

Predictors of in-hospital mortality in very elderly patients presenting with acute coronary syndrome: A single-center study

Akut koroner sendrom ile başvuran çok ileri yaşta hastalarda hastane içi mortalitenin öngördürücüleri: Tek merkezli çalışma

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ABSTRACT

Objective: Acute coronary syndrome (ACS) has become more frequent in the elderly population due to increased life expectancy. The aim of this trial was to determine clinical and laboratory factors related to in-hospital mortality in patients over 80 years of age who presented with ACS.

Methods: A total 171 patients (86 men, median age 83 years) who were over 80 years of age and were hospitalized due to a diagnosis of ACS were enrolled in this study. The patients' demographic data, clinical features, and laboratory values were screened retrospectively from hospital records.

Results: During the follow-up period, 19 of 171 patients (11.1%) died. The causes of death were cardiogenic shock (n=6, 31.5%), acute renal failure (n=6, 31.5%), arrhythmia (n=4, 21%), and septic shock (n=3, 15.7%). ST-segment elevation myocardial infarction presentation was more common among those who died [14 (73.7%) vs. 31 (20.5%); p<0.001]. Patients who died during in-hospital follow-up also had higher peak troponin [3.1 ng/mL (7.2) vs. 0.3 ng/mL (1.6); p<0.001] and creatine kinase-MB levels [96.7 ng/mL (194) vs. 10.9 ng/mL (36.2); p<0.001]. The results indicated that a high Global Registry of Acute Coronary Events (GRACE) risk score [odds risk (OR): 1.074, 95% confidence interval (CI): 1.039–1.110; p<0.001], ejection fraction (EF) ≤40% (OR: 8.113, 95% CI: 1.101–59.773; p=0.040), or no use of an angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) (OR: 0.075, 95% CI: 0.006–0.995; p=0.049) was significantly associated with in-hospital mortality.

Conclusion: Presentation with a high GRACE risk score, no use of an ACEI/ARB, and a low EF at admission were associated with in-hospital mortality in ACS patients more than 80 years old.

ÖZET

Amaç: Yaşam sürelerinin uzaması ile birlikte akut koroner sendrom (AKS) tanısı konan yaşlı birey sayısı günden güne artmaktadır. Bu çalışmadaki amaç 80 yaş ve üzeri hastalarda AKS'nin hastane içi mortalite öngördürücülerinin belirlenmesidir.

Yöntemler: Akut koroner sendrom tanısı ile hastaneye yatırılan 80 yaş üzerinde 171 hastanın (86 erkek, ortalama yaş 83 yıl) demografik, klinik ve laboratuvar özellikleri hastane kayıtlarından geriye dönük olarak incelendi.

Bulgular: Hastane içi mortalite 19 hastada (%11.1) gelişti. Ölüm nedenleri kardiyojenik şok (n=6, %31.5), akut böbrek yetersizliği (n=6, %31.5), aritmi (n=4, %21) ve septik şok (n=3, %15.7) idi. Ölen hastalarda ST yükselmeli miyokart enfarktüsü (STYME) oranı daha fazla [14'e (%73.7) karşı 31 (%20.5), p<0.001], zirve troponin [3.1 (7.2) ng/mL'e karşı 0.3 (1.6) ng/mL, p<0.001] ve CK-MB değerleri [96.7 (194) ng/mL'e karşı 10.9 (36.2), p<0.001] anlamlı olarak daha yüksekti. Lojistik regresyon analizinde yüksek GRACE risk skoru [OR (odds oranı): 1.074, GA (güven aralığı) %95 (1.039–1.110), p<0.001], ejeksiyon fraksiyonunun ≤%40 olması [OR: 8.113, GA %95 (1.101–59.773), p=0.040] ve anjiyotensin dönüştürücü enzim inhibitörü/anjiyotensin reseptör blokörü (ACEI/ARB) kullanılmaması [OR: 0.075, GA %95 (0.006–0.995), p=0.049] ölüm ile ilişkili bulunmuştur.

Sonuç: Akut koroner sendrom tanısı alan 80 yaş ve üzeri hastalarda yüksek GRACE risk skoru, öncesinde ACEI/ARB kullanılmaması ve başvuru anındaki düşük ejeksiyon fraksiyonu hastane içi mortalite ile ilişkilidir.

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The number of very elderly patients presenting with acute coronary syndrome (ACS) is steadily increasing due to increased life expectancy.^[1] Patients aged more than 75 years account for more than one-third of those presenting with ACS and constitute more than 50% of in-hospital mortality due to ACS.^[2] ACS in the very elderly population is a complex entity, not only because of the greater ischemic risk, but also as a result of more treatment-related complications.

Scientific evidence concerning very elderly patients with ACS is scarce. Most randomized trials have excluded such patients, despite the rate at which this population is growing. Though there are no specific guidelines concerning the very elderly, it is accepted that the standard treatment should not be less effective in this population.^[3] Indeed, over the last decade, an almost linear decrease in the rate of mortality after ACS has been reported in all age classes, including the elderly, in association with the increased use of early percutaneous coronary intervention (PCI) and recommended medications.^[4]

According to the Turkish Statistical Institute, the average life expectancy has increased to 75 years for males and 80 years for females in Turkey.^[5] Data on the clinical characteristics and outcomes of octogenarian ACS patients in Turkey are limited. In previous studies of octogenarians with ACS, in-hospital mortality was determined to be between 15% and 20%.^[6,7] A recent study from Turkey indicated that octogenarians had a 10.6-fold higher mortality risk after ACS compared with younger patients.^[7] The aim of this study was to determine clinical and laboratory factors related to in-hospital mortality in patients over 80 years of age presenting with ACS.

METHODS

The records of consecutive patients aged over 80 years and hospitalized in Pamukkale University Hospital (Denizli, Turkey) between August 2014 and October 2017 due to a diagnosis of ACS were screened retrospectively. Pamukkale University hospital is a tertiary center with the capability to perform coronary angiography and PCI 24 hours a day, 7 days a week. Patients with suspected ACS were evaluated by the emergency team and cardiologists until a final diagnosis could be made.

Clinical and demographic characteristics of the patients were recorded on admission. Serum levels of fasting blood glucose, hemoglobin, C-reactive protein, and a lipid panel including low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and

triglyceride level measurements obtained within the first 24 hours were also documented. Hypertension was defined as previous documentation of a systolic blood pressure of 140 mm Hg and/or a diastolic blood pressure of 90 mm Hg in at least 2 measurements or active use of any antihypertensive agent. Diabetes mellitus was defined as a fasting plasma glucose level over 126 mg/dL, a glucose level over 200 mg/dL, or a glycated hemoglobin level over 6.5% in any measurement, or the active use of an antidiabetic agent.

All of the patients received medications as recommended in the current guidelines.^[8,9] A loading dose of 300 mg acetylsalicylic acid was administered to all of the patients after the diagnosis of ACS. Clopidogrel (300 mg or 600 mg loading dose) or ticagrelor (180 mg loading dose) was also administered according to the preference of the patients' primary physician. Unfractionated heparin or low-molecular-weight heparin was given according to the patient's weight. Statin treatment was also initiated for all of the patients. The decision to perform coronary angiography, and the timing and type of revascularization procedure were determined by patient's cardiology consultant.

In-hospital bleeding events were classified according to the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria.^[10] Major bleeding was defined as any intracranial bleeding or clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥ 5 g/dL or a $\geq 15\%$ absolute decrease in hematocrit. Minor bleeding was defined as clinically overt, resulting in hemoglobin drop of 3 to < 5 g/dL or $\geq 10\%$ decrease in hematocrit or no observed blood loss in case of ≥ 4 g/dL decrease in the hemoglobin concentration

Abbreviations:

ACEI	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
ARB	Angiotensin receptor blocker
CABG	Coronary artery bypass graft
CI	Confidence interval
EF	Ejection fraction
GRACE	Global Registry of Acute Coronary Events
OR	Odds ratio
PCI	Percutaneous coronary intervention
ROC	Receiver operating characteristic
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction

or $\geq 12\%$ decrease in hematocrit. Minimal bleeding was defined as any clinically overt sign of hemorrhage associated with a < 3 g/dL decrease in hemoglobin concentration or $< 9\%$ decrease in hematocrit.

The analyses were conducted using IBM SPSS Statistics for Windows, Version 24.0. (IBM Corp., Armonk, NY, USA). To test the distribution pattern, the Kolmogorov-Smirnov and Shapiro-Wilk tests were used, as well as assessment of skewness and kurtosis. Continuous data that were not distributed normally were presented as median (interquartile range) and categorical variables were described as percentages. Categorical variables were compared with a chi-square test. Yates' correction was used as necessary. Fisher's exact test was used when expected frequencies were less than or equal to 5. Continuous variables were compared using the Mann-Whitney U test. Multivariate, stepwise backward logistic regression analysis was used to detect the independent predictors of mortality. All of the parameters in the univariate analysis with a p value < 0.25 and variables that are known risk factors for coronary artery disease were selected in the multivariate model. An exploratory evaluation of additional cut points was performed using receiver operating characteristic curve analysis (ROC). A p value of < 0.05 was considered statistically significant.

This study was performed in compliance with the principles outlined in the Declaration of Helsinki and was approved by the local ethics committee.

RESULTS

A total of 171 patients (86 males, 50.3%) with a median age of 83 (4) years were included in the study. The initial diagnosis was unstable angina pectoris in 37 (21.6%), ST-segment elevation myocardial infarction (STEMI) in 45 (26.3%) patients, and non-STEMI in 89 (52%). Coronary angiography was performed in 97 cases (56.7%) and 74 patients (43.3%) were only followed up medically. Among the patients who underwent coronary angiography, 61 patients (62.8%) had 3-vessel disease, 22 patients (22.7%) had 2-vessel disease, and 14 patients (14.4%) had 1-vessel disease. In all, 57 (58.7%) patients underwent PCI, 23 (23.7%) patients underwent coronary artery bypass graft (CABG) surgery, and 17 (17.5%) patients were followed up medically according to the results of coronary angiography. The primary reason for medi-

cal follow-up was refusal of coronary angiography by the patient or their relatives (n=61, 82.4%). Other reasons included the presence of kidney problems (n=10, 13.5%), active gastrointestinal bleeding (n=2, 2.7%), or end-stage malignancy (n=1, 1.35%). None of the patients received thrombolytic therapy. Eight patients received a tirofiban infusion after coronary angiography. According to the TIMI bleeding classification, 5 patients (2.9%) had minor bleeding and 11 patients (6.4%) had minimal bleeding. There was a significant difference in the bleeding rate between patients who died and those who survived in-hospital (p=0.083).

During follow-up, 19 of 171 patients (11.1%) died in-hospital. The causes of death were cardiogenic shock (n=6, 31.5%), acute renal failure (n=6, 31.5%), arrhythmia (n=4, 21%), and septic shock (n=3, 15.7%).

The demographic and clinical features of patients according to in-hospital mortality are presented in

Table 1. Comparison of demographic and clinical features of patients according to in-hospital mortality

	Deceased (n=19)	Surviving (n=152)	p
Age (years)	85.0 (6.0)	83.0 (4.0)	0.226
Male sex, n (%)	8 (42.1)	78 (51.3)	0.607
ACS type, n (%)			
Unstable angina	0 (0)	37 (24.3)	< 0.001
Non-STEMI	5 (26.3)	84 (55.3)	
STEMI	14 (73.7)	31 (20.4)	
Ejection fraction ≤ 0.40	16 (84.2)	55 (36.2)	< 0.001
Diabetes mellitus	10 (52.6)	61 (40.1)	0.426
Hypertension	14 (73.7)	99 (65.1)	0.627*
Hyperlipidemia	2 (10.5)	37 (24.3)	0.249*
Prior CAD history	13 (68.4)	82 (53.9)	0.341
Chronic kidney disease	6 (33.3)	31 (20.5)	0.232*
COPD	2 (11.1)	14 (9.3)	0.681*
Malignancy	3 (16.7)	6 (4.0)	0.057*
Smoking, n (%)			
Active smoker	2 (10.5)	3 (2)	0.225
Ex smoker	6 (31.6)	58 (38.2)	
Never smoked	11 (57.9)	91 (59.9)	

Data is presented as median (IQR) or number (percentage). *Fisher's exact test. ACS: Acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease.

Table 2. Prehospital and in-hospital management of the study group

	Deceased (n=19)	Surviving (n=152)	<i>p</i>
Prior to admission, n (%)			
Acetylsalicylic acid	7 (38.9)	64 (42.4)	0.975
Beta blocker	11 (61.1)	73 (48.3)	0.439
ACEI/ARB	2 (11.1)	64 (42.4)	0.021
Mineralocorticoid			
receptor antagonist	2 (10.5)	11 (7.2)	0.641
Ca channel blocker	4 (22.2)	23 (15.2)	0.494*
Nitrates	2 (11.1)	26 (17.2)	0.741*
Statins	1 (5.2)	15 (9.8)	0.541
In-hospital management, n (%)			
Beta-blocker	5 (26.3)	148 (97.3)	<0.001
ACEI/ARB	2 (10.5)	138 (90.7)	<0.001
Mineralocorticoid			
receptor antagonist	0	0	–
Primary PCI	10 (52.6)	47 (30.9)	0.055
CABG	0	21 (13.8)	0.056*
Insertion of IABP	0	0	–

*Fisher exact test. ACEI/ARB: Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CABG: Intra-aortic balloon pump; PCI: Percutaneous coronary intervention.

Table 1. There was no significant difference in terms of age, sex, or cardiovascular risk factors. However, among the deceased patients, STEMI was a more frequent type of ACS presentation when compared with patients who survived [14 (73.7%) vs 31 (20.5%); $p<0.001$]. The prehospital medications used by the patients are presented in Table 2. The patients who died during in-hospital follow-up were less likely to be taking an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) before admission (10.5% vs 42.1%, $p=0.01$).

The most common presenting symptom upon arrival at the hospital was chest pain (73.1%). Other presenting symptoms were dyspnea (11.7%), syncope (8.5%), and other non-cardiac symptoms (5%), such as nausea, dizziness, or stomach pain. The duration of time between symptom onset to hospital admission was 22.1 hours (0.5–96 hours). A total of 135 patients (79.9%) had sinus rhythm, 27 patients (16%) had atrial fibrillation, 5 patients (2.9%) had an atrioventricular

block, and 2 patients (1.2%) had pacemaker rhythm on their admission electrocardiography. A comparison of the hemodynamic profile of patients at admission indicated that the deceased patients had a significantly lower systolic arterial pressure [90.0 mm Hg (25.0) vs 130.0 mm Hg (33.0); $p<0.001$] diastolic arterial pressure [60.0 mm Hg (8.7) vs 72.0 mm Hg (12.0); $p=0.003$], and increased heart rate [90.0 bpm (31.0) vs 80.0 bpm (25.0); $p=0.042$]. Seven patients presented with cardiogenic shock and 6 of them died during follow-up (31.5% of the deceased group, 0.65% of the surviving group; $p<0.001$). Eleven of the 19 patients in the deceased group (57.8%) and 86 of the 152 patients in surviving group (56.5%) underwent coronary angiography ($p=0.913$). An intra-aortic balloon pump was not used in any patient.

A comparison of the laboratory and echocardiographic parameters of the deceased and surviving patients is provided in Table 3. The median fasting glucose level [200.0 mg/dL (114.0) vs 121.0 mg/dL (55.0); $p<0.001$], peak troponin [3.1 ng/mL (7.2) vs 0.3 ng/mL (1.6); $p<0.001$] and creatine kinase-MB levels [96.7 ng/mL (194.0) vs 10.9 ng/mL (36.2); $p<0.001$] were significantly higher in the patients who died during in-hospital follow-up. The ejection fraction (EF) as determined by transthoracic echocardiography at presentation was also significantly lower

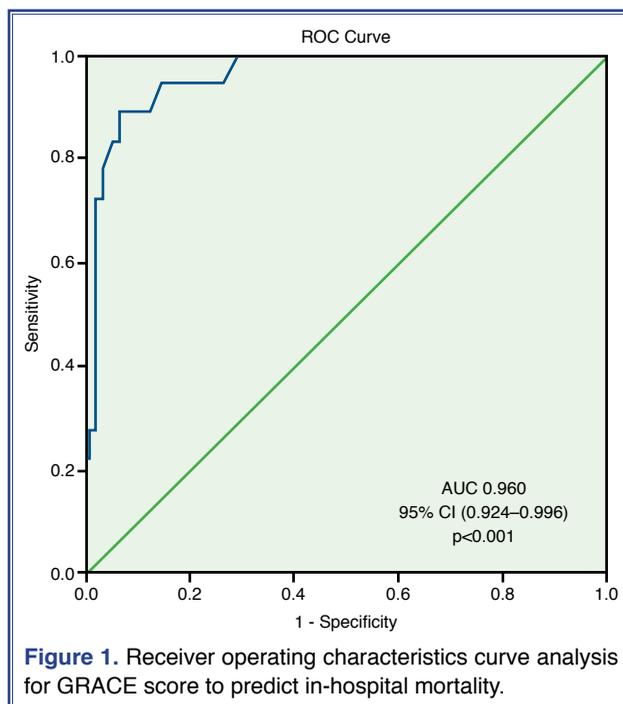


Table 3. Comparison of hemodynamic features, and laboratory parameters of patients according to in-hospital mortality

	Deceased (n=19)	Surviving (n=152)	p**
Glucose (mg/dL)	200.0 (114.0)	121.0 (55.0)	<0.001
Creatinine (mg/dL)	1.2 (0.5)	1.0 (0.5)	0.002
Uric acid (mg/dL)	8.1 (3.1)	5.8 (2.3)	<0.001
Total cholesterol (mg/dL)	157.0 (63.0)	165.0 (63)	0.838
Low-density lipoprotein cholesterol (mg/dL)	92.0 (37.0)	97.0 (52.0)	0.398
High-density lipoprotein cholesterol (mg/dL)	40.0 (23.0)	41.0 (17.0)	0.288
Triglycerides (mg/dL)	111.0 (74.0)	102.0 (58.0)	0.119
Peak troponin t (ng/mL)	3.1 (7.2)	0.3 (1.6)	<0.001
Peak CK-MB (ng/mL)	96.7 (194)	10.9 (36.2)	<0.001
Hemoglobin (g/dL)	11.5 (2.2)	12.1 (2.6)	0.312
White blood cell count (x10 ³ /mm ³)	12.8 (5.13)	8.7 (3.9)	<0.001
C-reactive protein (mg/dL)	2.0 (5.3)	0.6 (2.9)	0.025
Systolic blood pressure*	90.0 (25.0)	130.0 (33.0)	<0.001
Diastolic blood pressure*	60.0 (8.7)	72.0 (12.0)	0.003
Heart rate*	90.0 (31.0)	80.0 (25.0)	0.042
GRACE risk score	224.0 (50.5)	162.0 (22.0)	<0.001

Data is presented as median (IQR). *Systolic blood pressure, diastolic pressure, and heart rate of patients at the time of hospital admission. **Mann-Whitney U test ***Fisher's exact test. CK-MB: Creatinine kinase MB; GRACE: Global Registry of Acute Coronary Event.

in the deceased patients [35.0% (10.09) vs. 45.0% (17.0); p<0.001] compared with those who survived.

In order to determine independent predictors of mortality, backward stepwise logistic regression analyses were performed ($R^2=0.720$). A high GRACE risk score (OR: 1.074, 95% CI: 1.039–1.110; p<0.001), EF $\leq 40\%$ (OR: 8.113, 95% CI: 1.101–59.773; p=0.040), and less use of ACEI/ARB (OR:0.075, 95% CI: 0.006–0.995; p=0.049) were significantly associated with in-hospital mortality in patients over 80 years of age who presented with ACS.

In ROC analysis, a cut-off value of a GRACE score of 170 could predict in-hospital mortality with a 100% sensitivity, 71% specificity, and 26.9% positive and 100% negative predictivity [area under the curve: 0.960, 95% CI: 0.924–0.996; p<0.001] (Fig. 1).

DISCUSSION

In this single-center study, we tried to determine factors related to in-hospital mortality in very elderly patients presenting with ACS. Among the clinical factors evaluated, a high GRACE risk score, a low EF

on admission (<0.40), and no use of an ACEI/ARB before admission were found to be independent risk factors related to mortality.

The percentage of the population that is very elderly is increasing steadily in developed and developing countries. In Turkey, they represented 8% of the population in 2018.^[5] Advanced age per se is a strong risk factor for increased risk of mortality from myocardial infarction.^[11] Additionally, the elderly have more advanced and extensive coronary artery disease.^[12] However, clinical experience tells us that uncertainties remain regarding both the diagnosis and the treatment of elderly patients with ACS. When they present with ACS, symptoms in the elderly can be atypical and electrocardiography results can be more difficult to interpret due to the higher incidence of left bundle branch block or other rhythms.^[13,14] Cardiac troponins are more often elevated in the elderly even in the absence of ACS, which could add further to the uncertainty of whether or not the patient has a myocardial infarction.

Age is not only a powerful risk factor for cardiovascular disease but also an independent risk factor for adverse outcomes after cardiovascular events, for

complications of cardiovascular procedures and interventions, and for side effects of pharmacotherapy, particularly from antithrombotic therapies.^[15] In a trial conducted by Scechter et al.,^[16] it was demonstrated that ACS patients over 80 had more in-hospital major adverse cardiac events (including re-infarction, post-infarction angina, ischemic stroke, high-degree atrioventricular block, acute renal failure, and major bleeding) and also had a four- to fivefold higher mortality rate than younger patients.

Additionally, the hemodynamic impact of a given infarct size may be more pronounced in the elderly as a result of reduced cardiac reserve.^[17] There is also a greater likelihood of comorbid illnesses with advancing age. Not only do these comorbidities obscure the presentation of ACS, they also contribute to poorer outcomes. As we found in our study, the presence of a diabetes is related to mortality in this age group.

We found a statistically significant relationship between reduced EF and in-hospital mortality in the elderly population with ACS. Similar to our results, in another study from Turkey, Atas et al.^[6] found that presentation with STEMI, hypotension, and a low left ventricular EF were independent predictors of in-hospital mortality, while hyponatremia, atrial fibrillation, and renal dysfunction were independent predictors of long-term mortality in elderly patients with ACS.

Though elderly patients have more severe coronary disease than younger patients at coronary angiography, they are more likely to be treated medically and they experience more adverse outcomes.^[15] A post-hoc analysis of a large randomized trial revealed that the oldest patients with ACS benefited most from an invasive treatment strategy.^[18] In this study, 33% (n=57) of the patients underwent PCI and 13.4% (n=23) of patients underwent CABG surgery. However, a recent dedicated randomized clinical trial in the elderly addressing the question of the benefit of an invasive treatment strategy in ACS showed a reduction in mortality only in elderly patients with high cardiac troponins.^[19] Whether or not age is a true effect modifier in ACS remains a matter of debate.^[20]

According to the TIMI bleeding classification, none of our patients had major bleeding during their in-hospital stay. Elderly patients are more prone to bleeding due to their greater risk profile. However, we may not have seen any major bleeding in our study as a result of the small size of the study population.

The GRACE score is a strong, independent predictor of adverse events and mortality in patients with ACS.^[21] Vassali et al.^[22] reported that for elderly patients presenting with ACS who were referred for PCI within 24 hours of admission, the GRACE score, independent from other risk scores, predicted 30-day mortality. Similarly, we also found that the admission GRACE score was associated with in-hospital mortality.

Current guidelines recommend the use of ACE inhibitors or ARBs in patients with an impaired left ventricle EF ($\leq 40\%$) or who have experienced heart failure after ACS.^[21] However, in our study, use of these drugs before presentation was found to be protective against mortality. However, use of mineralocorticoid receptor antagonists before hospital admission was not found to be related to mortality.

There are some limitations to our study. First, this study had a retrospective, cross-sectional design using single-center data. Due to the retrospective retrieval of the patient data and the small number of patients included, our study results can't be generalized to the whole elderly population. Second, the diagnosis of ACS in the elderly population is challenging; multiple cofactors may affect cardiac enzyme elevation and some patients could be misdiagnosed. Finally, the presence of multiple comorbidities and fragility also affect in-hospital mortality rates in elderly patients.

In conclusion, due to increased life expectancy, physicians will be confronted with an increasing number of elderly and very elderly patients presenting with ACS. Physicians should be aware of clinical factors related to increased mortality in this age group. Although we didn't find that invasive treatment had a significant positive impact on in-hospital mortality, these are generally safe procedures and advanced age should not be a reason to withhold potentially life saving procedures and interventions.

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