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Long Term Survival and Hospital Admission Following Acute Coronary Syndrome; a Cohort Study

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ABSTRACT

Identification of survival predictors can be as a guide to formulate preventive strategies to reduce mortality. The purpose of this study was to identify factors affecting death and readmission due to acute coronary syndrome based on acute coronary syndrome registry in Kermanshah in 2010-2011. Data was collected according to the questionnaire used in Euro Heart Study-ACS Registry. For the purpose of this study, we used data recorded in patients' medical files as well as interviews with doctors and patients if it was necessary. A nurse on collected all relevant data for each patient regarding prehospital history, hospital course and one year after discharge. To calculate survival and readmission of patients and the factors affecting on them COX regression was used. Of total 1972 people who were studied, 101 patients died during follow-up and 1030 patients were rehospitalized due to acute coronary syndrome or complications of heart diseases. The most important factors affecting survival and after adjustment for other factors, were age more than 75 years (HR = 14.90, 95% CI: 3.47 -63.85), female gender (HR = 1.38, 95% CI: 1.00-2.35), and chronic condition (HR = 2.42, 95% CI: 1.42-4.10). The most important predictors of readmission were also age less than 50 years (HR = 1.98, 95% CI: 1.52-2.59), male gender (HR = 1.17, 95% CI: 1.00-1.39) and having Q wave MI (HR = 1.22, 95% CI: 1.01-1.46). Women had higher mortality and lower readmission after ACS, the fact that need to be addressed in future health interventions. Other modifiable factors related with survival and hospital readmission need to be investigated and tackled in future studies and population based interventions.

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Introduction

Studies from different countries show that the world is in the pandemic of coronary artery disease (CAD) and increase in number of such cases in developing countries is alarming [1,2]. Also this disease is the most common cause of death in Iran and each year it accounts for a large amount of the disease burden [3-5] so that it comprises 38% of total death in the country [6] and is the third leading cause of disease burden in Iran [7].

Many factors can be suggested which can contribute to an observed increase in death due to CAD. Among these factors aging as well as increase in some risk factors including dietary factors (increase in use of unhealthy food), obesity, diabetes, reduced physical activity, stress and smoking can be mentioned. In addition to increase in prevalence of such risk factors, age of patients with CAD is also decreasing [8-12].

Acute coronary syndrome (ACS) is sudden and severe conditions for heart in which blood and oxygen cannot meet the need of heart muscle. ACS includes a variety of clinical presentation called unstable angina (UA), ST segment elevation myocardial infarction (STEMI), and non-ST segment elevation myocardial infarction (NSTEMI) [13-15]. According to different studies, death due to ACS is 5-10% and it is the main cause of hospitalization so that approximately 30% of patients will require readmission within the next 6 months [16,17].

In studies conducted in different parts of the world, factors such as age and gender [18,19], hypertension, family history, diabetes mellitus, smoking, prior history of myocardial infarction have been suggested as predictors of death due to heart attack [19]. Identification of predictors of death and readmission can help policy makers to formulate and implement preventive strategies for reduction of mortality, readmission and ultimately the burden of disease. The present study is a result of collaboration with European Society of Cardiology using the same questionnaire and aimed to identify factors affecting death and readmission due to ACS in Kermanshah.

Materials and Methods

This research is a prospective cohort study based on data recorded in ACS registry in Kermanshah. According to this program, all patients with ACS who came to Imam Ali Heart Hospital in Kermanshah from December 2010 to March 2012 (16 months) were included. Kermanshah district is located in the western part of Iran with a population of about 1033512 people of whom 667465 are above 20 years. Imam Ali Hospital is the largest teaching and referral center in west of Iran and provides cardiovascular specialized services to patients in provinces of Kermanshah, Kurdistan, Ilam and Lorestan. This hospital is equipped with departments of angiography and cardiac surgery and more than 90% of patients with heart diseases in Kermanshah are admitted and treated in this hospital.

In Kermanshah ACS registry program, the required information was collected according to the form used in the Euro Heart Survey on ACS. The latter was a prospective multicenter study across Europe on relative frequency, diagnosis and treatment of ACS and aimed to investigate ACS management pattern in different regions of Europe and review of patients' characteristics and their differences in different areas. The first Euro heart survey on ACS was done in 2000 and it collected data from 25 different countries. The patients were registered for 4 months and followed up within 30 days. The main cause of death and disability was investigated in this study [20].

The second Euro heart survey on ACS was conducted in 2004 in 190 medical centers in 32 European and Mediterranean countries. In the study, patients' characteristics and compliance with therapeutic guidelines were examined [21]. The ACS snapshot survey was started in 2009 and patients were followed up for one year [22]. The data collection form includes seven sections: identification and past history, chronic home medication, admission data, investigations, medication during hospital stay, outcome and follow-up.

All required information collected by a trained nurse with supervision of a medical doctor who was expert in the field of cardiovascular disease. Every morning, the nurse in charge of the work, extracted the necessary information from patients records. When it was necessary, the required information was collected from the cardiologist in charge of patients. The source of data collection forms included information in patients' records, ECG Completed forms were collected daily and were entered into computer. All registered patients were followed up for at least one year after the end of patients' registration. For the purpose of this study, we included all patients with a final diagnosis of myocardial infarction (with or without elevated ST) and patients with unstable angina who were older

than 20 years. We excluded those who were not resident of Kermanshah and those who had suffered from ACS after coronary interventional procedures (cardiac surgery, balloon or angioplasty).

Variables examined in this study included gender, age, total cholesterol, hypertension, smoking, diabetes mellitus, family history of CAD, body mass index, heart failure, ECG ST changes, heart rate, discharge diagnosis, chronic condition, prior history of CVD and coronary artery reperfusion (medical or surgical). In this study, an individual with known diabetes mellitus (KDM) was referred to as one whose diabetes before admission to hospital had been diagnosed and he/she was under treatment with diet with or without medical treatment.

An individual with newly diagnosed diabetes mellitus (NDM) was someone whose fasting serum glucose was ≥ 126 mg/dl and whose diabetes was diagnosed at the time of admission to hospital due to ACS. Also serum cholesterol level was determined by the first serum measurement and values ≥ 240 mg/dl were considered hypercholesterolemia. Obesity was determined based on body mass index (BMI) and BMI<25 was considered normal, BMI of 25-35 was considered as overweight and obese and greater than 35 was considered as sever obesity.

Heart rate was referred to as the first heart rate measured after the start of attack which was taken by a doctor, nurse, or other service provider. Heart rate at rest below 60 per minute was classified as bradycardia, 60-100 was classified as normal and more than 100 was classified as tachycardia.

Chronic condition was referred to as conditions that the patient suffered from at least one of the chronic pulmonary diseases or chronic renal diseases or after admission the serum creatinine was above 1.2 in the first measurement. Prior history of CVD referred to as a condition that the patient had a history of at least one type of heart disease or PCI and/or CABG had been done for him.

Also reperfusion referred to as performing one of the reperfusion strategies including thrombolysis, reperfusion by PCI and CABG.

Heart Failure (HF) was considered having at least one of four conditions: HF was recorded by a doctor during the hospitalization, Killip class above 1 during the hospitalization, left ventricular (LV) function with moderately reduced (31-40%) or severely reduced (<30%) or diuretic drug was administered in the hospital in the absence of hypertension and chronic kidney disease. In this study, death refers to all-cause mortality during follow-up period and readmission refers to all cause hospital admission due to heart disease during follow-up period.

Statistical Analysis

To compare the baseline characteristics in different groups (Q wave MI, non Q wave MI and unstable angina), we used ANOVA and Chi square test.

In order to investigate factors affecting survival and the risk of readmissions, we first examine the proportional hazard assumption using Schoenfeld residuals. We then used Kaplan-Meier nonparametric method and Cox regression analysis. The probability of cumulative survival was also measured by Kaplan-Meier method and log rank test was used to investigate cumulative survival difference between groups.

To control potential confounding factors, multivariate Cox regression model was performed and the adjusted hazard ratio was reported with 95% confidence interval. Variables that had a p-value below 0.25 were entered into the model. All analyses were performed in Stata software version 12.

Results

Totally, 1972 patients with acute coronary syndrome admitted to the hospital during the period of study. The mean ages of men and women were 58.4 ± 13.0 and 63.1 ± 11.6 years, respectively and unstable angina constituted the highest number of patients with acute coronary syndrome. Unlike MI which occurred mainly in men, unstable angina occurred more frequently in women (**Table 1**).

From a total of 1972 people, 533 were smokers. The distribution of these people among three groups was different and the highest percentage belonged to those with Q-wave MI.

Among those with ACS, 456 (23.1%) patients had diabetes under treatment with diet, or with or without medical treatment. Diabetes in 67 patients was diagnosed when they were admitted in Imam Ali hospital.

Most people with high blood pressure were in unstable angina group ($p<0.001$) but people with hypercholesterolemia were more among patients with MI so that the percentage of patients with hypercholesterolemia in MI groups was approximately 2 times as much as those in unstable angina group ($p<0.001$) (**Table 1**).

Table 1. Characteristics of the cohort of patients with ACS.

		Q wave MI	Non Q wave MI	Unstable Angina	P-value
N		316	461	1195	----
Age (mean ± SD)		57.05 ± 10.99	61.18 ± 13.93	60.87 ± 12.51	0.893
Sex (male %)		250 (79.1)	320 (69.4)	589 (49.3)	< 0.001
Smoking	Former	6 (1.9)	13 (2.8)	39(3.3)	< 0.001
	Current	139 (44.0)	143 (31.0)	251 (21.0)	
Diabetes	Known diabetes mellitus (KDM)	56 (17.7)	106 (23.0)	294 (24.6)	0.047
	Newly diagnosed diabetes mellitus (NDM)	14 (4.4)	22 (4.8)	31 (2.6)	
Hypertension		113 (35.8)	202 (43.8)	653 (54.6)	< 0.001
Total Cholesterol	<240	261 (82.6)	386 (83.7)	1044 (87.4)	< 0.001
	>240	42 (13.3.)	62 (13.4)	91 (7.6)	
BMI	<25	167 (52.8)	242 (52.6)	580 (48.5)	0.006
	25-35	146 (46.2)	211 (45.8)	596 (49.9)	
	>35	1 (0.2)	3 (0.7)	13 (1.1)	
Family history of CAD		34 (10.8)	35 (7.6)	119 (10)	0.261
Heart Failure		301(95.3)	363(78.7)	752(69.9)	< 0.001
Heart rate	Normal	277 (87.7)	412 (89.4)	1111(93.0)	0.018
	Bradycardia	34 (10.8)	27 (5.9)	44 (3.7)	
	Tachycardia	5 (1.6)	22 (4.8)	40 (3.3)	
Serum creatinine	<1.2 (normal)	281 (88.9)	386 (83.7)	1062 (88.9)	0.372
	>1.2	35 (11.1)	75 (16.3)	132 (11.0)	
Medical history of CVD	History of prior myocardial infarction	30 (9.5)	66 (14.3)	194 (16.2)	0.110
	History of prior angina pectoris	71 (22.5)	180 (39.0)	643 (58.3)	< 0.001
	History of congestive heart failure	7 (2.2)	24 (5.2)	77 (6.4)	0.146
	History of stroke	7 (2.2)	12 (2.6)	30 (2.5)	0.958
	History of peripheral vascular disease	1 (0.3)	1 (0.2)	6 (0.5)	0.800
	History of chronic renal failure	4 (1.3)	10 (2.2)	24 (2.0)	0.641
	History of Chronic lung disease	4 (1.3)	17 (3.7)	45 (3.8)	0.082
	Prior PCI	22 (7.0)	73 (15.8)	306 (25.6)	< 0.001
	Prior CABG	4 (1.3)	29 (6.3)	128 (10.7)	< 0.001
Reperfusion	Reperfusion by PCI	3 (0.9)	5 (1.1)	13 (1.1)	0.216
(medical or surgical)	Revascularization	3 (0.9)	5 (1.1)	14 (1.2)	0.778
	Thrombolysis	293 (92.7)	0 (0.0)*	0 (0.0)*	< 0.001
	Coronary artery bypass graft (CABG)	3 (0.9)	8 (1.7)	31 (2.6)	0.156

*No ECG Criteria

Of the people under study, 970 suffered from one of the types of overweight, obesity and morbid obesity. According to set criteria for HF, totally 1416 (71.8%) patients had HF and the highest percentage belonged to Q wave MI group ($p<0.001$). In 242 patients serum creatinine level was higher than normal and the highest percentage belonged to non Q wave MI group (**Table1**). Cumulative survival after follow-up period was estimated 79.0% (91.0% for men and 68.1% for women). Median survival time of the patients was 16.1 months (16.0 – 16.2), and median time to readmission was 2.3 (2.0 – 2.5) months. The mean survival time of men (22.1 months) was greater than that of women (21.2 months) and the mean time to readmission in women (4.9 months) was greater than that in men (3.9 months) (**Table 2**). It was found that the most effective predictor of patients' death was old age and the risk of death increased with increasing age so that in ages over 75 years, the risk of death was 14.90-fold (95%CI: 3.47-63.85).

In fact, with each year increase in age, the risk of death increased 7%. Chronic condition (HR=2.42, 95%CI: 1.42-4.10) and HF (HR=1.95, 95%CI: 1.05-3.61) ranked next. Hypertension, prior history of heart diseases, reperfusion, tachycardia, patients with Q wave MI and non Q wave MI were at higher risk of death, however, these relationships were not statistically significant (**Table 2**).

Table 2. Factors associated with mortality of patients with diagnosis of ACS (in-hospital and fatality after hospital discharge) using cox-proportional hazard model.

Variable	Category	HR $_{crude}$	HR $_{adjusted}$
Sex	Male	1	1
	Female	1.46	1.38
		(1.00-2.20)*	(1.00- 2.35)
Age	<50	1	1
	50-59	1.95	1.96
		(0.51 – 7.36)	(0.39 -9.80)
	60-74	7.13	6.07
		(2.18- 23.32)	(1.41- 26.16)
	>75	18.89	14.90
		(5.67 – 61..04)	(3.47 – 63.85)
Total Cholesterol		1.00	0.99
		(0.99 – 1.00)	(0.98 – 1.00)
Hypertension	No	1	1
	Yes	1.92	1.31
		(1.25 – 2.96)	(0.80- 2.26)
Chronic Condition[#]	No	1	1
	Yes	2.40	2.42
		(1.43– 3.49)	(1.42 – 4.10)
Prior history of CVD[¥]	No	1	1
	Yes	2.25	1.57
		(1.35 – 3.75)	(0.85 – 2.90)
Heart failure[Ψ]	No	1	1
	Yes	3.06	1.95
		(1.61 – 4.78)	(1.05 – 3.61)
Reperfusion (medical or surgical)[Φ]	No	1	1
	Yes	0.69	1.18
		(0.37 -1.27)	(0.25 – 4.57)
ECG STT changes	No	1	1
	Yes	1.60	0.65
		(0.90 – 2.83)	(0.29 – 1.48)
Heart rate	normal	1	1
	Bradycardia	0.98	0.88
		(0.42 – 2.27)	(0.27 – 2.90)
	Tachycardia	2.00	2.07
		(1.01 – 4.95)	(0.63 – 6.83)
Discharge Diagnosis	Unstable Angina	1	1
	Non Q wave MI	0.76	1.12
		(0.39 – 1.45)	(0.22 –5.62)
	Q wave MI	1.33	1.29
		(0.83– 2.13)	(0.72– 2.34)

***** 95% confidence interval

[#]chronic obstructive lung disease/ chronic renal failure/Serum creatinin >1.2

[¥]History of prior myocardial infarction/ History of prior angina pectoris/ History of congestive heart failure/ History of stroke/ History of peripheral vascular disease/ History of chronic renal failure/ History of Chronic lung disease/ Prior PCI/ Prior CABG

[Ψ]Heart failure/ Killip class>1/Left ventricular (LV) function= Moderately reduced (31-40%)& Severely reduced (<30%)/ Diuretics use if no chronic renal failure& if no Hypertensio

[Φ] Reperfusion/ revascularization/ reperfusion by PCI/ thrombolysis, CABG

The most important predictor of readmission (**Table 3**) was also patients' age so that people who are under 50 years of age are at greater risk for readmission and the chances of their readmission was 1.98 times greater (95%CI: 1.52–2.59) than those who were aged 75 years or more. Generally, for each year that the patient is younger the risk of readmission increases 2%. In addition, men and those with Q wave MI were more likely to have readmission. The results indicated that patients who suffered from heart failure were less likely to have readmission after discharge from hospital (**Table 3**).

Table 3. Univariate and multivariate hazard for rehospitalisation (cox proportional hazard model).

Variable	Category	HR_{crude}	$HR_{adjusted}$
Sex	Male	1.20 (1.06 – 1.36)*	1.17 (1.00 – 1.39)
	Female	1	1
Age	<50	2.06 (1.64 – 2.58)	1.98 (1.52 – 2.59)
	50-59	1.69 (1.37 – 2.09)	1.72 (1.34 – 2.20)
	60-74	1.46 (1.21- 1.83)	1.64 (1.30- 2.08)
	>75	1	1
Hypertension	Yes	0.81 (0.71 – 0.91)	0.89 (0.76 – 1.03)
	No	1	1
smoking	Current	1.14 (1.00 – 1.31)	0.91 (0.59– 1.45)
	Former	1.10 (0.74 – 1.62)	0.85 (0.59 – 1.40)
	No	1	1
Heart failure	Yes	0.80 (0.69- 0.94)	0.82 (0.68- 0.99)
	No	1	1
Prior history of CVD	Yes	0.80 (0.70 – 0.92)	0.95 (0.81 – 1.12)
	No	1	1
Reperfusion (medical or surgical)	Yes	1.16 (1.00 – 1.34)	0.97 (0.65 – 1.46)
	No	1	1
Discharge Diagnosis	Unstable Angina	1	1
	Non Q wave MI	1.14 (0.98 – 1.32)	1.19 (0.77– 1.85)
	Q wave MI	1.24 (1.05- 1.45)	1.22 (1.01 – 1.46)

*95% confidence interval

Discussion

The results showed that the median survival time in men was greater than that in women, and the mean time to readmission in women was greater than that in men. The most predictors of patients' survival were age, chronic condition, HF and gender (female). In addition, next hospital admission to hospital were mostly predicted with age, gender (male) and being in one of the MI groups. With the difference that female gender and increasing age had a worse prognosis for survival while male gender and younger age had a worse prognosis for readmission.

It has been indicated that men suffered from ACS more earlier than women. This difference has been attributed to estrogen hormone and it has been already known that after menopause the incidence of heart diseases becomes almost equal in both genders [23]. The result of our study in showing that women on average suffer from ACS 5 years later than men is in line with other studies elsewhere [24,25]. According to the Greek Study of Acute Coronary Syndrome (GREECS) the most common type of acute coronary syndrome in men is Q wave MI (35%) and in women is unstable angina (42%) [26]. This was similar with our findings in present study.

Our study showed differences between men and women regarding survival and hospital readmission. In a retrospective cohort study in Scotland, evaluation of 117,718 patients admitted with MI over 10 years showed that the median survival in men was 7.3 years and in women was 3.5 years [27]. Another study reported that 17% of men and 16% of women required readmission [27]. In our study, the median survival in women was less than that in men, but the mean time to readmission in men was greater than that in women.

Women are more subjected to overweight, obesity and diabetes with increasing age, which affect worse prognosis and increase fatality.

In calculating the risk score for predicting survival in Canadian population, a final model for short-term and long-term survival prediction was proposed. In the study, age over 75 years, Killip class>1, systolic blood pressure over 100, heart rate>100 were introduced as the most important predictors [28]. In a multinational prospective study, GRACE, the risk of death was calculated 6 months after MI. In the study, 43810 people were reviewed during six years from 1999 to 2005. Of these, 1989 patients died in the hospital and 1466 patients died during the 6-month follow-up. Age, heart failure, prior history of heart diseases, systolic blood pressure, Killip class, serum creatinine, ST segment deviation, cardiac arrest on admission and elevated initial cardiac markers were identified as predictors [29].

In evaluation of factors affecting survival, gender is an important factor and has been taken into consideration. The results of various studies indicate that there is a higher risk of death due to heart attack in women [30,31]. In a study, the risk of death due to heart attack in women was estimated 1.7 times greater than that in men [32] because poor prognostic factors in women are greater than those in men. In the current study, hazard ratio in women was estimated 1.38 times greater than that in men (**Table 2**). This result is consistent with the results of the aforementioned studies.

With increasing age, the risk of death increases exponentially and it is one of the determinants of patients' six-month survival [33]. In several studies [34,35], it has been shown that in calculation of risk prediction of the Canadian population, the age over 75 years is an important factor and another study showed that with increase in every year of age, the probability of death after MI is 1.25 times [28]. In the present study, the most important predictor of survival during follow-up was patients' age and patients aged over 75 years had the worst prognosis. In this study, there was an inverse relationship between older age and readmission. In evaluation of readmission, it was found that angiography and CABG were the leading causes of readmission at younger ages. This can be attributed to the fact that physicians perform these interventions for younger people with less concern and greater frequency.

The effect of risk factors of diabetes, hypertension, smoking and dyslipidemia on survival following acute coronary syndrome after myocardial infarction has also been investigated in several studies. A study in the Netherlands examined 14434 patients with MI admitted between the years 1985-2008. Two-thirds of patients had at least one risk factor. Hazard ratio in three time intervals 1985-1990, 1990-2000, 2000-2008 was calculated for those who had at least one risk factor. Hazard ratio in the first interval was 1.2, in the second interval was 0.89 and in the third interval was 0.89. The result of the study indicated that there was a relationship between having at least one risk factor and decreased survival and this effect has decreased over the past three decades [36]. In

another study in Germany in 2005, the relationship between smoking, diabetes and long-term survival was reviewed. The study period was 0.8 years and 747 patients were evaluated. Hazard ratio for smoking was 1.95 [37].

In the current study, those who had quit smoking had lower odds of readmission, but no significant relationship was seen between smoking and readmission. This contradiction was also observed in other studies including prospective study GRACE [38] and Spain registry study [39]. The reason for this contradiction is not fully understood but a possible explanation might be that smokers, compared to non-smokers can take more advantage of the earlier intervention strategies. People with history of having hypertension had a higher risk of death. In contrast, such patients had fewer readmissions. In fact, such patients are usually more careful about their hypertension and try to have better control by visiting their doctors.

In study of GRACE, hazard ratio for past medical history of chronic condition was 1.3, for serum creatinine was 1.1 and for Killip class > 1 was 1.4 [23] [26]. In another study in which 329 patients with ACS undergoing PCI were investigated, creatinine was introduced as an independent predictor for survival and hazard ratio for creatinine over 3 was 2.45 [40]. In the present study, no significant relationship was found between prior history of heart diseases and fatality. High serum creatinine level, chronic renal disease and pulmonary diseases were also the most important predictors of survival in univariate analysis but not significant in multivariable analysis (**Table 2**). Based on the findings of a study conducted in Canada, HF increased the risk of death among those with ACS [41]. Such finding has been supported by other studies such as GRACE [42].

In the present study, developing heart failure in the hospital although increased hazard of death, had opposing effect on readmission so that people with heart failure had lower odds ratio for readmission during follow-up. It should be noted that heart failure in our study refers to mostly acute failure that could have improved in the hospital while majority of other studies have focused on chronic heart failure [41,43]. Similar to other studies in developing countries the follow up of patients was one of the most challenging part in the present study. Except in a few cases, it was difficult and sometimes impossible to have access to future files of patients and therefore the follow-up data collection form was designed so that it can be completed by using several oral questions without the need for referring to the patients.

Registering four phone numbers from patients and his/her family as well as linkage of data with registered deaths by Kermanshah health center minimized non follow-up cases. However, the present study is one of the few studies conducted in Iran on registry of ACS with a large sample size and standard questionnaire which allow to investigate the association of different risks with prognosis of ACS.

Conclusion

Higher fatality of ACS among women with lower hospital admission need to be investigated more precisely. Health policy maker should implement appropriate strategies for decrease the fatalities among women. Aging, chronic condition and HF are other important predictors of survival after ACS. The most important predictors of readmission include male gender and younger age of patients. Age and gender are among non-reversible factors, but for other factors need to be addressed appropriately.

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