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Original Research

A simple combination of biomarkers for risk stratification in octogenarians with acute myocardial infarction

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The aim of this observational study was to assess long-term prognosis of a contemporary octogenarian population admitted to an Intensive Cardiac Care Unit with acute myocardial infarction (MI), and the prognostic value of two simple biomarkers obtained at admission: glucose blood level (ABG) and estimated glomerular filtration rate (eGFR). A total of 293 consecutive patients were included (202 with ST elevation MI and 91 with non-ST elevation MI) with median age 83.9 years, 172 (58.7%) male. The optimal cut-off points for all-cause death defined by ROC curves were ABG >186 mg/dL and eGFR <50 mL/min/1.73 m^2. The cohort was segregated into 3 groups according to these values: no biomarker present (group 1), either of the two biomarkers present (group 2) or both biomarkers present (group 3). Patients in group 3 were more frequently female, with worse Charlson index, Killip class and ventricular function, and higher GRACE scores. PCI was performed in 248 patients (84.6%). The highest in-hospital and long-term mortality, and composite MACE was observed in groups 2 and 3. All-cause mortality (median follow-up 2.2 years) was 44%. In multivariate analysis, ABG >186 mg/dL and eGFR <50 mL/min/1.73 m^2 were associated with a 4.2 odds ratio (OR) (Model 1: medical history variables) and 2.6 OR (Model 2: admission event variables) of mortality. The addition of these variables to ROC curves improved long-term risk prediction for Model 1 (C-statistics 0.718 versus 0.780, $p = 0.006$) and reclassification and discrimination in both models.

Keywords

Elderly; Acute coronary syndrome; Mortality; Hyperglycaemia; Estimated glomerular filtration rate; Acute myocardial infarction; Octogenarian; Long-term outcome

1. Introduction

Due to a longer life expectancy, the number of people above age 80 years is growing rapidly in Europe and Northern America. Consequently, elderly patients account for an increasing proportion of patients admitted to Intensive Cardiac Care Units (ICCU) with acute coronary syndromes (ACS). Currently about one-third of ICCU admissions are of patients aged >75 years [1]. Comorbidities and geriatric syndromes worsen prognosis and make management and risk stratification more complex in these patients [2]. Although there are many risk scoring tools for ACS, it is important to acknowledge that each individual score has limitations and that octogenarians have been under-represented in their development. As age itself is incorporated into most risk score algorithms, elderly patients will be often classified as high-risk based on their age alone.

The oldest patients, and particularly octogenarians, have been excluded from most randomized clinical trials conducted before 2010. The available data in patients with ACS aged ≥80 years are derived from registry data and come mainly from studies with in-hospital and one year follow-up. Long-term data are very limited. There is a long way to go to improve risk prediction and management in this subgroup of elderly patients.

Elevated blood glucose and renal function are well established prognostic risk factors in ACS [3–6]. Their contribution to long term prognosis in octogenarians is less known and with controversial results [7, 8]. Therefore, the aim of our study was to assess long-term prognosis of a contemporary octogenarian population admitted to an ICCU with acute myocardial infarction, and the predictive value of two simple parameters obtained at admission: glucose blood level and estimated glomerular filtration rate (eGFR).

2. Material and methods

2.1 Study population

The University Hospital Joan XXIII from Tarragona, Spain, is the primary medical centre for a population of 250,140 inhabitants and serves as a secondary cardiac centre performing coronary angiography and percutaneous coronary intervention (PCI) for a population about 802,547, with primary PCI service 24 hour/7 days a week.

Data from all patients consecutively admitted to our ICCU are prospectively collected in the RENACI (REgistro NA-

cional de Cardiopatía Isquémica) database, approved by the Ethics Committee (CEIm65/2008). In this study we analyse all patients who were 80 or more years old, with a final diagnosis of ST segment elevation myocardial infarction (STEMI) or non-ST segment elevation myocardial infarction (NSTEMI), admitted between January 2015 and December 2019. For patients with several hospital stays, only the first stay was considered in analysis. Patients presenting as cardiac arrest were excluded.

2.2 Study variables

Data on age, gender, risk factors for coronary artery disease, past medical history including previous coronary heart disease, cardiac failure, obstructive pulmonary disease, history of atrial fibrillation, peripheral or cerebrovascular disease, hepatic disease or neoplasm and chronic kidney disease (CKD) were recorded. CKD was defined as an eGFR $<$60 mL/min/1.73 m^2. Diagnosis of dementia and a subjective graded medical assessment of dependence (partial, total or absent) were also collected. Registered data corresponding to the index event were final diagnosis, higher Killip class, rhythm at admission, PCI, number of coronary vessels affected, left ventricular ejection fraction (LVEF), other treatments and procedures (invasive or non-invasive mechanical ventilation, intra-aortic balloon pump counterpulsation, vasoactive drugs). Serum glucose (mg/dL), creatinine (mg/dL), troponin and haemoglobin (gr/dL) at admission were also collected. All patients had elevated troponin levels but values are not shown because of a change in the determination method in May 2019, from Troponin I-Ultra to High-Sensitivity Troponin I Assay (Advia Centaur, Siemens Healthineers, Erlangen, Germany), with distinct reference values. The new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, recommended by the National Kidney Foundation in clinical practice, was used to calculate eGFR at admission [9]. Charlson comorbidity index [10] and Global Registry of Acute Coronary Event (GRACE) risk score [11] were calculated.

2.3 Primary and secondary end-points

The primary end-point was all-cause mortality with a maximum follow-up of 3.5 years. Secondary end-points were readmission for MI or heart failure and a composite of major adverse cardiac events (MACE: first admission for non-fatal MI or heart failure or all-cause death). Vital status and events at follow-up were obtained from electronic medical records.

2.4 Statistical analysis

Categorical variables are expressed as numbers and percentages whereas continuous variables are expressed as medians and interquartile range (IQR). Comparisons of categorical data were performed with chi-squared tests or Fisher's exact test when expected frequencies were $<$5, whereas numerical data were analysed with the Kruskal-Wallis test. The optimal cut-off points for all-cause death were defined from receiver operating characteristic (ROC) curves using the Youden index. Patients were classified into three groups according to ABG and eGFR. Survival probabilities were estimated by the Kaplan-Meier method and compared with the log-rank test.

To determine if patients' groups were associated with primary and secondary endpoints, univariate and multivariate Cox regressions were performed with the backward stepwise procedure. In the multivariate analysis, clinically relevant and significant variables in the univariate analysis were included. Clinical model 1 was adjusted by age, male sex, Charlson index, dependence status and medical history of myocardial infarction, heart failure, cerebrovascular disease, chronic kidney disease and chronic pulmonary disease and model 2 was adjusted by age, male sex, atrial fibrillation/flutter at admission, Killip class $>$1, haemoglobin, GRACE score, PCI, LVEF $<$40%, use of non-invasive mechanical ventilation, use of invasive mechanical ventilation and use of vasoactive drugs. The proportional hazards assumption was analysed by Schoenfeld residuals. Multicollinearity was searched by calculating the variance inflation factor. For heart failure and non-fatal MI related hospitalization during follow-up, all-cause death was included in all the analyses as a competing risk, and the Grey method was used. Cumulative incidence curves were generated by using the competing risk model.

Finally, to estimate the ability of admission glucose concentration and eGFR to improve long-term risk prediction of all-cause death beyond clinical model 1 and 2 we performed ROC curve analyses and the Hosmer-Lemeshow test. The clinical models were compared before and after adding glycemia concentration $>$186 mg/dL and eGFR $<$50 mL/min/1.73 m^2. We also calculated overall continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI), as described by Pencina *et al.* [12]. Differences were considered statistically significant at $p <$ 0.05. STATA 14.2 (StataCorp, College Station, TX, USA) was used for statistical analysis.

3. Results

3.1 Patients

Between 1 January 2015 and 31 December 2019 there were 3582 admissions to the ICCU, of which 603 (17%) were 80 or more years old. The leading cause (61.5%) for admission in this population was acute myocardial infarction (STEMI and NSTEMI). After excluding recurrent episodes, patients presenting with cardiac arrest and patients lost to follow-up (11 patients), the final study cohort included 293 patients (Fig. 1).

3.2 Baseline characteristics

Median (IQR) patient age was 83.9 (81.8–86.8) years and 172 (58.7%) were male. Twenty-four patients (8.2%) were 90 or more years old. Of all patients, 202 (68.9%) were admitted with STEMI and 91 (31.1%) with NSTEMI. Median (IQR) admission glycemia concentration was 153 (125–222) mg/dL and the best cut-off point for the prediction of all-cause death was 186 mg/dL (area under the curve [AUC] 0.585 (95% confidence interval [CI] 0.526–0.642); sensitiv-

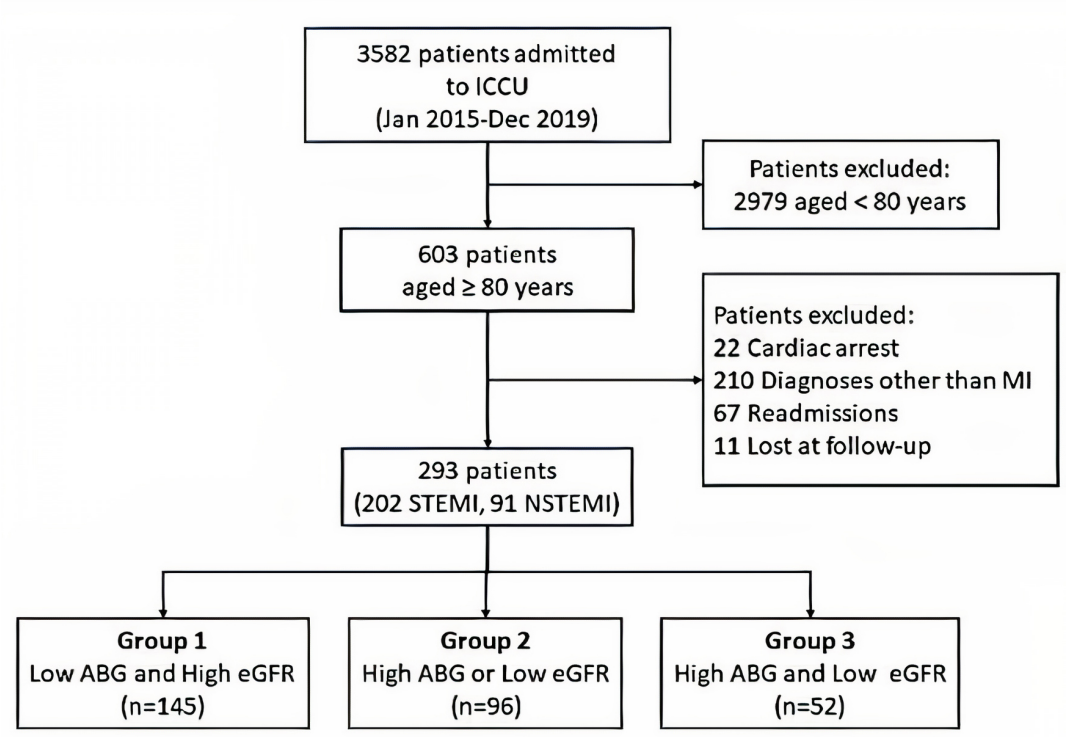

Fig. 1. Study flowchart. ABG, admission blood glucose; eGFR, estimated glomerular filtration rate; ICCU, Intensive Cardiac Care Unit; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction. Group 1: Low ABG (≤186 mg/dL) and High eGFR (≥50 mL/min/1.73 m^2); Group 2: High ABG (>186 mg/dL) or Low eGFR (<50 mL/min/1.73 m^2); Group 3: High ABG (>186 mg/dL) and Low eGFR (<50 mL/min/1.73 m^2).

ity 44%; specificity 77%). Median (IQR) eGFR was 60.9 (39.0–78.1) mL/min/1.73 m^2 and the best cut-off point for the prediction of all-cause death was 50 mL/min/1.73 m^2 (AUC 0.661 (95% CI 0.604–0.715); sensitivity 81%; specificity 49%). Patients were classified into three groups according to their ABG and eGFR. Patients in group 1 had glycemia concentration ≤186 mg/dL and eGFR ≥50 mL/min/1.73 m^2; group 2 patients had either glycemia concentration >186 mg/dL or eGFR <50 mL/min/1.73 m^2 and group 3 patients fulfilled both conditions ABG >186 mg/dL and eGFR <50 mL/min/1.73 m^2. According to this classification there were 145 (49.49%) patients in group 1, 96 (32.76%) in group 2 and 52 (17.74%) patients in group 3.

Baseline characteristics in the overall population and comparison between the three groups are presented in Table 1. Patients in group 3 were more frequently female, non-smoker, diabetic, with medical history of CKD and worse Charlson index.

3.3 Clinical characteristics, laboratory findings, procedures and mortality during admission.

Hyperglycaemia >186 mg/dL on admission was present in 31 (16.9%) of the 183 individuals without known history of diabetes mellitus and in 65 (59.1%) of 110 patients with established diabetes. An eGFR <50 mL/min/m^2 was present in 104 patients (35.49%), whereas 144 patients (49.15%) and 40 (13.65%) had an eGFR <60 or <30 mL/min/m^2, respectively. Patients with higher admission glucose level and lower eGFR (Group 3) were more likely to have a worse Killip class, lower haemoglobin concentration, a higher GRACE score, and ventricular dysfunction (LVEF <40%). They also needed to be treated more frequently with invasive and non-invasive mechanical ventilation and with vasoactive drugs (Table 2). No differences were observed in discharge diagnosis (STEMI or NSTEMI) between the groups.

In the subgroup of 202 STEMI patients, a primary PCI was performed in 179 (88.61%), a delayed PCI in 9 (4.45%) and only one underwent rescue PCI — a total of 189 (93.6%) invasively treated STEMI patients. In the subgroup of 91 NSTEMI patients a PCI was performed in 59 (64.84%) and only one patient was referred for coronary by-pass surgery. Finally, 32 deaths (10.9%) were seen during hospitalization with the highest mortality in groups 2 and 3 (11.5% and 28.9%, respectively) and a relatively low mortality in group 1 (4.1%).

3.4 Primary end-point: all-cause mortality

During 3.5 years of follow-up (median 2.2 [IQR 0.8–3.5] years), 129 (44%) patients died, with the highest mortality in group 2 and group 3 (Table 3, Fig. 2). Univariate and multivariate Cox regression analysis were performed. The variables that remained statistically significant in the multivariate analysis were age, previous MI or cerebrovascular disease, GRACE score, LVEF <40% and treatment with non-invasive

Table 1. Demographics, cardiovascular risk factors and medical history according to admission blood glucose and eGFR.

Variable	Overall (N = 293)	Group 1 (N = 145)	Group 2 (N = 96)	Group 3 (N = 52)	*p* Value
Demographics					
Age, years	83.9 (81.8–86.8)	84.0 (82.0–87.1)	83.2 (81.6–86.5)	84.0 (81.8–86.5)	0.424
Male sex	172 (58.7)	91 (62.8)	61 (63.5)	20 (38.5)	0.005
Cardiovascular risk factors					
Current or past smoker	90 (30.7)	52 (35.9)	29 (30.2)	9 (17.3)	0.045
Hypertension	235 (80.2)	111 (76.6)	80 (83.3)	44 (84.6)	0.294
Diabetes mellitus	110 (37.5)	32 (22.1)	46 (47.9)	32 (61.5)	<0.001
Hypercholesterolemia	164 (56.0)	78 (53.8)	61 (63.5)	25 (48.1)	0.148
Medical history					
Myocardial infarction	66 (22.5)	33 (22.8)	23 (24.0)	10 (19.2)	0.802
Heart failure	21 (7.2)	8 (5.5)	8 (8.3)	5 (9.6)	0.445
Cerebrovascular disease	37 (12.6)	15 (10.3)	13 (13.5)	9 (17.3)	0.409
Peripheral arterial disease	33 (11.3)	10 (6.9)	14 (14.6)	9 (17.3)	0.057
Chronic kidney disease	58 (19.8)	7 (4.8)	28 (29.2)	23 (44.2)	<0.001
Chronic pulmonary disease	66 (22.5)	28 (19.3)	25 (26.0)	13 (25.0)	0.423
Atrial fibrillation/flutter	35 (12.0)	13 (9.0)	13 (13.5)	9 (17.3)	0.237
Charlson index	1 (0–3)	1 (0–2)	2 (1–4)	2 (1–4)	<0.001
Partial or total dependence	51 (17.4)	22 (15.2)	16 (16.7)	13 (25.0)	0.269
Dementia	18 (6.1)	9 (6.2)	4 (4.2)	5 (9.6)	0.440

Data represent the number (percentage) or median (interquartile range). Group 1: ABG $\leq$186 mg/dL and eGFR $\geq$50 mL/min/1.73 m^2; Group 2: ABG >186 mg/dL or eGFR <50 mL/min/1.73 m^2; Group 3: ABG >186 mg/dL and eGFR <50 mL/min/1.73 m^2. ABG, admission blood glucose; eGFR, estimated glomerular filtration rate.

and invasive mechanical ventilation. A higher haemoglobin concentration and being treated with PCI were protective factors. In both models, a high admission glucose level and/or low eGFR (group 2 and 3) were independently associated with a higher risk of all-cause death, with the strongest association observed in group 3 patients (Table 4).

3.5 Secondary endpoints

During follow-up, in 162 (55.3%) patients the composite of MACE events was observed. Distribution among groups is presented in Table 3. Patients with high ABG and/or low eGFR (group 2 and 3) presented the highest number of events (Table 3, Fig. 2). In multivariate Cox regression analysis, group 2 and especially group 3 were independently related with a higher risk of MACE (**Supplementary Table 1**).

A total of 43 (14.7%) patients developed a new MI during follow-up and 36 (12.3%) required hospitalization for heart failure (Table 3). Multivariate competing risk analysis revealed a statistically significant association only for heart failure admission in group 3. Cumulative incidence of readmission for myocardial infarction and heart failure is shown in Fig. 2.

3.6 Analysis of ROC curves and risk prediction

ROC curves were evaluated with AUC to determine whether admission glycemia concentration >186 mg/dL and eGFR <50 mL/min/1.73 m^2 could improve long-term risk prediction of all-cause death. C-statistics were 0.718 (95% CI 0.660–0.777) for the clinical Model 1 and 0.780 (95% CI 0.727–0.832) for the clinical Model 1 and ABG >186 mg/dL and eGFR <50 mL/min/1.73 m^2. This improvement was statistically significant (p = 0.006). For Model 2, addition of these two variables achieved an improvement that was not statistically significant. AUC were 0.795 (95% CI 0.744–0.846) for the clinical Model 2 and 0.815 (95% CI 0.767–0.864) for the clinical Model 2 and ABG >186 mg/dL and eGFR <50 mL/min/1.73 m^2 (p = 0.079) (Fig. 3).

Reclassification and discrimination were also improved in both clinical models after the addition of glycemia concentration >186 mg/dL and eGFR <50 mL/min/1.73 m^2. Clinical model 1: NRI 0.494 (95% CI 0.267–0.722); $p < 0.001$ and IDI 0.078 (95% CI 0.047–0.108); $p < 0.001$. Clinical model 2: NRI 0.507 (95% CI 0.277–0.738); $p < 0.001$ and IDI 0.032 (95% CI 0.013–0.052); p = 0.001.

4. Discussion

The main findings of our study are:

(1) In this contemporary cohort of octogenarian patients with ACS admitted to an ICCU a high proportion of patients was treated invasively, especially the subgroup with STEMI.

(2) Despite that, nearly half of the patients died within 3.5 years (median follow up 2.2 years) after admission.

(3) An ABG >186 mg/dL and eGFR <50 mL/min/1.73 m^2 supported identification of the subgroups with the highest in-hospital and long-term risks.

Table 2. Admission clinical characteristics, laboratory findings, procedures and outcome.

	Overall	Group 1	Group 2	Group 3	*p* Value
	(N = 293)	(N = 145)	(N = 96)	(N = 52)	
Physical examination at admission					
Atrial fibrillation/flutter	50 (17.1)	22 (15.2)	18 (18.8)	10 (19.2)	0.694
Killip class >I	129 (44.0)	48 (33.1)	44 (45.8)	37 (71.2)	<0.001
Laboratory findings at admission					
Glycemia (mg/dL)	153 (125–222)	134 (113–157)	166 (135–244)	246 (223–337)	<0.001
eGFR (mL/min per 1.73 m^2)	60.9 (39.0–78.1)	75.5 (62.3–84.2)	49.3 (30.9–67.5)	34.7 (27.2–40.9)	<0.001
Haemoglobin (g/dL)	12.3 (10.8–13.4)	12.5 (11.4–13.7)	12.5 (11.0–13.5)	11.1 (9.8–12.8)	0.002
GRACE score					
GRACE score	163 (144–183)	159 (139–177)	168 (148–185)	179 (153–214)	<0.001
Coronary disease					
Significant three vessels or left main stenosis	78 (26.6)	29 (20.0)	34 (35.4)	15 (28.9)	0.027
PCI	248 (84.6)	127 (87.6)	77 (80.2)	44 (84.6)	0.298
Fibrinolysis	3 (1.0)	2 (1.4)	1 (1.0)	0 (0.0)	1.000
LVEF					
LVEF <40%	89 (31.0)	34 (23.6)	34 (36.6)	21 (42.0)	0.020
Intensive management during hospitalization					
Non-invasive mechanical ventilation	15 (5.1)	3 (2.1)	7 (7.3)	5 (9.6)	0.037
Invasive mechanical ventilation	18 (6.1)	2 (1.4)	9 (9.4)	7 (13.5)	0.001
Vasoactive drugs	43 (14.7)	8 (5.5)	19 (19.8)	16 (30.8)	<0.001
Intra-Aortic balloon pump	7 (2.4)	2 (1.4)	5 (5.2)	0 (0.0)	0.112
Discharge diagnostic					
STEMI	202 (68.9)	101 (69.7)	61 (63.5)	40 (76.9)	0.236
NSTEMI	91 (31.1)	44 (30.3)	35 (36.5)	12 (23.1)	0.236
Death during hospitalization					
All-cause death	32 (10.9)	6 (4.1)	11 (11.5)	15 (28.9)	<0.001

Data represent the number (percentage) or median (interquartile range). Group 1: ABG ≤186 mg/dL and eGFR ≥50 mL/min/1.73 m^2; Group 2: ABG >186 mg/dL or eGFR <50 mL/min/1.73 m^2; Group 3: ABG >186 mg/dL and eGFR <50 mL/min/1.73 m^2. ABG, admission blood glucose; eGFR, estimated glomerular filtration rate.

(4) These variables, when added to a medical history based (Model 1) or an index event based predictive model (Model 2), improved long-term risk prediction of all-cause death.

At present, a universal definition for "elderly" is lacking. Even if biological age may not correspond with chronological age, most now consider "elderly" as those aged ≥80 years. In the Western world the proportion of octogenarians is expected to triple by the year 2050 [13]. Life expectancy in Spain continues to increase, and a person who reaches 80 years of age can expect to live an average of 9 additional years in men and 10.9 years in women [14]. To undergo randomized clinical trials in elderly patients with ACS is difficult, due to slow enrolment or high selection bias. In spite of the difficulties, over the last decade solid evidence has been obtained about the clinical benefit of an invasive approach [15]. Despite the lack of randomized studies of primary PCI including distinctively elderly patients, the European Society of Cardiology (ESC) 2017 guidelines state that "there is no upper age limit with respect to reperfusion, especially with primary PCI" [16].

Randomized trials have failed to demonstrate a mortality benefit with an invasive approach in elderly population, probably due to the fact that this invasive strategy is still limited to the lower risk population and less comorbid patients and that only half of the patients undergoing angiography will undergo revascularization, the procedure with a potential impact on mortality [17–19]. However, consistent mortality reductions have been observed in real-world registries of elderly patients with Non-ST Elevation Acute Coronary Syndrome (NSTE-ACS) over the last 20 years, concomitant with an increase in the use of an early invasive approach [20, 21]. Based upon this evidence, the ESC 2020 guidelines for management of ACS without persistent ST-segment elevation recommend to apply for older people the same interventional strategies used for the younger ones, although with a more personalized approach [22].

We have included consecutive octogenarian patients, with a median age of 84 years old, admitted to an ICCU with STEMI and NSTE-ACS. Although NSTEMI is the most frequent clinical presentation of ACS in the elderly, in our study two thirds were STEMI patients, reflecting the fact that our hospital is the reference site for primary PCI for a large population. Index event related variables also exhibited high-risk features. Nearly 50% of patients presented Killip class >I and

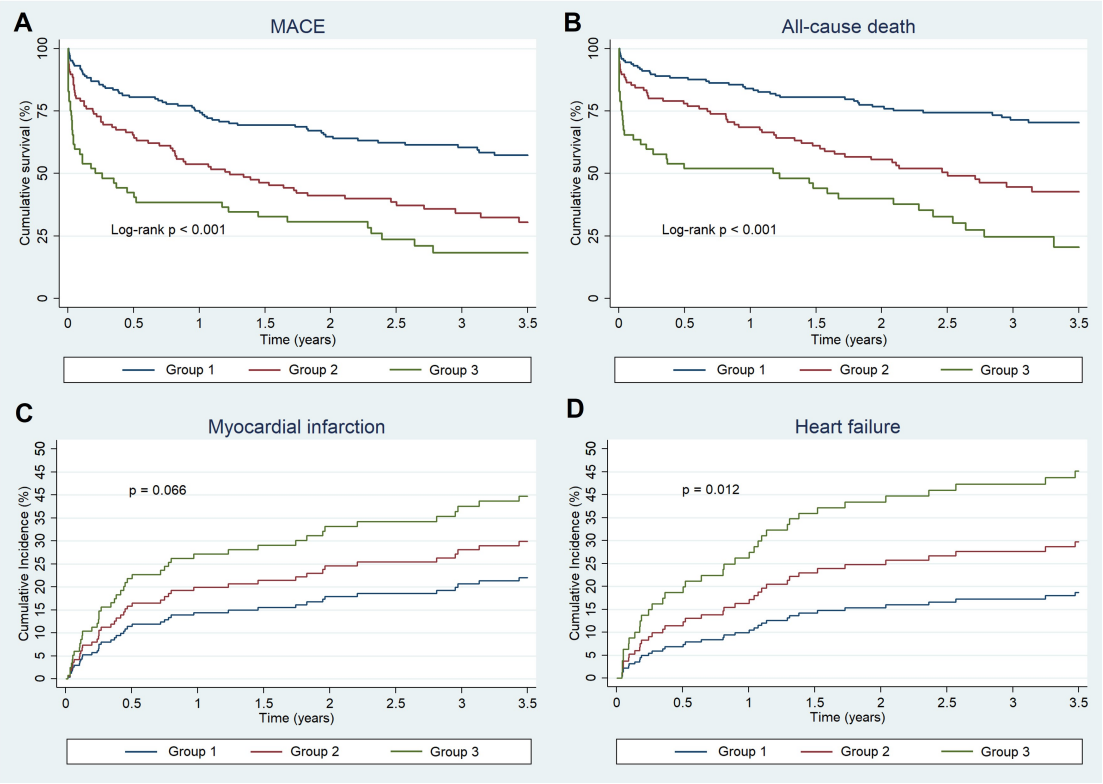

Fig. 2. All-cause death and MACE cumulative survival (A and B) and cumulative incidence of readmission for myocardial infarction and heart failure (C and D). Group 1 (blue line): AGL ≤186 mg/dL and eGFR ≥50 mL/min/1.73 m^2; Group 2 (red line): AGL >186 mg/dL or eGFR <50 mL/min/1.73 m^2; Group 3 (green line): AGL >186 mg/dL and eGFR <50 mL/min/1.73 m^2. ABG, admission glucose level; eGFR, estimated glomerular filtration rate; MACE: major cardiac events including all cause-death or readmission for non-fatal myocardial infarction or heart failure.

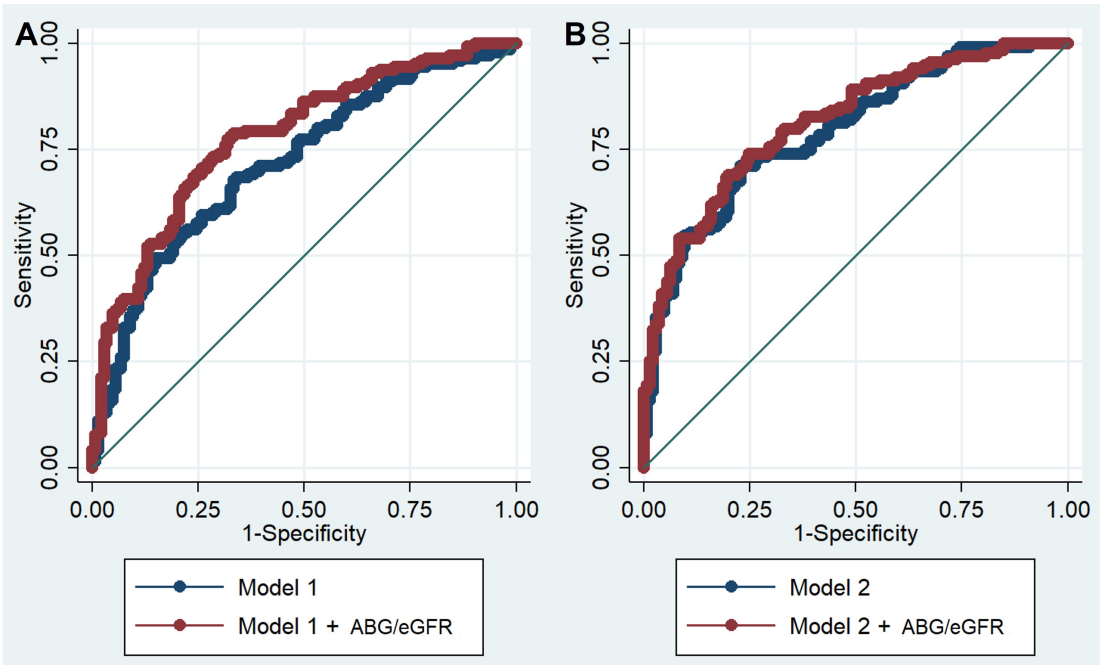

Fig. 3. ROC curves for predicting all-cause death before (blue line) and after (red line) the addition of ABG >186 mg/dL and eGFR <50 mL/min/1.73 m^2. (A) Model 1. AUC 0.718 (95% CI 0.0660–0.777) for the clinical Model 1 and 0.780 (95% CI 0.727–0.832) for Model 1 and ABG + eGFR (p = 0.006). (B) Model 2. AUC 0.795 (95% CI 0.744–0.846) for the clinical Model 2 and 0.815 (95% CI 0.767–0.846) for Model 2 + ABG and eGFR (p = 0.079). ABG, admission blood glucose; AUC, area under the ROC curve; eGFR, estimated glomerular filtration rate.

Table 3. Follow-up events according to admission blood glucose and estimated glomerular filtration rate.

Variable	Overall (N = 293)	Group 1 (N = 145)	Group 2 (N = 96)	Group 3 (N = 52)	*p* Value
MACE					
1 year	112 (38.2)	36 (24.8)	44 (45.8)	32 (61.5)	<0.001
2 years	142 (48.5)	50 (34.5)	56 (58.3)	36 (69.2)	<0.001
3.5 years	162 (55.3)	58 (40.0)	63 (65.6)	41 (78.8)	<0.001
All-cause death					
1 year	78 (26.6)	23 (15.9)	30 (31.3)	25 (48.1)	<0.001
2 years	106 (36.2)	33 (22.8)	42 (43.8)	31 (59.6)	<0.001
3.5 years	129 (44.0)	40 (27.6)	51 (53.1)	38 (73.1)	<0.001
Myocardial infarction					
1 year	31 (10.6)	13 (9.0)	12 (12.5)	6 (11.5)	0.255
2 years	37 (12.6)	15 (10.3)	16 (16.7)	6 (11.5)	0.143
3.5 years	43 (14.7)	18 (12.4)	19 (19.8)	6 (11.5)	0.082
Heart failure					
1 year	21 (7.2)	5 (3.4)	9 (9.4)	7 (13.5)	0.003
2 years	31 (10.6)	11 (7.6)	12 (12.5)	8 (15.4)	0.021
3.5 years	36 (12.3)	14 (9.7)	14 (14.6)	8 (15.4)	0.037

Data represent the number (percentage) or median (interquartile range). Group 1: ABG $\leq$186 mg/dL and eGFR $\geq$50 mL/min/1.73 m^2; Group 2: ABG >186 mg/dL or eGFR <50 mL/min/1.73 m^2; Group 3: ABG >186 mg/dL and eGFR <50 mL/min/1.73 m^2. ABG, admission blood glucose; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular events including all cause death or readmission for heart failure or myocardial infarction.

one third with ventricular dysfunction (LVEF <40%). Median GRACE score was 163 points (high risk). Although a comparison between STEMI and NSTEMI patients is beyond the scope of our analysis, included NSTEMI patients probably represent a selected subgroup of patients of higher risk but also with better general health and functional status [23]. The percentage of invasively treated patients was high (84.6%), with a PCI performed in 93.6% of STEMI patients and 64.84% of NSTEMI patients.

Scarce information is available with respect to long-term survival of elderly patients with ACS. Kvakkestad *et al.* [24] analysed in-hospital mortality and long-term survival in a cohort of STEMI patients according to age. In the subgroup of patients $\geq$80 years (68% treated with PCI) in-hospital mortality and 3-year survival were 13% and 52%, respectively [24]. In our series, including STEMI and NSTEMI patients, with a higher rate of PCI, in-hospital mortality was 11.9% and 3.5-years survival 56%. In a recently published retrospective study of NSTEMI patients aged $\geq$75 years, comparing complete revascularization and culprit revascularization, all-cause mortality with a median follow-up of 45.7 months was 40.4% [25].

On admission to hospital, it is recommended to evaluate glycaemic status in all patients with ACS, regardless of a history of diabetes, and to assess kidney function by eGFR for prognostic reasons and to identify patients at risk of contrast-induced nephropathy [16, 22]. In the present study, we have applied the best cut-off points for all-cause death prediction for admission blood glucose and eGFR and segregated the cohort into 3 groups, according to the presence of both, either or no values beyond the cut-offs, allowing discrimination of the subgroups (group 2 and group 3) of patients with a higher long-term mortality and MACE risk. We have focused on these two biomarkers because, unlike some scores, they can be easily obtained and are linked to diabetes and CKD, two established conditions related to the prognosis and severity of presentation of ACS.

Chronic kidney disease is a common condition in elderly ACS patients. The proportion of patients with CKD is increasing constantly as elderly people are living longer, but also because of an increasing prevalence of hypertension and diabetes mellitus. CKD is associated with adverse outcomes through the entire spectrum of ACS [4, 8, 26, 27]. An advanced age and CKD, frequently associated with comorbidities and geriatric syndromes, are often used as reasons to withhold patients from undergoing angiography and PCI [4, 8, 27], despite evidence of improvement in one year [4] and long-term survival with PCI in NSTEMI patients with CKD [27].

Assessment of renal function in elderly people is debated, the issue being whether the lower eGFR values observed at older ages can be attributed to physiologic aging or is associated with kidney disease and comorbidities. There is not a general agreement about which is the best method to estimate GFR rate at advanced ages. We have decided to use the recommended CKD-EPI formula [9] that has also demonstrated good performance with respect to measured GFR in acute STEMI patients [28]. In our cohort, a lower threshold (eGFR <50 mL/min/m^2) than the value that defines significant kidney disease (eGFR <60 mL/min/m^2) was calculated as the best cut-off point for all-cause death prediction. In one of the first studies that established the impact of renal function on clinical outcomes after PCI, a creatinine clearance <50 mL/min had a higher association with death than any variable except for congestive heart failure on presentation [29]. Morici *et al.* [4] in the Italian Elderly ACS study with patients aged $\geq$75 years old, selected a 45 mL/min/m^2 threshold. This lower value is in concordance with the threshold of 45 mL/min/m^2 recently proposed to define CKD in patients older than 65 years old [30].

Several studies suggest that the association of a lower eGFR with mortality is weaker with increasing age [7, 26]. In the LONGEVO-SCA registry, including NSTEMI patients aged $\geq$80 years, after adjusting for all potential confounders, this association became non-significant in frail patients [8]. In our study, an eGFR <50 mL/min/1.73 m^2 identified a subgroup of octogenarians with increased long-term all cause death. These high-risk patients need close surveillance after PCI, minimization of contrast dose and deferring of nephrotoxic drug initiation to reduce the risk of contrast-associated acute kidney injury (CA-AKI). In a large series of older adults

Table 4. Hazard ratios associated with all-cause death in univariate and multivariate Cox regression analysis.

MODEL 1	Univariate cox regression		Multivariate cox regression	
Variables	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Age	1.07 (1.02–1.12)	0.008	1.08 (1.03–1.13)	0.002
Male sex	0.92 (0.65–1.31)	0.652	-	-
Previous myocardial infarction	1.50 (1.02–2.19)	0.039	1.55 (1.05–2.29)	0.026
Previous heart failure	1.86 (1.08–3.18)	0.025	-	-
Previous cerebrovascular disease	1.77 (1.13–2.78)	0.013	1.70 (1.08–2.68)	0.023
Chronic kidney disease	1.61 (1.09–2.39)	0.017	-	-
Chronic pulmonary disease	1.56 (1.07–2.27)	0.022	-	-
Charlson index	1.13 (1.04–1.22)	0.004	-	-
Partial or total dependence	1.53 (1.13–2.09)	0.006	-	-
Group 2	1.47 (1.03–2.09)	0.034	2.46 (1.62–3.73)	<0.001
Group 3	2.88 (1.97–4.21)	<0.001	4.19 (2.67–6.57)	<0.001
MODEL 2	Univariate cox regression		Multivariate cox regression	
Variables	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Age	1.07 (1.02–1.12)	0.008	1.08 (1.03–1.14)	0.003
Male sex	0.92 (0.65–1.31)	0.652	1.60 (1.08–2.37)	0.019
Atrial fibrillation/flutter	1.65 (1.09–2.51)	0.019	-	-
Killip class >I	2.38 (1.68–3.38)	<0.001	-	-
Haemoglobin	0.81 (0.74–0.89)	<0.001	0.86 (0.78–0.95)	0.005
GRACE score	1.02 (1.01–1.02)	<0.001	1.01 (1.00–1.02)	0.004
PCI	0.38 (0.25–0.56)	<0.001	0.37 (0.25–0.56)	<0.001
LVEF <40%	2.67 (1.87–3.80)	<0.001	1.73 (1.17–2.55)	0.006
Non–invasive mechanical ventilation	3.33 (1.87–5.93)	<0.001	2.12 (1.11–4.02)	0.022
Invasive mechanical ventilation	4.59 (2.62–8.05)	<0.001	3.33 (1.71–6.47)	<0.001
Vasoactive drugs	3.70 (2.47–5.54)	<0.001	-	-
Group 2	1.47 (1.03–2.09)	0.034	1.80 (1.17–2.79)	0.008
Group 3	2.87 (1.97–4.21)	<0.001	2.56 (1.55–4.22)	<0.001

CI, confidence interval; GRACE, Global Registry of Acute Coronary Events score; Group 2: admission blood glucose >186 mg/dL or eGFR <50 mL/min/1.73 m^2. Group 3: admission blood glucose >186 mg/dL and eGFR <50 mL/min/1.73 m^2. HR, hazard ratio; LVEF, left ventricle ejection fraction; PCI, any percutaneous coronary intervention.

(≥70 years) who underwent coronary angiography, CA-AKI occurred in 16% of patients even with strict hydration protocols, and was an independent predictor of 3-month mortality [31]. One third of these patients did not return to baseline creatinine values, being the group with the highest mortality. We can speculate that further deterioration of renal function could prevent the clinician from prescribing guideline-adherent medications.

Hyperglycaemia during ACS may reflect stress-induced hyperglycaemia (SIH), worsening glycaemic control among diabetic patients or identify previously undiagnosed diabetes. SIH is considered an acute response of the body to many critical illnesses, including ACS, and many observational studies have documented that hyperglycaemia occurs frequently in this context. The association between blood glucose levels on admission and long-term mortality in patients with ACS has been previously recognised regardless of diabetic status [5, 32]. In patients >65 years with acute MI this relationship has also been verified, particularly in those without recognized diabetes [5, 6]. We have selected admission serum glucose concentration because it is easily and routinely assessed. Based on ROC curves, the best cut-off point for the prediction of all-cause death was 186 mg/dL, with good specificity (77%). There are still many questions to solve with respect to the relationship between hyperglycaemia and ACS. It is not clear in the literature which is the best parameter to predict outcomes: admission blood glucose, glucose variability, fasting glucose or maximum blood glucose [33]. Besides, the best cut-off point is not established and it has been suggested that in diabetic patients, a higher value could be more appropriate [6, 34]. New metrics have been proposed, including glycaemic gap and stress hyperglycaemia ratio, which eliminate the influence of chronic glycaemic levels. However, it remains unclear whether SIH is a risk factor contributing directly to the poor clinical outcome or a marker of severity of the disease.

5. Limitations of the study

Several limitations to this study should be considered. This is a single centre study that includes patients 80 or more years old with ACS, predominantly STEMI, admitted to an ICCU. The population studied probably excluded patients

with poor general health and cognitive status, who would have been treated non-invasively outside the ICCU, especially in the subgroup of NSTEMI patients. It is an observational study and we cannot exclude a selection bias and/or uncontrolled confounders. Data regarding medical treatment on admission and at follow-up are lacking. Glucose and creatinine were measured on admission but we are unaware if the time between symptom onset and sample extraction could improve or worsen the observed results. We have not used validated scales for geriatric syndromes or frailty measurements, although STEMI was the more frequent type of ACS seen in our population (more than two thirds of included patients) and a comprehensive geriatric assessment is very difficult in the STEMI scenario. Because our study was limited to octogenarian patients the results may not apply to younger patients. However, we believe that despite these limitations our study provides interesting data regarding risk stratification and prognosis in this subgroup of patients.

6. Conclusions

Our study evaluates the predictive value for all-cause death of the combination of ABG and eGFR in octogenarian patients with STEMI and NSTEMI. Long-term mortality was high despite PCI being performed in a significant proportion of patients. A high glycaemia concentration on admission ($>$186 mg/dL) and a low eGFR ($<$50 mL/min/1.73 m^2) identify a subgroup of patients with very high risk and worse outcomes. These biomarkers, when added to clinical models, significantly improved their predictive power.

The scope for further reductions in long-term mortality is likely to be much greater for older than for younger patients with acute myocardial infarction. The variables identified in this study provide more opportunities for risk stratification. Treating non-recognised diabetic patients, prescribing guideline adherent therapies in CKD patients and providing access to cardiac rehabilitation teams, together with the use of other specific instruments for geriatric population such as nurse intervention [35], simplifying treatments, and enhancing care transitions, could help improve outcomes in this population.

Author contributions

ESG, OP and GB—conceived and designed the study; JRL, CS, MFG, KV and ARN—collected data; OP and GB—analysed the data; ESG, OP and GB—wrote the paper; AB revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee (CEIm65/2008).

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://rcm.imrpress.com/EN/10.31083/j.rcm2204179.

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