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Short and Long Term Mortality Predictors in Octogenarians with Acute Coronary Syndromes

Abstract

Purpose: Octogenarians with acute coronary syndromes have higher mortality and morbidity due to higher prevalence of comorbidities and frailty. The aim of this study was to explore the predictors of short and long term mortality in octogenarians with ACS.

Methods: Ninety-eight consecutive octogenarians presenting with acute coronary syndrome (mean age:84±3 years, 56 male) were included. All patients underwent coronary angiography and were given optimal medical treatment. The primary end point was cardiovascular mortality in hospital and at one year.

Results: Fifteen patients died during hospitalization and 20 patients died after discharge within the first year. ST-segment-elevation myocardial infarction and hypotension were significantly more prevalent in the in-hospital mortality group while atrial fibrillation and hyponatremia were more prevalent in the long-term mortality group. All deceased patients had significantly lower left ventricular ejection fraction and glomerular filtration rate. Cox analysis revealed ST-segment-elevation myocardial infarction, hypotension and left ventricular ejection fraction as independent predictors of in-hospital mortality while hyponatremia, atrial fibrillation and renal dysfunction as independent predictors of long term mortality.

Conclusion: It would be reasonable to pay further attention to octogenarians with acute coronary syndrome if they are presenting with ST-segment-elevation myocardial infarction, and have hypotension, impaired left ventricular function, hyponatremia, atrial fibrillation or renal dysfunction, which are associated with increased mortality.

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Age is a major cardiovascular risk factor and cardiovascular diseases (CVD) are the most common cause of death in the elderly [1-3]. The octogenarian constitute an increasing segment of the population and 83.0% of men and 87.1% of women aged 80 or more have CVD and about 66% of all cardiovascular deaths occur in people aged 75 or older [4]. They carry higher prevalence of cardiovascular morbidities such as diabetes mellitus, hypertension, peripheral vascular disease, cerebral vascular event, and heart failure making management and risk stratification difficult in these patients [5].

Acute coronary syndromes (ACS) in the elder people might be quite lethal to them. Octogenarians with ACS have higher mortality and morbidity rates compared to younger patients due to higher prevalence of comorbidities and frailty [6-9]. However, there is little known about the management and clinical outcomes in the very elderly ACS patients, because most of clinical trials were based on relatively younger patients, and the population of the very elderly ACS patients constitute very small portion [10].

The aim of this study is to establish short and long term mortality predictors in octogenarians with ACS.

Subjects and Methods

The investigation conforms with the principles outlined in the Declaration of Helsinki. The study was approved by Marmara University Faculty of Medicine Research Ethics Committee. Informed consent was obtained from all individual participants included in the study. Patients were selected among cases admitted to the intensive coronary care unit of a community tertiary hospital between July 2012 and November 2013.

Ninety-eight consecutive patients aged 80 or older with ACS were recruited into the study. The patients with stable coronary artery disease or known active malignancy were excluded. The diagnosis of ACS was based on symptoms, electrocardiography and cardiac markers. ST segment elevation myocardial infarction (STEMI) was defined as the presence of chest pain with persistent ST-segment elevation of at least 0.1 mV in at least two contiguous leads or a new left bundle-branch block. Patients with chest pain during the previous 48 hours with ST-segment and T wave changes on electrocardiography indicating ischemia were grouped as unstable angina pectoris (USAP) or non ST elevation myocardial infarction (NSTEMI) based on a negative or a positive troponin test, respectively.

All patients underwent careful physical examination and blood samples including cardiac markers (high sensitive

troponin T (Elecsys high sensitive troponin T immunoassay, Roche, Germany) and creatine kinase MB), hemogram, glucose, creatinine, sodium, potassium, alanine transaminase, aspartate transaminase, and lipid profiles were obtained on admission. Blood tests were repeated when necessary. Anemia was defined as a hemoglobin concentration of 12 g/dl for women and 13 g/dl for men, according to the recommendations of the World Health Organization [11]. Creatinine clearance was estimated according to modification of diet in renal disease (MDRD) formula [12]. Renal dysfunction was defined as creatinine clearance <60 ml/min. Hyponatremia was defined as serum sodium level <136 mg/dL [13].

Bedside echocardiographic examination was performed with a portable echocardiographic device (General Electric Vivid I, Horten, Norway) equipped with a 2.5 MHz phased-array transducer with harmonic capability. Left ventricular ejection fraction was assessed with transthoracic echocardiography by using Simpson method.

Management of the patients was in accordance with the current guidelines. Patients with STEMI were immediately transferred to coronary angiography laboratory for primary percutaneous intervention. Patients with USAP or NSTEMI underwent coronary angiography within 48 hours. All patients were given standard medical therapy including aspirin, clopidogrel, beta-blocking agent, angiotensin converting enzyme inhibitor and statin unless there was a contraindication.

The primary end point of the study was cardiovascular mortality during hospitalization and at one year. Data of long term mortality was obtained from hospital record, telephone contact with relatives of patients and social healthy organization. The mean follow-up period of 451.2±262.3 days.

Statistical Analysis:

All statistical tests were performed with a commercially available statistical analysis program (SPSS 20.0 for windows, IBM Corporation Software Group, New York, United States of America). Continuous variables were expressed as mean ± standard deviation if they were normally distributed or as median (quartiles) when they were not normally distributed. Categorical variables were expressed in ratio. Distribution of data was assessed by using one-sample Kolmogorov-Smirnov test. Mann-Whitney U test was used to compare continuous variables while chi-square test was used for comparison of categorical variables. Backward multivariate Cox proportional hazards models were used to assess independent associations

with in-hospital and one year cardiovascular mortality. *p* values <0.05 were interpreted as statistically significant.

Results

Ninety-eight ACS patients were consecutively included into the study. The mean age of the patients was 84 ± 3 years (range 80-94 years) years, and 56 patients (56.6%) were men. Thirty-four patients (35.7%) were presented with STEMI while 50 patients (50.0%) had NSTEMI and 14 patients (14.3%) had USAP. Coronary intervention was performed in 31 STEMI patients and 33 NSTEMI/USAP patients. Five NSTEMI/USAP patients underwent coronary artery bypass surgery. Twenty-nine patients (three patients with STEMI and 26 patients with NSTEMI/USAP) were followed conservatively.

Fifteen patients (15.3%) died during hospitalization. The characteristics and laboratory parameters of these patients were shown in Table 1. STEMI and hypotension were significantly more prevalent in the in-hospital mortality group while these patients had significantly lower left ventricular ejection fraction and glomerular filtration rate and higher heart rate. Twenty-four patients had hypotension and 17 of these patients had STEMI while only seven NSTEMI/USAP patients had hypotension ($p < 0.001$). Out of the nine hypotensive patients who died in hospital, eight had STEMI.

Eighty-three patients were discharged from the hospital with standard medical treatment. Twenty patients (24.1%) died during the first year. Baseline characteristics of these patients were presented in Table 2. Atrial fibrillation and hyponatremia on admission were significantly more prevalent in the patients with mortality. They also had significantly lower left ventricular ejection fraction and glomerular filtration rate.

Backward multivariate Cox proportional hazards models were used to assess the predictors of in-hospital and long term mortality in our cohort. STEMI, hypotension, heart rate, hemoglobin levels, glomerular filtration rate, left ventricular ejection fraction, coronary intervention and diabetes were included in the regression model as potential confounders for in-hospital mortality. Age, gender, atrial fibrillation, hemoglobin levels, hyponatremia, glomerular filtration rate and left ventricular ejection fraction were included in the regression model as potential confounders for one year mortality. Presenting with STEMI, presence of hypotension on admission, lower left ventricular ejection fraction and higher heart rate were independent predictors of in-hospital mortality while presence of hyponatremia, atrial fibrillation

and renal dysfunction were independent predictors of long term mortality in our study group (Table 3).

Discussion

Our study confirms that although standard medical and invasive procedures were applied to octogenarian patients with ACS, they had high in-hospital and one year mortality, which might be predicted by certain baseline features.

In-hospital mortality was associated with STEMI, hypotension on admission, higher heart rate and lower left ventricular ejection fraction in our study. Although majority of the patients presenting with STEMI underwent primary percutaneous intervention and were given optimal medical treatment including dual antiplatelet therapy, 12 patients (35.3%) died during hospitalization while only three patients died in NSTEMI/USAP group (4.7%). However, within the first year, five STEMI patients (22.7%) and 15 NSTEMI/USAP patients (24.6%) died showing similar mortality rates between the groups. In accordance with our results, three recent studies conducted in younger patients also noted that STEMI patients displayed poor early term clinical outcome compared to NSTEMI patients, who rather displayed poor late-term clinical outcome [14-16]. Ren *et al.* [14] proposed that these worse in-hospital prognoses in STEMI could be attributed to a higher incidence of cardiogenic shock and cardiac rupture. We also found that hypotension was more prevalent in STEMI patients and in in-hospital mortality group. Eight out of the nine patients who had hypotension and died during hospitalization had STEMI.

Left ventricle ejection fraction is the main indicator of left ventricular systolic function and an important marker of prognosis in ACS [17,18]. Steg *et al.* [19] evaluated the characteristics and prognosis of post-ACS heart failure and observed a 2.2-fold higher risk of death for patients with heart failure compared to those without heart failure. Two recent studies have also found left ventricular ejection fraction as a predictor of in-hospital mortality in ACS patients undergoing percutaneous coronary intervention [20,21]. Similarly, in our study in-hospital mortality group had significantly lower left ventricular ejection fraction.

On the other hand, long term mortality was associated with hyponatremia, atrial fibrillation and renal dysfunction in our study. Hyponatremia is common in hospitalized patients and often signifies poor prognosis [22]. Acute myocardial infarction is associated with a complex neurohormonal activation. The release of atrial natriuretic peptide and catecholamines and activation of renin-angiotensin system during the course of ACS may cause hyponatremia, peripheral

TABLE 1. The characteristics and laboratory parameters of the patients according to in-hospital mortality

	Deceased during hospitalization (n=15)	Survived (n= 83)	P
Age (years)	86.1±4.8	84.7±3.0	0.344
Male Sex (n - %)	7 (46.7%)	48 (57.8%)	0.423
STEMI (n - %)	12 (80%)	23 (27.7%)	<0.001
Coronary intervention/CABG/conservative	13/0/2	51/5/27	0.155
Diabetes (n - %)	8 (53.3%)	26 (31.3)	0.099
Hypertension (n - %)	9 (60%)	61 (73.5%)	0.287
Hyperlipidemia (n - %)	4 (28.6%)	24 (28.9%)	1
Chronic obstructive pulmonary disease (n - %)	3 (20%)	14 (16.9%)	0.721
Prior CAD (n - %)	5 (33.3%)	34 (41%)	0.578
Prior stroke (n - %)	2 (13.3%)	8 (9.6%)	0.648
Hypotension (n - %)	9 (60%)	15 (18.5)	0.001
Heart rate (/min)	91 ± 20	76 ± 13	0.012
Atrial fibrillation (n - %)	4 (26.7%)	14 (16.9%)	0.467
Anemia (n - %)	11 (73.3%)	41 (49.4%)	0.100
Hemoglobin (g/dL)	11.3 ± 2.0	12.3 ± 2.1	0.084
Hyponatremia (n - %)	4 (26.7%)	9 (10.8)	0.110
Sodium (mEq/L)	138 ± 4	139 ± 3	0.402
Glomerular filtration rate (mL/min)	51 ± 20	63 ± 20	0.038
Creatinine (mg/dL)	1.5 ± 0.9	1.2 ± 0.5	0.039
Left ventricular ejection fraction (%)	39 ± 10	51 ± 9	<0.001
Peak Troponin T Median (25 th to 75 th percentile)	502 (91 - 3440)	713 (250 - 2420)	0.509
Peak Creatine kinase MB Median (25 th to 75 th percentile)	40 (8 - 115)	24 (10 - 101)	0.919

STEMI: ST segment elevation myocardial infarction; CAD: coronary artery disease; CABG: coronary artery bypass surgery

vasoconstriction, reduction in glomerular filtration rate and myocardial hypertrophy, with potential to worsen survival in ACS [23-26]. Similar to our study, Burkhardt *et al.* [27] reported that patients with incident AMI and hyponatremia on admission showed a significantly higher risk of long-term mortality.

Atrial pressure may increase during ACS due to atrial ischemia or increased left ventricular filling pressure resulting in atrial fibrillation. Bang *et al.* [28] showed that ACS patients

with new-onset atrial fibrillation had an increased risk of all-cause mortality; either due to cardiovascular events such as stroke or re-infarction or noncardiovascular complications such as bleeding. As our study included elderly patients, the risk of both stroke and bleeding was high and this might explain the independent association of atrial fibrillation with long term mortality in our cohort.

Elderly patients often have high morbidity associated with hypertension, diabetes mellitus, and other diseases, leading to

TABLE 2. The baseline characteristics and laboratory parameters of the patients according to long term mortality

	Deceased during first year (n= 20)	Survived (n= 63)	P
Age (years)	85.9 ± 3.5	84.4 ± 2.7	0.097
Male Sex (n – %)	14 (70%)	34 (54%)	0.206
STEMI (n – %)	5 (25%)	18 (28.6%)	0.756
Coronary intervention/CABG/conservative	12/1/7	39/4/20	0.949
Diabetes (n – %)	6 (30%)	20 (31.7%)	0.883
Hypertension (n – %)	17 (85%)	44 (69.8%)	0.249
Hyperlipidemia (n – %)	6 (30%)	18 (28.6%)	0.902
Chronic obstructive pulmonary disease (n – %)	4 (20%)	10 (15.9%)	0.735
Prior CAD (n – %)	8 (40%)	26 (41.3%)	0.920
Prior stroke (n – %)	3 (15%)	5 (7.9%)	0.392
Hypotension (n – %)	2 (10%)	13 (21.3)	0.336
Heart rate (/min)	79 ± 14	75 ± 13	0.21
Atrial fibrillation (n – %)	7 (35%)	7 (11.1%)	0.013
Anemia (n – %)	12 (60%)	29 (46%)	0.276
Hemoglobin (g/dL)	11.9 ± 3.0	12.4 ± 1.7	0.301
Hyponatremia (n – %)	5 (25%)	4 (6.3)	0.033
Sodium (mEq/L)	138 ± 4	140 ± 3	0.018
Glomerular filtration rate (mL/min)	51 ± 19	67 ± 19	0.004
Creatinine (mg/dL)	1.4 ± 0.5	1.1 ± 0.5	0.002
Left ventricular ejection fraction (%)	47 ± 4	52 ± 10	0.031
Peak Troponin T Median (25 th to 75 th percentile)	1423 (459 - 4430)	656 (184 - 1982)	0.155
Peak Creatine kinase MB Median (25 th to 75 th percentile)	65 (13 - 129)	21 (10 - 49)	0.112

STEMI: ST segment elevation myocardial infarction; CAD: coronary artery disease

the development of glomerular sclerosis and renal dysfunction. Renal failure may also be involved in the development of hypertension, hyperlipidemia, endothelial disorders, and neuroendocrine disorders, which are all important contributors to the further advancement of atherosclerosis. In our study, patients who died either during hospitalization or in long term had lower GFR and higher creatinine levels. Similar to our results, Liu *et al.* [29] investigated the impact of renal dysfunction on long-term outcomes in elderly patients with

ACS and found that renal dysfunction was an independent risk factor for cardiac events in patients with ACS. In addition to renal failure, they also found that anemia was associated with prognosis in elderly patients with ACS. However, we did not find such an association between anemia and mortality in our cohort. Anemia is a common comorbidity in elderly patients and it was highly prevalent in our study. Similar to our study, Ariza-Sole *et al.* [30] detected anemia in 40.4% of the elderly patients. They reported anemia as an independent

TABLE 3. COX regression analysis showing the predictors of in-hospital and long-term all-cause mortality

In-hospital mortality		
	Hazard ratio (95% CI)	P
STEMI	4.10 (1.02-16.43)	0.048
Hypotension	5.29 (1.56-17.93)	0.007
Left ventricular ejection fraction	0.90 (0.85-0.96)	0.002
Heart rate	1.06 (1.04-1.08)	0.020
One year mortality		
Hyponatremia	3.06 (1.09-8.71)	0.035
Atrial Fibrillation	4.84 (1.68-13.93)	0.003
Glomerular filtration rate	0.96 (0.94-0.99)	0.002

STEMI: ST segment elevation myocardial infarction

predictor of overall mortality, cardiac mortality and non-cardiac mortality in the overall cohort. However, they did not find a significant association between anemia and mortality in the elderly and suggested that the impact of anemia on mortality differed according to age subgroup.

Study Limitations

The major limitation of our study was the small sample size. We evaluated cardiovascular mortality and all deaths in the in-hospital mortality group were documented by our hospital recordings. However, one year cardiovascular mortality data might be based on documentations of other hospitals or clinics. Although all the patients were given optimal medical therapy, we could not evaluate compliance of the patients to medical treatment in the long term. Revascularization was not achieved similarly in all patients and patients had different coronary lesions and atherosclerotic burden, which might also affect their short and long term mortality. Although the decision to admit the octogenarian patients with ACS to coronary care unit was not based on the eligibility of the patients for coronary angiography, we did not know the exact number of the octogenarian patients admitted to emergency department with ACS, how many of them were admitted to coronary care unit and the prognosis of those who were not hospitalized. Data about the frailty of the patients were not collected, which was another limitation of our study. Frailty is a short-term prognostic marker in acute coronary syndrome of elderly patients [31].

Conclusion

Despite growing number of octogenarian patients with ACS, there is limited data about optimal management and prognosis of these patients. They have higher in-hospital and one year cardiovascular mortality. Simple measures such as blood pressure, ejection fraction, blood sodium levels, GFR and electrocardiogram showing atrial fibrillation or STEMI may be used to discriminate those with higher in-hospital or long term mortality. Special care then may be given to these patients to reduce mortality.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Standards Statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

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