Biomedical & Pharmacology Journal Vol. **10**(3), 1197-1206 (2017)

Clinical Characteristics, Medical Management and Outcomes of Patients with ST-Elevation Myocardial Infarction in Sanglah General Hospital, Denpasar, Bali, Indonesia

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http://dx.doi.org/10.13005/bpj/1221

(Received: August 18, 2017; accepted: August 29, 2017)

ABSTRACT

Acute coronary syndrome (ACS), particularly ST-elevation myocardial infarction (STEMI), is a major health problem in Indonesia, including Bali. To evaluate clinical characteristics of ACS patients and the clinical outcome after reperfusion therapy for STEMI patients.This was a cross-sectional study using data from ACS 2016 registry in Bali. Subjects were consecutive adult ACS patients (minimum age of 18 years) who were hospitalized in Sanglah General Hospital (SGH), Denpasar, Bali Island. Diagnosis of ACS was established according to WHO criteria and was divided into unstable angina pectoris (UAP), non-STEMI, and STEMI. A total of 696 patients were enrolled; 75.7% of them were men. Patients' mean age was 58.3 $\pm$ 11.79 years. Diagnoses were 260 (37.4%) UAP, 161 (23.1%) non-STEMI, and 275 (39.5%) STEMI. Reperfusion therapy was given to 196 patients (71.3%), consisted of 86 (31.3%) fibrinolysis and 110 (40.0%) primary PCIs. The median time from onset to hospital admission was 6 hours. The median door-to-needle (DTN) time was 50 (10-295) minutes, while the median door-to-device (DTD) time was 144 (19-1028) minutes. Mortality rate was 8.2% in patients receiving fibrinolysis and 5.5% in patients underwent primary PCI. Mortality was associated with higher age, higher heart rate, lower blood pressures, higher serum creatinine levels, higher troponin T1 levels, higher GRACE, TIMI, and CRUSADE risk scores. Timely reperfusion for STEMI is still not achieved in most of the cases. Patients with high GRACE risk score or TIMI score had the highest risk of death. Door-to-device-time also tended to be longer in patients who died. Early recognition of ACS symptoms, pre-hospital transfer and emergency care in hospital should be improved in the future.

Keywords: Acute coronary syndrome, Acute myocardial infarction, Fibrinolysis, Percutaneous coronary intervention, Reperfusion, ST-elevation myocardial infarction (STEMI)**.**

INTRODUCTION

Acute coronary syndrome (ACS) is a heterogeneous condition, consisted of unstable angina pectoris (UAP), non-ST elevation myocardial infarction (non-STEMI) and STEMI. In Indonesia, acute myocardial infarction (AMI) is the most common cause of death with an estimated incidence

rate of 200 events per 100,000 population annually.[1] In-hospital mortality related to ACS in Asia-Pacific is relatively high at about 5%.[2] Prognosis of ACS differs greatly and mortality can be predicted using a risk stratification system, such as the Global Registry in Acute Coronary Events (GRACE)[3] and the Thrombolysis in Myocardial Infarction (TIMI) scores.[4]

ACS registry in Bali was started in 2016 as part of the Indonesia STEMI project. This registry provides information about diagnostic work-up for ACS symptoms, risk stratification, acute management of STEMI, and in-hospital mortality. Timely reperfusion is an important goal in STEMI management and a focus of quality assessment of a hospital. By analyzing a large data set in the ACS registry, clinical outcomes and the problems of delivering timely effective therapies could be studied and improved in the future. Reperfusion therapy, either fibrinolysis or primary percutaneous coronary intervention (PCI) is the standard treatment of STEMI aiming to restore the coronary flow and oxygenation of the myocardial tissue.[5,6] The ideal timing to give reperfusion therapy has been set as door-to-needle (DTN) time within 60 minutes for fibrinolysis and door-to-device (DTD) time within 90 minutes for primary PCI.[7]

The Province of Bali lies between Java and Lombok Islands. It consists of Bali Island as the main island and several smaller islands, i.e. Nusa Penida, Nusa Lembongan, Nusa Ceningan, Serangan, and Menjangan Islands. The total area is 5,634.40 hectares.[8] Sanglah General Hospital is the only PCI-capable hospital employed by the Government of Bali. It is a type A hospital with 746-bed capacity and a comprehensive cardiac care.[9] Besides SGH, there is only another private hospital capable for PCI near Denpasar city. Both PCI-capable hospitals are located in the southern part of Bali Island (Figure 1).

Although international guidelines for ACS management are clear and concise, it is not known how these guidelines applied in the real practice, especially in rural areas with limited PCI-capable centers. This study was aimed to evaluate the characteristics of patients with ACS and clinical outcome after reperfusion therapy in patients with acute STEMI in the Province of Bali, Indonesia.

METHOD

Study design and subjects

Data from ACS registry 2016 in Bali was used in this cross-sectional study. The study subjects consisted of consecutive adult ACS patients (minimum age of 18 years) who were hospitalized in Sanglah General Hospital (SGH), Denpasar, Bali Island. SGH is a third referral hospital in Bali Island and has a specialized heart center with cardiac surgery facility and heart catheterization laboratory performing high volume percutaneous coronary interventions (PCI).

The study protocol and case report form were approved by the Ethical Committee in all of the participating institutes of Indonesia STEMI. Patients were enrolled between January and December 2016. History and clinical data were compiled by trained general physicians from medical records. Data entry was done through the website of Indonesia STEMI registry and then were cleaned by an external auditor before verified and analyzed.

Diagnosis of ACS

Diagnosis of STEMI was established according to the World Health Organization (WHO) criteria, i.e. ST elevation > 1 mm in the two consecutive leads or new or presumed new left bundle branch block (LBBB) and the symptom of chest pain compatible with ACS for more than 20 minutes and elevated biochemical markers of myocardial necrosis either CK-MB or troponin. Diagnosis of non-STEMI (NSTEMI) was determined by chest pain compatible with ACS and abnormal ST depression or T wave inversion with elevated biochemical markers of myocardial necrosis. If cardiac markers were normal, the patient was diagnosed as unstable angina pectoris (UAP). Both NSTEMI and UAP were combined as NSTE-ACS.

Patients received medical treatment per protocol for each diagnosis. For patients with STEMI, reperfusion therapy was done as fibrinolysis or percutaneous coronary intervention (PCI) as recommended in international guidelines.[5,6] Patients underwent primary PCI received clopidogrel 300 mg (loading dose) or ticagrelor 180 mg prior to the procedure.

Statistical analyses

Patients' demography and clinical data were presented descriptively. Categorical variables were expressed in number and percentage, while continuous variables were expressed as mean and standard deviation. Comparison between two groups was tested using Chi-square test or Fisher's exact test. Mean differences were analyzed using student *t* test for normally distributed data Mann-Whitney U test for skewed data. A *p* value of less than 0.05 was considered significant.

RESULTS

A total of 696 patients were registered during the study period; male patients were predominated with a male-to-female ratio of 3:1. The peak age was between 51 and 60 years old, ranging from 19 to 90 years old. Diagnoses were 260 (37.4%) UAP, 161 (23.1%) non-STEMI, and 275 (39.5%) STEMI. About 90.5% patients had a blunt chest pain and 92.2% patients had chest pain last

Table 1: Characteristics of the study subjects (n=696)

Characteristics	Mean ± SD Median (Min-Max)	n	%
Male sex		527	75.7
Age (years)	58.3 ± 11.79		
History of acute myocardial infarction		99	14.2
History of previous PCI		53	7.6
History of peripheral vascular disease		2	0.3
History of coronary artery bypass grafting		1	0.1
History of hypercholesterolemia		119	17.1
History of premature CAD in family		13	1.9
History of heart failure		158	22.7
History of asthma or COPD		15	2.2
History of angina		149	21.4
History of cerebrovascular disease		31	4.5
Smoker		277	39.8
Diabetes mellitus		186	26.7
Hypertension		398	57.2
Sign of heart failure			
No sign		489	70.3
Rales in <1/3 field		140	20.1
Rales in >1/3 field		19	2.7
Cardiogenic shock		48	6.9
Cardiac arrest		22	3.2
Heart rate (bps)	83 ± 26.0		
Systolic blood pressure (mmHg)	128 ± 27.4		
Diastolic blood pressure (mmHg)	79 ± 16.7		
Creatinine serum (mg/dL)	1.7 ± 2.15		
CK-MB1	13.5 ± 30.1		
Troponin T1	329.7 ± 531.3		
GRACE risk score (n=431)	119.3 ± 33.9		
Median TIMI score NSTEMI (n=161)	3 (1-6)		
Median TIMI score STEMI (n=275)	4 (1-14)		
Median time since onset to hospital admission (hours)	6 (0-192)		

for 20 minutes or more. Other clinical characteristics were presented in Table 1.

The most common location for STEMI was anterior infarction, followed by inferior infarction and inferoposterior infarction (Table 2).

STEMI diagnosis was significantly higher in male, patients with age of ≤60 years, smoker, and those with a history of hypercholesterolemia. Patients with STEMI were also found with significantly more cardiac arrest and sign of heart failure at admission (Table 3).

Median time interval from the onset of symptom to admission in Sanglah Hospital was significantly shorter in STEMI than NSTE-ACS patients (5.5 vs. 7.0 hours; $p<0.001$). There was no data on time of first medical contact and patients' transfer. However, patients who came by their own had time from onset shorter than patients who were referred from other hospital (6 vs. 6.75 hours; $p=0.011$).

Table 2: Location of STEMI (n=275)

Location	n	%
Anterior	154	22.1
Inferior	56	8.0
Posterior	10	1.4
Lateral	4	0.6
Anterior & Inferior	2	0.3
Anterior & Lateral	10	1.4
Inferior & Posterior	35	5.0
Anterior, Inferior & Posterior	1	0.4
Inferior, Posterior & Lateral	1	0.4
Anterior, Inferior, Posterior & Lateral	2	0.3

Reperfusion therapy was given to 196 (71.3%), consisted of 86 (31.3%) fibrinolysis and 110 (40.0%) primary PCIs. The median door-to-needle (DTN) time was 50 (10-295) minutes, while the median door-to-device (DTD) time was 144 (19-1028) minutes. There were 3 patients loss-to-follow-up. The overall mortality rate among STEMI patients was 9.2%. It tended to be lower in patients who received reperfusion therapy than patients who did not (7.2% vs. 14.1%; p=0.075). Mortality rate was 8.2% in patients receiving fibrinolysis and 5.5% in patients underwent primary PCI.

Mortality of patients STEMI was associated with older age, higher heart rate, lower blood pressures, higher serum creatinine levels, higher troponin T1 levels, higher GRACE, TIMI, and CRUSADE scores. Patients with GRACE risk score of >140 had almost 30 times increased risk of death, whereas TIMI risk score of ≥4 were associated with 18 times higher risk of death during hospitalization. Patients who died also tended to have longer DTD time and shorter length-of-stay in the hospital;

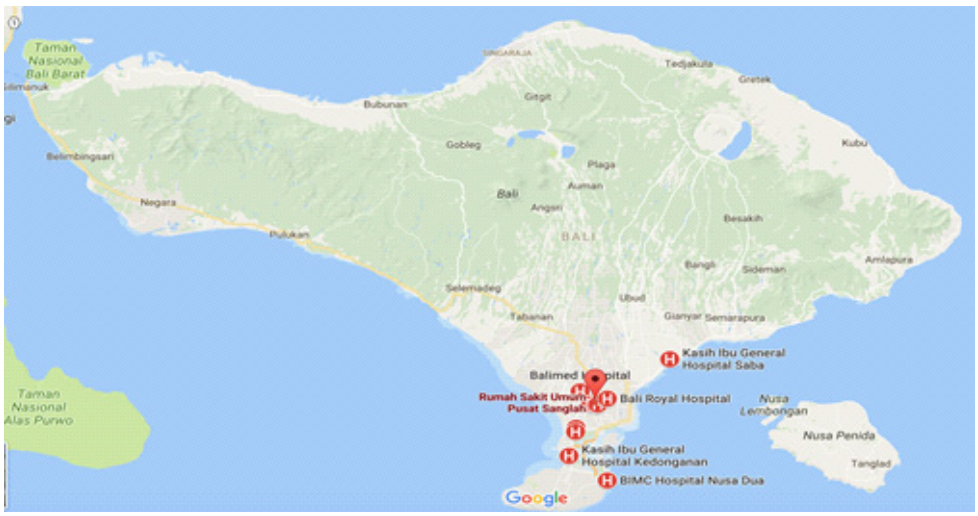

Fig. 1: Map of Bali and the location of Sanglah General Hospital (red balloon)

however, time since onset of symptom to admission was not significantly different (Table 4).

DISCUSSION

This is the first ACS registry in Bali and the first report on the outcome of STEMI patients in Sanglah General Hospital, Bali. Data set from registry has been used extensively to evaluate the quality of healthcare system in developing countries and provide opportunity to improve the patients' clinical outcome in the future.

Our data showed that male gender, age 60 years or younger, smoking history and hypercholesterolemia were significant risk factors for acute STEMI. Similar findings were also observed in Thai ACS registry. Male patients were higher in STEMI compare to NSTEMI and UA (68.1% vs. 54.9% vs. 52.5%; $p<0.001$). Median age of patients with STEMI was also significantly younger than NSTEMI and UA (62.9 vs. 68.8 vs. 66.6 years, respectively; $p<0.001$).[1] Other risk factors (diabetes, hypertension, dyslipidemia, smoking and family history of coronary artery disease) were also significantly found to be associated with STEMI diagnosis in Thai ACS registry.[10]

Mortality rate in our study tended to decline from 14.1% in non-reperfused STEMI patients to

Table 3: Factors associated with STEMI diagnosis (n=696)

Characteristic	STEMI (n=275)	NSTE-ACS (n=421)	*p*	OR	95% CI
Gender					
Male	227 (43.1%)	300 (56.9%)	<0.001*	1.907	1.309-2.779
Female	48 (28.4%)	121 (71.6%)			
Age					
≤ 60 years	178 (42.5%)	241 (57.5%)	0.049*	1.371	1.001-1.876
> 60 years	97(35.0%)	180 (65.0%)			
Smoker					
Yes	142 (51.3%)	135 (48.7%)	<0.001*	2.262	1.654-3.092
No	133 (31.7%)	286 (68.3%)			
Diabetes mellitus					
Yes	64 (34.4%)	122 (65.6%)	0.096*	0.743	0.524-1.055
No	211 (41.4%)	299 (58.6%)			
Hypertension					
Yes	162 (40.7%)	236 (59.3%)	0.457*	1.124	0.826-1.529
No	113 (37.9%)	185 (62.1%)			
Hypercholesterolemia					
Yes	58 (48.7%)	61(51.3%)	0.024*	1.577	1.061-2.346
No	217 (37.6%)	360 (62.4%)			
History of CVD					
Yes	11 (35.5%)	20 (64.5%)	0.639*	0.836	0.394-1.772
No	264 (39.7%)	401 (60.3%)			
Cardiac arrest					
Yes	16 (72.7%)	6 (27.3%)	0.001*	4.273	1.651-11.060
No	259 (38.4%)	415 (61.6%)			
Sign of heart failure					
Yes	101 (48.8%)	106 (51.2%)	0.001*	1.725	1.241-2.398
No	174 (35.6%)	315 (64.4%)			

*Chi-square test ^Fisher's exact test

8.2% in patients receiving fibrinolysis to 5.5% in patients underwent primary PCI. A better pattern was shown in a recent report from Jakarta ACS registry, which found that mortality in non-reperfused vs. fibrinolytic therapy vs. primary PCI patients were 9.1% vs. 3.8% vs. 3.2%, respectively.[1]

There were several risk factors that might contribute to in-hospital mortality of STEMI patients. Mortality of STEMI was almost twice in women than men but the difference did not reach statistical significant. Several studies have been found a significant difference on clinical outcomes between men and women. [2,3] In Thailand, in-hospital mortality in women was significantly higher than in men (23.6% vs. 13.9%; unadjusted OR = 1.90; 95% CI = 1.60-2.26; p<0.001). However, after multivariate analyses, the gender difference for in-hospital mortality was no

Table 4: Clinical factors associated with mortality in STEMI patients (n=272)

Variable	Died (n=25)	Alive (n=247)	*p*	OR	95% CI
Gender					
Male	18 (8.0%)	208 (92.0%)	0.157*	0.482	0.189-1.231
Female	7 (15.2%)	39 (84.8%)			
Smoker					
Yes	11 (7.8%)	130 (92.2%)	0.410*	0.707	0.309-1.619
No	14 (10.7%)	117 (89.3%)			
Diabetes mellitus					
Yes	6 (9.5%)	57 (90.5%)	0.917*	1.053	0.401-2.761
No	19 (9.1%)	190 (90.9%)			
Hypertension					
Yes	15 (9.4%)	145 (90.6%)	0.900*	1.055	0.456-2.442
No	10 (8.9%)	102 (91.1%)			
Hypercholesterolemia					
Yes	3 (5.3%)	54 ((94.7%)	0.248*	0.487	0.141-1.690
No	22 (10.2%)	193 (89.8%)			
History of CVD					
Yes	5 (45.5%)	6 (54.5%)	0.001^	10.042	2.816-35.808
No	20 (7.7%)	241 (92.3%)			
Cardiac arrest					
Yes	5 (33.3%)	10 (66.7%)	0.001^	5.925	1.845-19.024
No	20 (7.8%)	237 (92.2%)			
Killip Class					
Killip II-IV	23 (23.2%)	76 (76.8%)	<0.001*	25.875	5.950-112.531
No	2 (1.2%)	171 (98.8%)			
GRACE risk score					
>140	19 (30.6%)	43 (69.4%)	<0.001*	29.752	8.428-105.031
≤140	3 (1.5%)	202 (98.5%)			
TIMI risk score					
≥ 4	24 (14.5%)	141 (85.5%)	<0.001*	18.043	2.403-135.493
< 4	1 (0.9%)	106 (99.1%)			
Reperfusion therapy					
Yes	14 (7.2%)	180 (92.8%)	0.075*	0.474	0.205-1.095
No	11 (14.1%)	67 (85.9%)			

*Chi-square test ^Fisher's exact test

longer existed despite the findings that women with STEMI were older, had higher incidence of diabetes, hypertension and congestive heart failure.[4] Higher risk of in-hospital mortality in women with STEMI was also observed in Malaysian ACS registry (OR = 1.29; 95% CI = 1.06 -1.59; p <0.012) but not after adjustment with other covariates.[5] In GRACE study, female gender was also not an independent risk factor or predictor of in-hospital mortality when included in the multivariate analyses.[3] In addition to ST segment elevation, all variables included in GRACE risk score were significantly associated with in-hospital mortality of STEMI patients in this current study, thereby confirming the benefit of risk stratification prior to treatment.

There are several time parameters to evaluate the quality of healthcare in STEMI patients. First is the time since the onset of symptoms to first medical contact (FMC), which reflect the patient's awareness of an ongoing cardiac event. Second, the time from first medical contact (FMC) to treatment, either door-to-needle (DTN) time in patients receiving fibrinolysis or door-to-device (DTD) in patients undergoing primary PCI. If the FMC is a non-PCI-capable hospital, the transfer time between FMC and referral hospital should also be counted. According to the US Guidelines, the ideal time from first medical contact (FMC) to device time is 90 minutes or less for emergency transfer to a hospital with capability to perform PCI.[5] This time standard was set to keep adequate reperfusion at the myocardial tissue level.[6]

In our registry, transfer time from FMC to Sanglah Hospital were not available. Therefore, we could only estimated the duration between the onset of symptoms and hospital admission. The median time of 6 hours from onset to hospital admission may reflect inefficient pre-hospital care of ACS management. When analyzed further, median time since the onset of symptoms to hospital admission is significantly shorter in self-walk-in patients compared to the referred patients (6.00 vs. 6.75 hours, respectively; p = 0.011; Mann-Whitney U test). However, the difference of 0.75 hour may not reflect the transfer time from FMC to Sanglah General Hospital as the patients may came from their rural residences at cost of the long driving time. In Jakarta ACS registry, the time parameter used is door-in to door-out (DI-DO) defined as the duration of time from arrival to discharge at the FMC or STEMI referral hospital.[7] The mean DI-DO time in Jakarta ACS registry was 3.1 hours,[11] which also far beyond

Table 5: Clinical Factors Associated with Mortality in STEMI patients (n=272)

Variable	Died (n=25)	Alive (n=247)	*p*
Mean age (years)	62.2	56.7	0.024
Mean Heart rate (bps)	94.4	81.2	0.005
Mean systolic blood pressure (mmHg)	102.7	127.2	<0.001
Mean diastolic blood pressure (mmHg)	63.0	80.1	<0.001
Mean serum creatinine level (mg/dL) (n=267)	2.1	1.3	0.006
Mean CKMB1 level (ng/mL) (n=253)	41.3	22.9	0.054
Mean Troponin T1 level (ng/mL) (n=242)	1216.2	518.4	<0.001
Mean GRACE risk score (n=267)	170.8	115.0	<0.001
Mean TIMI score	15.2	4.4	<0.001
Mean CRUSADE score (n=266)	51.6	30.5	<0.001
Median time from onset (hr)	6.0	5.5	0.469
Median door-to-needle time (min)	65	47	0.516
Median door-to-device time (min)	275	134.5	0.091
Median length-of-stay (day)	1.5	5.0	<0.001*

*Mann-Whitney U test.

the recommended 30 minutes set by the American guidelines.[8]

Primary PCI has been the recommended treatment for STEMI patients since it was more effective to reduce the risk of recurrent infarct and death.[1] Fibrinolysis (thrombolysis) is recommended for patients who cannot meet the timely PCI, i.e. those who had FMC-to-device time of more than 120 minutes.[2] In our study, the median DTN (50 minutes) and DTD (144 minutes) times were still far from the recommended timely reperfusion. Similar pattern was also observed in other Southeast Asian countries. In Thai ACS registry the median DTN time was 85 minutes while the median DTD was 122 minutes.[10] Malaysian ACS registry found that the median DTN time was 49.7 minutes in men and 60.8 minutes in women ($p < 0.001$), whereas DTD time was 110.0 minutes in men and 121 minutes in women ($p = 0.244$).[15] As comparison, ACS registry in Henan Province, central China, found better timing. The median symptom onset to FMC, DTN, and DTD times was 168, 18, and 60 minutes, respectively.[3] Shorter DTN time was associated with reduced mortality. A study in the US found that DTN less than 30 minutes was associated with 2.9% in-hospital mortality compared with 4.1% at DTN 31-45 minutes and 6.2% at DTN of more than 45 minutes.[4]

The long driving time could be a reason for late presentation in our hospital. It may take 1-3 hours from the surroundings towns of Denpasar to reach SGH. US studies showed that 40%-75% of patients referred from a non-PCI capable hospital are not treated within the recommended 120 minutes.[20,5] However, it may be difficult to know the exact time of event onset due to the patient's recall bias or chest symptoms preceding the complete occlusion of the coronary artery. Symptoms of UAP and spontaneous reperfusion that might occur before the onset of STEMI may explain the benefit of late reperfusion in patients with symptom onset of 3-12 hours.[6,7] Furthermore, timely reperfusion may be less important in patients undergoing primary PCI than fibrinolysis if the STEMI patients have experienced the symptoms for about 2-3 hours.[8] The success rate of in-hospital fibrinolysis is comparable with primary PCI when initiated within the first 2-3 hours after the onset of symptoms. Therefore, fibrinolysis therapy should be given immediately if the transfer or driving time to a PCI-capable hospital will take more than 2 hours.[9]

CONCLUSION

Data from ACS registry are important to evaluate the overall quality of care given to ACS patients, particularly STEMI. Timely reperfusion for STEMI is still not achieved in most of the cases that could be due to long transfer or driving time to Sanglah General Hospital. Mortality of STEMI patients is still relatively high (9.2%) and tended to be higher in patients receiving fibrinolysis than primary PCI. Patients with high GRACE risk score or TIMI score had the highest risk of death. Patients underwent primary PCI who died also tended to have longer door-to-device-time than survived patients. In the future, education to early recognition of ACS symptoms, improved transfer time and emergency care in non-PCI capable hospital, and improved cardiac care in PCI capable hospital are needed to reduce mortality rate.

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