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Mortality Rate and Its Associated Factors in Patients with Non ST-Elevation-Acute Coronary Syndrome in Bali: Results from A Single Center Registry

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Non-ST elevation – acutecoronary syndrome (NSTE-ACS) consisted of non-ST elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP) diagnoses, which are common cardiac events in Indonesia, including Bali. To evaluate in-hospital mortality and its associated factorsin patients with NSTE-ACS patients in the Province of Bali. This was a cross-sectional study using data from ACS 2016 registry in Bali. Subjects were adult ACS patients whowere hospitalized in Sanglah General Hospital (SGH), Denpasar, Bali Island. Diagnosis of ACS was grouped into NSTEMI and UAP.Demography, clinical data, and anticoagulanttreatment were analyzed. Clinical outcome was in-hospital mortality. A total of 421NSTE-ACS patients were diagnosed; 300 (71.3%) among them were men. Patients' mean age was 59 ± 12.0 years. Diagnoses were UAP in 260 (61.8%) and non-STEMI in 161 (38.2%) cases.Heparin treatment was given to 409 (97.1%) patients, consisted of 96 (22.8%) unfractionated heparin (UFH), 177 (42.0%) fondaparinux, and 136 (32.3%) enoxaparin. There were 8 (1.9%) patients who underwent early PCI. The overall mortality rate of NSTE-ACS patients was 6.4%; it was higherin NSTEMI than UAP patients (13.0% vs. 2.3%; p<0.001; OR = 6.350; 95% CI = 2.504 – 16.101). Components of GRACE risk score and a score of >140 were risk factor for in-hospital death. Mortality rate was 12.5% with heparin therapy, 6.6% in patients treated with enoxaparin, and 2.3% in patients receiving fondaparinux. GRACE risk score is the only independent risk factor of death. Mortality of NSTE-ACS patients is still high (6.4%). High GRACE score is a significant risk factor of in-hospital death. The use of fondaparinux as anticoagulant agent may improve survival. Further studies are needed to confirm this finding.

Keywords: Acute coronary syndrome, acute myocardial infarction, non-ST-elevation myocardial infarction (NSTEMI), non-ST-elevation acute coronary syndrome (NSTE-ACS), unstable angina (UA).

Acute myocardial infarction (AMI) is the highest cause of death in Indonesia with an estimated incidence rate of 200 events per 100,000 populations annually.[1] Patients with AMI could present with ST-elevation (STEMI) or non-STEMI (NSTEMI). Those without ST-elevation are generally diagnosed as non-ST elevation acute coronary syndrome (NSTE-ACS), which will be further categorized as having NSTEMI or unstable angina (UA).[2]At myocardial tissue, the pathology

in NSTEMI is cardiomyocyte necrosis, whereas UA is marked by myocardial ischemia without cell loss.

In-hospital mortality related to ACS in Asia-Pacific is still relatively high at about 5%.[3]Patient factors are more important determinants of clinical outcome than community or hospital factors.[4] There are established guidelines for the management of NSTE-ACS patients, which includes optimal medical therapy, and invasive management for patients at intermediate- to high-risk.[5,6]In addition, initial risk stratification to estimate the patient's mortality risk, such as the Global Registry in Acute Coronary Events (GRACE)[7] and the Thrombolysis in Myocardial Infarction (TIMI) risk scores, should also be done.[8]

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.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. The Province of Bali lies between Java and Lombok Islands. It consists of Bali Island as the main island and several smaller islands with a total area of 5,634.40 hectares.[9]Sanglah General Hospital is ahospital employed by the Government of Bali with 746-bed capacity and a comprehensive cardiac care.[10]

Although international guidelines for ACS managementare 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 NSTE-ACS in the Province of Bali, Indonesia.

METHODS

Study design and subjects

Data from ACS registry 2016 in Bali was used in this cross-sectional study. Subjects were adult patients (aged 18 years or more) presenting with chest symptom and confirmed by electrocardiography and/or cardiac markers of myocardial infarction. Patients were hospitalized inSanglah General Hospital (SGH), Denpasar City, Bali Island. SGH is a third referral hospital in Bali Island and has a specialized heart center with cardiac surgery facility and catheterization laboratory.

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 werecompiled 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 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).

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 421NSTE-ACS patients were diagnosed during the study period; 300 (71.3%) among them were men. Patients' mean age was 59 $\pm$ 12.0 years, ranging from 19 to 90 years old. About 60% of patients were self-walk-in. Diagnoses were UAP in 260 (61.8%) and NSTEMI in 161 (38.2%) cases.Other clinical characteristics were presented in Table 1.Anticoagulanttherapy was given to 409 (97.1%) patients, consisting 96 (22.8%) unfractionated heparin (UFH), 177 (42.0%) fondaparinux, and 136 (32.3%) enoxaparin.Eight(1.9%) patients underwent

early PCI. Other treatments received were nitrate (89.1%), aspirin (99.0%), and clopidogrel (86.2%) or ticagrelor (7.8%).

The overall mortality rate of NSTE-ACS patients was 6.4%; it was higherin NSTEMI than UAP patients (13.0% vs. 2.3%; p<0.001; OR = 6.350; 95% CI = 2.504 – 16.101). Mortality was associated with older age, higher heart rate, lower blood pressures, higher serum creatinine levels, higher troponin T1 levels, higher GRACE, and CRUSADE scores. Patients with cardiac arrest, sign of heart failure, and GRACE risk score of >140 had increased risk of death (Table 2 and Table 3). TIMI risk score was only available in 161 (38.2%) cases;therefore, no further analysis was performed.

Mortality rate was 12.5% with unfractionated heparin therapy, 6.6% in patients treated with enoxaparin, and 2.3% in patients receiving fondaparinux. Patients with NSTEMI who were treated with UFH had increased risk of death compared with patients treated with low-molecular weight heparin (LMWH) (Table 4). In multivariate analyses, GRACE score of more than 140 was the only independent risk factor for in-hospital mortality. However, the use of fondaparinux as anticoagulant, which reached a borderline significance, could be an important protective factor of in-hospital death (Table 5).

Table 1. Characteristics of the study subjects (n=421)

Characteristics	Mean ± SD Median (Min-Max)	n	%
Male sex		300	71.3
Age (years)	59.0± 11.96		
History of acute myocardial infarction		85	20.2
History of acute myocardial infarction		85	20.2
History of previous PCI		44	10.5
History of peripheral vascular disease		2	0.5
History of coronary artery bypass grafting		1	0.2
History of hypercholesterolemia		61	14.5
History of premature CAD in family		7	1.7
History of heart failure		142	33.7
History of asthma or COPD		10	2.4
History of angina		126	29.9
History of cerebrovascular disease		20	4.8
Smoker		135	32.1
Diabetes mellitus		122	29.0
Hypertension		236	56.1
Sign of heart failure			
No sign		315	74.8
Rales in <1/3 field		82	19.5
Rales in >1/3 field		11	2.6
Cardiogenic shock		13	3.1
Cardiac arrest		6	1.4
Heart rate (bps)	83 ± 28.0		
Systolic blood pressure (mmHg)	130 ± 27.0		
Diastolic blood pressure (mmHg)	80± 15.6		
Creatinine serum (mg/dL)	1.9 ± 2.53		
CK-MB1	7.0 ± 21.78		
Troponin T1	188.9 ±356.29		
GRACE risk score (n=161)	117.7 ± 32.36		
Median TIMI score	3 (1-6)		
Median time since onset to hospital admission (hours)	7(0-193)		

Table 2. Clinical factors associated with mortality in NSTE-ACS patients (n=421)

Variable	Died (n=27)	Alive (n=394)	*p*	OR	95%CI
Gender					
Male	18 (6.0%)	282 (94.0%)	0.586*	0.794	0.347-1.821
Female	9 (7.4%)	112 (92.6%)			
Smoker					
Yes	7 (5.2%)	128 (94.8%)	0.480*	0.727	0.300-1.764
No	20 (7.0%)	266 (93.0%)			
Diabetes mellitus					
Yes	10 (8.2%)	112 (91.8%)	0.340*	1.481	0.658-3.333
No	17 (5.7%)	282 (94.3%)			
Hypertension					
Yes	10 (4.2%)	226 (95.8%)	0.040*	0.437	0.195-0.979
No	17 (9.2%)	168 (90.8%)			
Hypercholesterolemia					
Yes	2 (3.3%)	59 (96.7%)	0.400^	0.454	0.105-1.969
No	25 (6.9%)	335 (93.1%)			
History of CVD					
Yes	2 (10.0%)	18 (90.0%)	0.372^	1.671	0.367-7.610
No	25 (6.2%)	376 (93.8%)			
Cardiac arrest					
Yes	3 (50.0%)	3 (50.0%)	0.004^	16.292	3.121-85.045
No	20 (7.8%)	237 (92.2%)			
Sign of heart failure					
Yes	20 (18.9%)	86 (81.1%)	<0.001*	10.233	4.188-25.000
No	7 (2.2%)	308 (97.8%)			
GRACE risk score					
>140	12 (33.3%)	24 (66.7%)	<0.001^	6.444	2.444-16.993
≤140	9 (7.2%)	116 (92.8%)			
Anticoagulant					
UFH	12 (12.5%)	84 (87.5%)	0.003	3.297	1.450-7.493
Other	13 (4.2%)	300 (95.8%)			

*Chi-square test ^Fisher's exact test

Table 3. Clinical Factors Associated with Mortality in NSTE-ACS patients (n=421)

Variable	Died (n=25)	Alive(n=247)	*p**
Mean age (years)	64.5	58.6	0.013
Mean Heart rate (bps)	110.5	81.9	<0.001
Mean systolic blood pressure (mmHg)	119.3	131.5	0.023
Mean diastolic blood pressure (mmHg)	73.3	80.3	0.029
Mean serum creatinine level (mg/dL) (n=418)	3.5	1.8	<0.001
Mean CKMB1 level(ng/mL) (n=253)	13.6	6.5	0.106
Mean Troponin T1 level (ng/mL) (n=161)	470.7	168.4	<0.001
Mean GRACE risk score (n=161)	143.6	113.8	<0.001
Mean CRUSADE score (n=161)	58.3	40.2	<0.001

*Mann-Whitney U test

Table 4. Association between type of anticoagulant therapy and death (n=409)

Variable	Died(n=27)	Alive(n=394)	*p*	OR	95%CI
UAP (n=254)					
UFH	2(4.4%)	43 (95.6%)	0.288*	2.384	0.423-13.431
Other	4 (1.9%)	205(98.1%)			
NSTEMI (n=155)					
UFH	10 (19.6%)	41 (80.4%)	0.051^	2.575	0.974-6.806
Other	9 (8.7%)	95 (91.3%)			

*Fisher's exact test; ^Chi-square test

Table 5. Predictors of in-hospital mortality in NSTE-ACS patients (n=409)

Variable	b	SE	*p*	OR_{adj}	95% CI
GRACE score >140	1.665	0.506	0.002	4.892	1.816 – 13.177
Fondaparinuxanticoagulant	-1.860	1.058	0.079	0.156	0.020 – 1.239

SE: standard error of b coefficient

DISCUSSION

This is the first ACS registry in Bali reporting the outcome of NSTE-ACS patients in Sanglah General Hospital, Bali. Both European and American guidelines have been adopted in Indonesia for ACS management. Evaluation of registry data verifies the daily practice in real life and shows how recommendations are implemented into clinical practice.

Our data indicated that mortality rate of NSTE-ACS is higher(6.4%) than those reported by European registries, such as in PRAIS-UK (1.5%),[11] GRACE high risk NSTE-ACS (2.8%),[12] and EURO-Heart Survey ACS (2.4%).[13] In Thai 2007 ACS registry, the in-hospital mortality rate of NSTE-ACS was 9.5%;[14] however, a more recent single ACS registry found that in-hospital mortality was only 3.5%.[15]

Our data showed that older age (>60 years), higher heart rate, lower blood pressures, higher serum creatinine levels, higher troponin T1 levels, cardiac arrest, and heart failure were significantly associated with mortality in NSTE-ACS. These variables are components of GRACE risk score and thus, high GRACE score is a single risk factor for in-hospital mortality. Similar pattern was also observed in Thai ACS registry; the risk factors for in-hospital death were age ≥65 years (OR = 2.2; 95% CI = 1.54 – 3.09); shock at presentation (OR = 4.6; 95% CI = 2.91 – 7.32); heart failure (OR = 3.1; 95% CI = 2.15 – 4.38); positive cardiac marker (OR = 1.7; 95% CI = 1.18 – 2.53); arrhythmia (OR = 12.3; 95% CI = 8.71 – 17.35); major bleeding (OR = 2.9; 95% CI = 1.84 – 4.51), and cerebrovascular accident (OR = 4.9; 95% CI = 2.42 – 9.97).[14] Furthermore, in-hospital death was higher in NSTEMI than UAP patients; NSTEMI had more cardiac death than UA (7.6% vs. 2.4%; $p<0.001$).[16]

Other than GRACE risk score, we found that anticoagulant treatment has important role for patient's survival. Significantly more patient died when UFH was used as anticoagulant. Worldwide, UFH remains the most common used anticoagulant in NSTE-ACS patients.[17]Thai ACS registry also found higher mortality rate in patients receiving UFH than LMWH (9.3% vs. 5.2%; $p<0.001$).[16] Enoxaparin is the most widely used LMWH agent in NSTE-ACS. A meta-analysis comparing enoxaparin vs. UFH in ACS showeda slightly reduction of death or myocardial infarction at 30 days in favor of enoxaparin (10.0% vs. 11.0%; OR = 0.90;95% CI = 0.81 – 0.996); $p= 0.043$).[18] Mortality rate was lowest in patients receiving fondaparinux, a selective factor Xa inhibitor. Itwas reportedto have better reduction of major bleeding and long-term survival than enoxaparin.[19]

Latest meta-analyses conclude that fondaparinux is a better choice than enoxaparin to prevent short to midterm bleeding events, but mortality rate was similar with enoxaparin when use to patients with NSTEMI. [20]In this study, we did not assess major or minor bleeding events. However, there could be a selection bias when choosing the anticoagulant agent. We assess each patient's bleeding risk using the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of ACC/AHA [American College of Cardiology/ American Heart Association] Guidelines) score. Fondaparinux was given to only 9 (19.1%) patients with CRUSADE score >50, while enoxaparin was received by 21 (36.8%) and UFH was administered to 27 (52.9%) of patients with CRUSADE score >50 (data was not shown). Further study is needed to evaluate the practice use of anticoagulant agent in preventing bleeding events and mortality among NSTE-ACS patients.

CONCLUSION

Data from ACS registry are important to evaluate the overall quality of care given to ACS patients. Mortality of NSTE-ACS patients is still high (6.4%).Host factors, which are reflected by high GRACE score is significant risk factor of in-hospital death. The use of fondaparinux as anticoagulant agent may improve survival. Further studies are needed to confirm this finding.

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