 (25)	23 (22)	7 (47)	< 0.001	14 (17)	16 (41)	0.01
Previous therapeutic anticoagulation use	16 (13)	15 (14)	1 (7)	0.345	10 (12)	6 (15)	0.77
Admission category							
Medical	94 (78)	81 (77)	13 (87)	0.292	67 (83)	27 (69)	0.10
Emergency surgery	17 (14)	15 (14)	2 (13)	0.27	9 (11)	8 (21)	0.17
Scheduled surgery	9 (8)	9 (8)	0	0.66	5 (6)	4 (10)	0.50

Site of infection[c]							
Lung	71 (59)	64 (61)	7 (47)	0.56	48 (59)	23 (59)	> 0.99
Urological	24 (20)	23 (22)	1 (7)	0.44	17 (21)	7 (18)	0.81
Abdominal	19 (16)	15 (14)	4 (27)	0.29	12 (15)	7 (18)	0.79
Others	11 (9)	8 (8)	3 (20)	0.14	4 (5)	2 (5)	> 0.99
SAPS II on ICU admission	50 (37–60)	49 (37–58)	58 (46–68)	< 0.001	47 (35–54)	58 (50–74)	< 0.001
Septic shock on ICU admission	79 (66)	67 (64)	12 (80)	0.03	47 (58)	32 (82)	0.01
Management on the day of AMI							
Antithrombotic drug	79 (66)	67 (64)	12 (80)	0.34	61 (75)	18 (46)	0.002
Aspirin	72 (60)	62 (59)	10 (67)	0.01	55 (68)	17 (44)	0.02
Clopidogrel	11 (9)	5 (5)	6 (40)	0.27	9 (11)	2 (5)	0.50
Anticoagulation	49 (41)	40 (38)	9 (60)	0.24	38 (47)	11 (28)	0.07
Early reperfusion[d]	10 (8)	6 (6)	4 (27)	0.56	9 (11)	1 (3)	0.16
Catecholamines	87 (73)	77 (73)	10 (67)	0.55	50 (62)	37 (95)	< 0.001
Norepinephrine	67 (56)	58 (55)	9 (60)	0.95	39 (48)	28 (72)	0.02
Epinephrine	33 (28)	30 (29)	3 (20)	0.76	17 (21)	16 (41)	0.02
Dobutamine	26 (22)	19 (18)	7 (47)	0.02	14 (17)	12 (31)	0.09
Invasive mechanical ventilation	81 (68)	68 (65)	13 (87)	0.003	46 (57)	35 (90)	< 0.001
Renal replacement therapy	14 (12)	11 (11)	3 (20)	0.38	9 (11.1)	10 (26)	0.18

Continuous variables are expressed as median (interquartile range), and categorical variables as number (%). Distributions of categorical and continuous variables were compared using Fisher's test and the Mann-Whitney-Wilcoxon test (all-cause death), and cause-specific Cox regression (ischaemic event). AMI: acute myocardial infarction; ICU: intensive care unit; SAPS II: Simplified Acute Physiology Score II.

[a] Variable for Thrombolysis In Myocardial Infarction (TIMI) risk score.

[b] Variable for Global Registry of Acute Coronary Events (GRACE) risk score.

[c] Patients could have more than one site of infection.

[d] Median time from AMI to early reperfusion with percutaneous coronary intervention: 1 (0.5–2) day.

Table 3 Characteristics of acute myocardial infarction, according to in-hospital severe ischaemic event and all-cause death.

Variables[a]	Total	Severe ischaemic event			All-cause death		
		No	Yes	*P*	No	Yes	*P*
	(*n* = 120)	(*n* = 105)	(*n* = 15)		(*n* = 81)	(*n* = 39)	
Risk scores							
SOFA	8 (5–12)	8 (5–12)	11 (7–14)	< 0.001	7 (4–10)	12 (9–15)	< 0.0001
GRACE	192 (154–223)	188 (154–220)	194 (155–225)	0.06	184 (152–212)	206 (174–228)	0.03
TIMI	3 (2–4)	3 (2–4)	3 (1.5–4.5)	0.15	3 (1–3)	3 (2–4)	0.23
Clinical variable							
Clinical sign of myocardial ischaemia[b]	14 (12)	12 (11)	2 (13)	0.72	9 (11)	5 (13)	0.77
Heart rate (beats/min)[c]	115 (99–137)	115 (100–137)	114 (84–134)	0.10	120 (100–137)	115 (90–137)	0.49
Systolic arterial blood pressure (mmHg)c	85 (76–107)	85 (76–109)	82 (80–94)	0.002	90 (77–112)	80 (75–93)	0.04
Killip class[c,d]	1 (1–4)	1 (1–4)	1 (1–4)	> 0.99	1 (1–4)	2 (1–4)	0.22
Cardiac arrest[c]	1 (1)	0	1 (7)	> 0.99	1 (1)	0	> 0.99
Electrocardiography and cardiac troponin							
ST-segment elevation[b,c]	23 (19)	20 (19)	3 (20)	0.91	16 (20)	7 (18)	> 0.99
New-onset left bundle branch block	8 (7)	6 (6)	2 (13)	0.42	6 (7)	2 (5)	> 0.99
ST-segment depression[b,c]	31 (26)	27 (26)	4 (27)	0.88	21 (26)	10 (26)	> 0.99

T-wave inversion	41 (34)	36 (34)	5 (33)	0.71	30 (37)	11 (28)	0.42
Cardiac TnI (pg/mL)[b,c,e]	786 (257–2474)	619 (220–1820)	2228 (812–4279)	0.003	1028 (280–2466)	486 (225–2137)	0.18
Cardiac TnI (pg/mL)[b,c,e]	1280 (539–3725)	1113 (381–3028)	6363 (1188–13336)	< 0.001	1228 (540–3208)	2230 (653–6253)	0.25
Echocardiography finding[f]							
LVEF (%)	30 (20–45)	30 (18–45)	25 (20–34)	0.005	33 (20–50)	22.5 (18–38)	0.02
LV systolic dysfunction (LVEF ≤ 45%)	89 (74.2)	78 (74)	11 (73)	0.002	53 (65.4)	36 (92.2)	0.001
Wall motion abnormality (MD = 22)	12 (10)	7 (7)	5 (33)	0.44	9 (11)	3 (8)	0.75

Continuous variables are expressed as median (interquartile range), and categorical variables as number (%). Distributions of categorical and continuous variables were compared using Fisher's test and the Mann-Whitney-Wilcoxon test (all-cause death), and cause-specific Cox regression (ischaemic event). AMI: acute myocardial infarction; CAD: coronary artery disease; LV: left ventricular; LVEF: left ventricular ejection fraction; MD: missing data; SOFA: Sequential Organ Failure Assessment; TnI: troponin I.

[a] On the day of AMI onset.

[b] Variable for Thrombolysis in Myocardial Infarction (TIMI) risk score.

[c] Variable for Global Registry of Acute Coronary Events (GRACE) risk score.

[d] Four risk classes as follows: class I: no sign of heart failure; class II: crackles in the lungs; class III: frank acute pulmonary oedema; and class IV: cardiogenic shock [14] .

[e] Cardiac TnI was first measured (June 2012 to November 2014) with the ARCHITECT method (Abbott, Lake Forest, IL USA); this assay demonstrated an upper reference limit (URL; 99th percentile) of 30 ng/mL; afterwards, the high-sensitivity assay from the same manufacturer (ARCHITECT STAT hsTnI assay), adapted to the same analyser, was used (URL 26 ng/mL); because of the excellent correlation between assays and the closeness of the two URLs used, a 1000 factor was applied to cardiac TnI to merge all troponin results obtained from these two periods [22].

[f] Median (interquartile range) time from AMI to echocardiography: 0 (0–1) day.

Table 4 Patient factors associated with in-hospital mortality.

Variable	Mortality odds ratio (95% confidence interval); *P*		
	Univariate	Multivariable for GRACE	Multivariable for TIMI
GRACE score[a]	1.01 (1.00–1.02); 0.04	0.997 (0.98–1.01); 0.63	-
TIMI score[a]	1.20 (0.92–1.58); 0.17	-	1.20 (0.75–1.93); 0.44
Previous aspirin use	3.33 (1.42–7.98); 0.01	5.29 (1.66–18.77); 0.01	3.14 (0.74–15.20); 0.13
SOFA score[a]	1.28 (1.16–1.44); 0.001	1.30 (1.15–1.49); < 0.001	1.31 (1.16–1.50); < 0.001
LV systolic dysfunction[b]	8.49 (2.33–54.83); 0.01	3.56 (0.80–25.33; 0.13	3.66 (0.82–26.57); 0.13

GRACE: Global Registry of Acute Coronary Events; LV: left ventricular; SOFA: Sequential Organ Failure Assessment; TIMI: Thrombolysis in Myocardial Infarction.

[a] On the day of the acute myocardial infarction.

[b] Defined as LV ejection fraction ≤ 45% at initial echocardiographic study.

Figure 1

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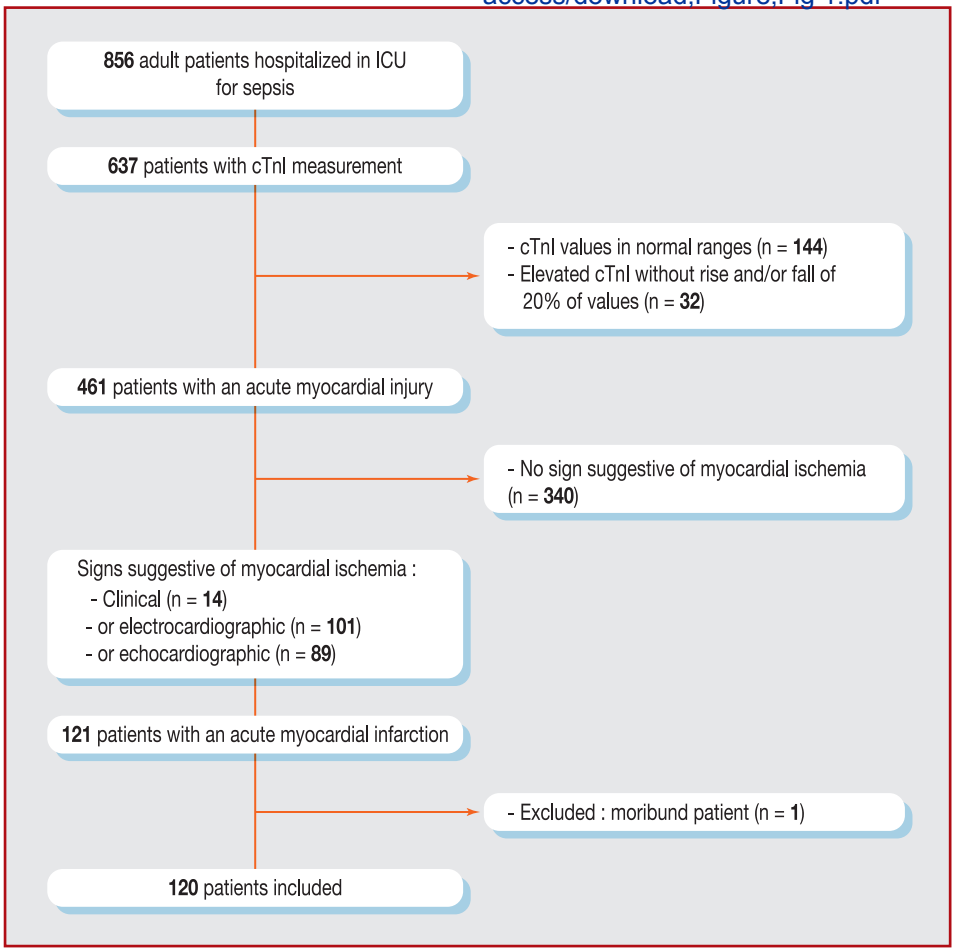

Figure 2

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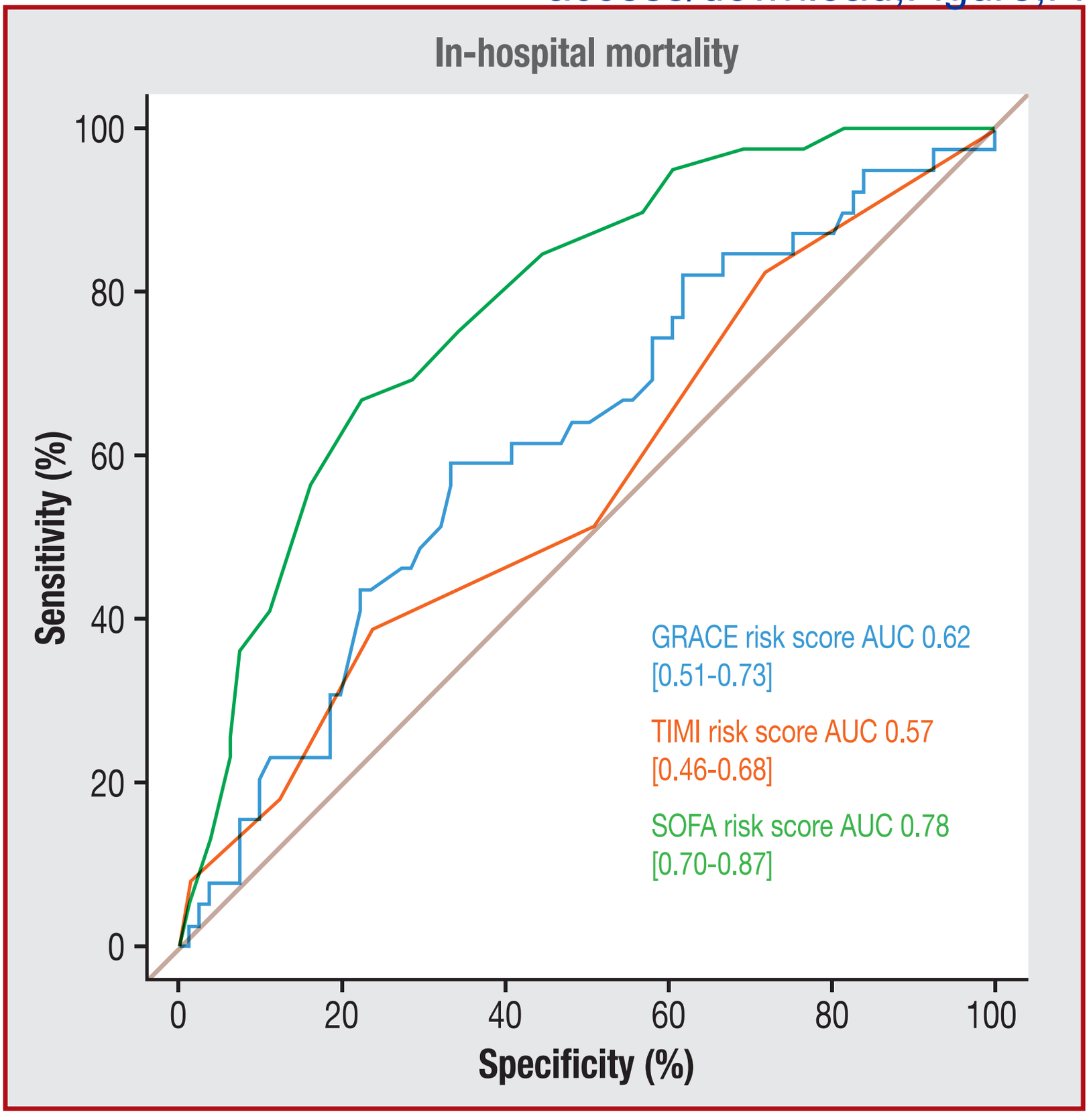

Appendix

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Table A.1 Definition of acute myocardial infarction, severe ischaemic events and major bleeding events.

Variable	Definition
Acute myocardial infarction [1]	
Myocardial injury	Elevated cTnI value above the 99th percentile upper reference limit, with a variation (rise and/or fall) of 20% in cTnI values [1, 2]
Clinical sign of myocardial ischaemia	Presence of typical (irradiated upper extremity and/or mandibular) or atypical (non-irradiated chest pain, epigastric pain) chest pain, indicative of myocardial ischaemia
Electrocardiographic signs of myocardial ischaemia	Indicative of new ST-T changes (ST segment either elevated or depressed > 1 mm, flat T-waves or T-wave inversion in systematized electrical coronary territories) or new-onset left bundle branch block
Echocardiographic signs of myocardial ischaemia	Acute LV systolic dysfunction, defined as LVEF ≤ 45% in the absence of a known baseline LVEF ≤ 45%, and/or a wall motion abnormality [3]
Severe ischaemic event	
Cardiac arrest	Any resuscitated cardiac arrest with a suspicion of cardiogenic origin
Ischaemic stroke	An acute episode of focal cerebral, spinal or retinal dysfunction, caused by infarction of central nervous system tissue; haemorrhage may be a consequence of ischaemic stroke; in this situation, the stroke is an ischaemic stroke with haemorrhagic transformation, and not a haemorrhagic stroke
Myocardial reinfarction [1]	Recurrent clinical signs and symptoms of ischaemia distinct from the index event, with concomitant electrocardiographic changes and serum biomarker evidence of myocardial necrosis, confirmed by

	coronary exploration
Major bleeding event	
Major bleeding event (ISTH definition [4])	Meets at least one of the following criteria: symptomatic bleeding in a critical area or organ, e.g. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; bleeding associated with a reduction in haemoglobin of ≥ 2 g/dL (1.24 mmol/L) or leading to transfusion of ≥ 2 units of blood or packed cells; fatal bleeding
Life-threatening bleeding event (RE-LY definition [5])	Meets at least one of the following criteria: fatal bleeding; symptomatic intracranial bleeding; bleeding with a decrease in haemoglobin of ≥ 50 g/L or bleeding requiring transfusion of ≥ 4 units of blood, necessitating surgical, endoscopic or endovascular action
Intracranial bleeding (ISTH definition [4])	Intracerebral bleedings, subdural bleedings, epidural bleedings or subarachnoid bleedings
Fatal bleeding (ISTH definition [4])	Bleeding event that is the primary cause of death or contributes directly to death.

cTnI: cardiac troponin I; ISTH: International Society on Thrombosis and Haemostasis; LV: left ventricular; LVEF: left ventricular ejection fraction; RE-LY: Randomized Evaluation of Long-Term Anticoagulation Therapy.

Table A.2 Haemodynamic variables at the time of transthoracic[a] echocardiographic studies, according to in-hospital mortality.

Variable	All patients (*n* = 120)	Survivors (*n* = 81)	Non-survivors (*n* = 39)	*P*
Time from acute myocardial infarction (days)	0 (0–1)	0 (0–1)	0 (0–1)	0.77
Mean arterial blood pressure (mmHg)	74 (66–87)	79 (68–94)	69 (61–80)	0.01
Heart rate (beats/min)	102 (89–118)	101 (88–117)	104 (93–124)	0.03
Norepinephrine	43 (36)	19 (23)	24 (62)	< 0.0001
Norepinephrine dose (μg/kg/min)[b]	0.3 (0.7–1.1)	0.26 (0.1–0.7)	0.51 (0.2–1.5)	0.08
Epinephrine	19 (16)	13 (16)	6 (15)	0.64
Epinephrine dose (μg/kg/min)[b]	0.33 (0.2–0.7)	0.24 (0.1–0.5)	0.6 (0.3–1.7)	0.05
Dobutamine	12 (10)	6 (7)	6 (15)	0.17
Dobutamine dose (μg/kg/min)[b]	7.5 (5–10)	6.2 (5–9.4)	8.8 (7.8–10)	0.54
Mechanical ventilation	60 (50)	35 (43)	25 (64)	0.05

Continuous variables are expressed as median (interquartile range), and categorical variables as number (%).

[a] Transoesophageal echocardiographic study in 13 patients.

[b] Only for patients receiving the drug at the time of the echocardiographic study.

Table A.3 Characteristics of acute myocardial infarction and organ dysfunction management, according to performance of coronary angiography.

Variables[a]	All patients (*n* = 120)	Coronary angiography (*n* = 32)	No coronary angiography (*n* = 88)	*P*
Risk scores				
SOFA	8 (5–12)	5 (2–8)	10 (6–12)	< 0.01
GRACE	192 (154–223)	193 (153–218)	189 (153–224)	0.9
TIMI	3 (2–4)	3 (2–4)	2 (1–4)	0.12
Clinical variables				
Clinical sign of myocardial ischaemia[b]	14 (12)	7 (22)	7 (8)	0.08
Heart rate (beats/min)[c]	115 (99–137)	112 (87–132)	120 (100–138)	0.30
Systolic arterial blood pressure (mmHg)[c]	85 (76–107)	85 (76–108)	85 (76–107)	0.75
Killip class[c,d]	1 (1–4)	1 (1–3)	1 (1–4)	0.41
Cardiac arrest[c]	1 (1)	1 (3)	0	0.27
Electrocardiographic and biological data				
ST-segment elevation[b,c]	23 (19)	9 (28)	14 (16)	0.13
New-onset left bundle branch block	8 (7)	3 (9)	5 (6)	0.44
ST-segment depression[b,c]	31 (26)	11 (34)	20 (23)	0.20
T-wave inversion	41 (34)	11 (34)	30 (34)	0.98

Cardiac TnI (pg/mL)[b,c,e]	786 (257–2474)	1820 (1071–3320)	465 (157–1406)	0.03
Cardiac TnI peak (pg/mL)[b,c,e]	1280 (539–3725)	2239 (1403–4680)	892 (255–3377)	0.09
Plasma creatinine (μmol/L)[f]	145 (84–231)	102 (66–162)	156 (89–241)	0.02
Echocardiography findings[g]				
LVEF (%)	30 (20–45)	38 (20–60)	28 (15–40)	0.02
LV systolic dysfunction (LVEF ≤ 45%)	89 (74.2)	18 (56)	71 (81)	< 0.01
Wall motion abnormality (MD = 22)	12 (10)	8 (25)	4 (5)	< 0.01
Organ dysfunction management				
Catecholamines	87 (73)	16 (50)	71 (81)	< 0.01
Norepinephrine	67 (56)	15 (47)	52 (59)	0.23
Epinephrine	33 (28)	3 (9)	30 (34)	< 0.01
Dobutamine	26 (22)	8 (25)	18 (20)	0.59
Invasive mechanical ventilation	81 (68)	17 (53)	64 (72)	0.04
Renal replacement therapy	14 (12)	4 (13)	10 (11)	1

Continuous variables are expressed as median (interquartile range), and categorical variables as number (%). Categorical variables were compared using Fisher's exact test, and continuous variables using the Mann-Whitney-Wilcoxon test. GRACE: Global Registry of Acute Coronary Events; LV: left ventricular; LVEF: left ventricular ejection fraction; MD: missing data; SOFA: Sequential Organ Failure Assessment; TIMI: Thrombolysis in Myocardial Infarction; TnI: troponin I.

[a] On the day of acute myocardial infarction onset.

[b] Variable for TIMI risk score.

[c] Variable for GRACE risk score.

[d] Four risk classes, as follows: class I: no sign of heart failure; class II: crackles in the lungs; class III: frank acute pulmonary oedema; and class IV: cardiogenic shock [6].

[e] Cardiac TnI was first measured (June 2012 to November 2014) with the ARCHITECT method (Abbott, Lake Forest, IL USA); this assay demonstrated an upper reference limit (URL; 99th percentile) of 30 ng/mL; afterwards, the high-sensitivity assay from the same manufacturer (ARCHITECT STAT hsTnI assay), adapted to the same analyser, was used (URL 26 ng/mL); because of the excellent correlation between assays and the closeness of the two URLs used, a 1000 factor was applied to cardiac TnI to merge all troponin results obtained from these two periods [7].

[f] In patients without renal replacement therapy on the day of acute myocardial infarction onset (n = 106).

[g] Median (interquartile range) time from acute myocardial infarction to echocardiography: 0 (0–1) day.

Table A.4 Multivariable analyses of factors associated with in-hospital mortality, excluding Global Registry of Acute Coronary Events (GRACE) and Thrombolysis in Myocardial Infarction (TIMI) scores.

Variable	Mortality odds ratio (95% confidence interval); *P*	
	Univariate	Multivariable
Previous aspirin use	3.33 (1.42–7.98); 0.01	4.74 (1.63–15.03); 0.01
SOFA score[a]	1.28 (1.16–1.44); 0.001	1.29 (1.15–1.47); < 0.001
LV systolic dysfunction[b]	8.49 (2.33–54.83); 0.01	3.47 (0.79–24.78); 0.139

Odds ratios are estimated with logistic regression models. LV: left ventricular; SOFA: Sequential Organ Failure Assessment.

[a] One the day of the acute myocardial infarction.

[b] Defined as LV ejection fraction ≤ 45% at initial echocardiographic study.

Table A.5 Multivariable analyses of factors associated with in-hospital severe ischaemic events.

Variable	In-hospital hazard ratio (95% confidence interval); *P*		
	Univariate	Multivariable for GRACE	Multivariable for TIMI
GRACE score[a]	1.00 (0.99–1.01); 0.60	1.00 (0.99–1.01); 0.81	-
TIMI score[a]	1.18 (0.83–1.67); 0.36	-	1.23 (0.86–1.76); 0.25
SOFA score[a]	1.06 (0.95–1.19); 0.28	1.06 (0.94–1.19); 0.33	1.08 (0.96–1.21); 0.20

Hazard ratios are estimated with cause-specific Cox regression models, accounting for the competing risk of death, with and without adjustment on the SOFA score. GRACE: Global Registry of Acute Coronary Events; SOFA: Sequential Organ Failure Assessment; TIMI: Thrombolysis in Myocardial Infarction.

[a] On the day of the acute myocardial infarction.

Figure A.1. Calibration plots for the Global Registry of Acute Coronary Events (GRACE), Thrombolysis in Myocardial Infarction (TIMI) and Sequential Organ Failure Assessment (SOFA) scores. Observed probabilities of in-hospital death are estimated, with their 95% confidence intervals, for different classes of predicted probabilities (TIMI scores with a common class for scores ≥ 5; quintiles of GRACE and SOFA scores). Predicted probabilities are reported as the mean value in the class. The grey line represents what would be expected for a perfect calibration.