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THE IN-HOSPITAL OUTCOME OF CARDIOGENIC SHOCK COMPLICATING ST-ELEVATION MYOCARDIAL INFARCTION IN MALAYSIA: AN OVERVIEW OF THE MALAYSIAN NATIONAL CARDIOVASCULAR DATABASE – ACUTE CORONARY SYNDROME REGISTRY YEAR 2006 TO 2013

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Long Title:

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Short title:

CARDIOGENIC SHOCK COMPLICATING ST-ELEVATION MYOCARDIAL INFARCTIONS IN MALAYSIAN PATIENTS

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Abstract

Objectives:

Cardiogenic shock (CS) complicating ST-elevation myocardial infarction (STEMI) carries an extremely high mortality. Its incidence and outcome in Malaysia has never been fully reported. The purpose of our study is to explore the extent of CS in our population.

Design:

Patients were identified from the Malaysian National Cardiovascular Disease – Acute Coronary Syndrome database registry (NCVD-ACS) from 2006 to 2013.

Participants:

16,517 STEMI patients

Primary Outcome Measures:

Relative mortality risk ratios and clinical predictors of in hospital mortality among CS patients.

Results:

CS complicated 10.6% of all STEMI. They had unfavorable premorbid conditions and poor outcomes. The in-hospital mortality rate was 34.1% with a risk ratio of 7.14. Intravenous thrombolysis remained as the main urgent reperfusion modality. Percutaneous coronary interventions (PCI) conferred a 40% risk reduction over non-invasive therapy but were done in only 33.6% of CS cases. Age over 65, diabetes mellitus, hypertension, chronic lung and kidney disease conferred higher risk of mortality.

Conclusion:

Mortality rates of CS complicating STEMI in Malaysia are high. In-hospital PCI confers a 40% mortality risk reduction but the rate of PCI among our patients with CS complicating STEMI is still low. Efforts are being made to increase access to invasive therapy for these patients.

Trial Registration Number: NMRR-07-20-250

Keywords: Cardiogenic shock; myocardial infarction; percutaneous coronary intervention; mortality; acute coronary syndrome

STRENGTHS AND LIMITATIONS

- To our knowledge, this is the first study in Malaysia to compare cardiogenic shock and non-cardiogenic shock patients using nationally representative data
- The analysis accounted for a multivariate adjustment and binary logistics regression in estimating the relative mortality risk ratios between the two groups.
- Efforts are being made to increase coverage of primary PCI through the development of a hub and spoke model for ST elevation myocardial.
- PCI in Malaysia is more costly than thrombolysis.
- There is insufficient data on intra-aortic balloon pump or assist devices in this registry.

INTRODUCTION

Cardiogenic shock (CS) is an important cause of death in acute ST elevation myocardial infarction (STEMI) (1-3). Despite the advancement in reperfusion therapy with invasive percutaneous coronary intervention (PCI), the mortality rate remains high. The in-hospital mortality rate even after successful PCI are reported to be as high as 40% (4-6). Although the incidence of CS complicating myocardial infarctions is only around 4% to 10% (1,7), it remains a big challenge in terms of clinical management.

Due to various limitations locally, the rate of coronary reperfusion with primary PCI in STEMI is only about 7% in Malaysia (8). Yet, the outcome of CS complicating myocardial infarctions in our population has never been fully described and no comparison ever made with other studies. Hence, we utilize data from the Malaysian National Cardiovascular Database – Acute coronary syndrome 2006 to 2013 (NCVD-ACS 2006 to 2013) to investigate the characteristics and outcome of CS complicating STEMIs in Malaysia.

METHODS:

Patient population

A total of 16,517 patients diagnosed with STEMI were identified from the Malaysian National Cardiovascular Database- Acute coronary syndrome (NCVD-ACS) from year 2006 to 2013. The NCVD is a national registry involving 18 hospitals nationally. It captures clinical data on all patients admitted with acute coronary syndromes. The Ministry of Health (MOH) Malaysia and the National Heart Association of Malaysia (NHAM) sponsor the registry. Data is collected upon admission and throughout the patient stay using a standardized case reporting form. A unique national identification number is given to each patient to avoid duplication. Parameters recorded include baseline characteristics and clinical presentation, in-hospital treatment, procedural details and clinical outcome.

STEMI is defined as a persistent ST-segment elevation of ≥1 mm in two contiguous electrocardiographic leads or the presence of a new left bundle branch block in the setting of positive cardiac markers and/or typical cardiac pain. Patients were divided into 2 groups based on their Killip class on presentation. Those in Killip class IV were grouped under 'cardiogenic shock' (n=1753) while those in Killip class I, II and III were grouped under 'non-cardiogenic shock' (n=14764). The 2 groups were compared in terms of clinical characteristics, in-hospital invasive treatment, pharmacotherapy and all cause in-hospital mortality. A cross check with the national death registry was also done to verify the patients' mortality status.

The results of the study will be made public in National Heart Association of Malaysia website through the National Cardiovascular Disease Database (NCVD) annual

reports in interest for the view of the participants. In this study we use retrospective cohort studies looking at data that has already been existing.

Definition of Killip class

Killip class IV is defined as the presence of hypotension with a systolic BP lower than 90mmHg and evidence of peripheral vasoconstriction. Below are the definitions of the other Killip classes:

Killip I: No clinical signs of heart failure,

Killip II: Presence of rales or crepitation in the lungs bases only or a third heart sound (S3),

Killip III: Presence of frank acute pulmonary oedema

Killip IV: Cardiogenic shock or hypotension (measured as systolic blood pressure < 90 mmHg), and evidence of peripheral vasoconstriction

Statictical analysis

Categorical variables were described as numbers and percentages. The differences were analysed by chi-square test or Fisher exact test. Continuous variables were expressed as median and differences were analysed using t-test. To avert biases in the estimates and loss of power, missing data for explanatory variables were assumed to be missing at random. A generalized linear model with a log link, binomial distribution, and a robust variance estimator was used to estimate the risk ratios. The risk ratios represent the relative risk for mortality of the non-cardiogenic shock group compared to the cardiogenic shock group. Subsequently, risk ratios of CS patients with PCI done and without PCI were also compared. Variables that were statistically significantly different (a 2-sided P value of less than 0.05) between the CS and non-CS patients, that were of clinical importance, and that had sufficient outcomes in the respective subcategories were adjusted for. Finally, binary logistics regression was executed to determine the independent predictor of in-hospital mortality

among CS patients. All analyses were conducted using SPSS statistical software (version 21, IBM SPSS Statistics, USA).

RESULTS:

Table I illustrates the comparison in baseline characteristics between the CS and non-CS group. Demographically, the CS group contained more patients over the age of 65 (28.6% Vs 22.6% P<0.001). Females and Malay ethnic groups were also seen to be significantly more prevalent in the cardiogenic shock group. In terms of cardiovascular risk factors, they had higher rate of diabetes and hypertension but unexpectedly lower rate of smoking, hyperlipidaemia and premature family history. Other related premorbid conditions were unfavourable to the CS group where they had higher rate of previous MI, cerebrovascular, peripheral vascular, chronic kidney and chronic lung diseases.

Table II compares the revascularisation treatment between the 2 groups. Intravenous thrombolysis remained the main emergency reperfusion therapy for both CS and non-CS patients. Although there was no significant difference of symptom to door times between the 2 groups, the door to needle time was significantly shorter for CS patients (45 minutes vs. 60 minutes P <0.001). The difference in the rate of primary PCIs between the 2 groups was small (11.7% CS vs. 10.0% non-CS). Total rate of in-hospital PCIs (inclusive of primary PCIs) was however significantly higher in CS patients (33.6% vs. 29.5% P=0.001). Table III shows the administrative rate of evidence-based pharmacotherapy during the admission, which favoured the non-CS patients across all class of medications especially antihypertensives.

Table IV compares the all cause in-hospital mortality rate between patients with CS and non-CS. The mortality rate was different between the 2 groups (34.1% CS vs. 5.6% non-CS, P value <0.001) After multivariate adjustment of confounding factors, we found that the CS group had 7.14 times higher mortality risk compared to the non-CS group.

Mortality data was obtained from official records from the National Registration Department of Malaysia and cross-referenced to patients, however we were unable to get information for 29 patients (0.017%) in the CS group for undetermined reasons. Table V sub-analyses the in-hospital mortality rates among CS patients. Those who had PCI done during the admission had a lower rate of in-hospital mortality (27.0% vs. 38.9%) compared to those who did not. Adjusted mortality risk ratio showed that there was a 40% mortality risk reduction in those with PCI done.

Table VI shows univariate analysis of clinical variables related to mortality in the CS group. All variables that were statistically significant from this table were then grouped into a multivariate logistic regression to determine the independent predictors of in-hospital mortality within the CS group. The result of the multivariate logistic regression is tabulated in Table VII. We found that the presence of hypertension, diabetes mellitus, chronic lung and kidney diseases, and age of over 65 carried statistically significantly higher mortality risks and hence they seem to be independent predictors of in-hospital mortality. Table VIII shows the length of stay between the two groups. Patients with CS have significantly longer duration of inpatient stay compared to non-CS.

DISCUSSION:

Cardiogenic shock (CS) is a clinical state where cardiac dysfunction results in inadequate tissue perfusion. CS is characterised by a state of haemodynamic insufficiency that may involve hypotension (systolic blood pressure <90 mmHg), significant decrease in mean arterial pressure (MAP) from baseline, and reduced cardiac index. CS can be multifactorial but most commonly occurs secondary to myocardial infarction (MI).

CS complicating a myocardial infarction more commonly occurs in ST elevation myocardial infarctions compared to non-ST elevation myocardial infarctions and is a predictor of poor prognosis. Data from our NCVD registry showed in-hospital mortality rates of 34.1%. This figure is lower than other MI registries and trials such as the SHOCK trial, which reported in hospital mortality rates of at least 48%. Reasons for the lower figures are unclear, but may be contributed to by a common practice of early hospital discharging of STEMI patients, which may not capture data on patients who died at home early after discharge that would be reflected in 30-day outcomes if this data was available.

Preexisting conditions including hypertension, diabetes mellitus, chronic kidney and lung disease conferred a higher risk of death in our patients, which may reflect poor pre-hospital reserve that is ill prepared to cope with a major stressor such as cardiogenic shock. Increasing age was also a predictor of mortality in our cohort with adults over 65 years of age

more than twice more likely to die in hospital if they had CS complicating a STEMI. Age was also found in another study to be the parameter most strongly associated with developing cardiogenic shock after a myocardial infarction with every 10-year increase in age the risk of developing shock was greater by 47%(11). We observed an interesting finding of significantly lower rates of smoking, family history and dyslipidaemia in the CS group. It is not clear whether this represents under-reporting or under-diagnosis of risk factors or these are paradoxical risk factors for developing CS in STEMI in our population. Nonetheless, further studies would be appropriate to investigate this further, perhaps with future data from NCVD.

Data shows that cardiogenic shock patients in the setting of acute myocardial infarction who were treated non-invasively had poorer outcome and primary PCI is superior to thrombolytic therapy (9-13). Similar to other registries and studies, our data showed improved survival for patients who underwent in-hospital PCI including primary PCI (12). The adjusted risk of death was reduced by 40% for patients who received PCI during the index admission compared to those who did not. Intravenous thrombolysis remains the most frequent mode of achieving reperfusion in Malaysia due to several factors. PCI in Malaysia is more costly than thrombolysis and primary or urgent PCI services are limited to patients presenting to one of several PCI centres or their network hospitals, which explains why around only 10% of patients received primary PCI. Nonetheless, in the SHOCK trial, thrombolysis was superior to medical therapy only and is recommended in many guidelines as a reperfusion strategy when PCI is not possible or delayed, particularly when patients present within 3 hours of symptoms (14). We did not have any data on intra-aortic balloon pump or assist devices in our patients in this registry. Our data showed a shorter door to needle time in patients presenting with CS compared to non-CS. We postulate several factors

- CS patients would be appear more ill during initial assessment and the presence of hypotension would likely push for more urgent and swift diagnostic and management steps. In our personal experience, patients with non-CS STEMI may also present in atypical ways that may delay or make assessment less urgent, hence explain the longer door to needle time. Ideally we would have included the door to balloon data for comparison, however that data is contained in a separate registry called the NCVD-PCI registry, which we did not have access to.

Efforts are being made to increase coverage of primary PCI through the development of a hub and spoke model for ST elevation myocardial infarctions called the MySTEMI Network. Non-PCI centres (hub) are paired with a PCI capable centre (spoke) whereby patients presenting to a non-PCI hospital with a STEMI are transferred to a PCI centre for primary PCI (15). We hope that with the rolling out of this MySTEMI Network nationally, we are able to offer PCI as the main reperfusion modality for STEMI patients. Efforts are also being made to improve prescribing rates of evidence-based therapy through clinical audits and CME sessions. There was a low rate of antiplatelet prescription particularly in the CS group, which has been noted in other local studies (8,16). Although the exact reasons to explain the low prescription rates in our population were not detailed in the NCVD registry, one factor could be the increased bleeding rates in patients with CS (17). We recognise that although our findings are based on the NCVD data, these may not be truly representative of the current situation. The current NCVD is incomplete as there are still several hospitals that are not yet fully contributing towards NCVD data; efforts are however being taken to improve this. Increased reporting will only improve the accuracy of future studies and allow better allocation of resources in improving outcomes.

CONCLUSION:

CS complicated STEMI in about 10.6% of our patients. The in-hospital mortality was high (34.1%) and invasive coronary revascularisation lowered the mortality rate substantially. Similar to other studies, multiple comorbidities including increased age were predictors of poor prognosis. Greater effort is needed to improve outcomes and increased effort is being made to improve the rate of primary and in-hospital PCI.

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CONTRIBUTORS

PV contributed in the writing of the manuscript and analyzing the data. YZZ, WAWA, MIAH, MFH contributed in the interpretation of the analysis. MDI and PV designed the study. ASMZ conceived the original idea of the study.

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This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS

None declared.

PATIENT CONSENT

Not required.

ETHICS APPROVAL

The NCVD registry study was approved by the Medical Review & Ethics Committee (MREC), Ministry Of Health (MOH) Malaysia in 2007 (Approval Code: NMRR-07-20-250). MREC waived informed consent for NCVD.

DATA SHARING STATEMENT

The data sets used for the current study are publicly available at https://figshare.com/s/25dfa5f2021730d78a0d

PROVENANCE AND PEER REVIEW

Not commissioned; externally reviewed.

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Table I: Baseline Characteristics of Patients with ST-Elevation Myocardial Infarction

	CS (Killip IV) (n= 1753)	Non-CS (Killip I to III) (n=14764)	P – value
Age:			
64 years or less	1214 (71.4%)	11141 (77.4%)	<0.001
>65	486 (28.6%)	3252 (22.6%)	
Gender			
Male	1455 (83.0%)	12687 (85.9%)	0.001
Female	298 (17.0%)	2077 (14.1%)	
Ethnicity			
Malay	1113 (63.5%)	8631 (58.5%)	
Chinese	285 (16.3%)	2632 (17.8%)	0.001
Indian	247 (14.1%)	2466 (16.7%)	
Others	108 (6.2%)	1035 (7.0%)	
Risk Factors			
Smoking (active/ex)	1109 (67.4%)	10020 (70.0%)	0.028
Diabetes	732 (51.3%)	5257 (42.3%)	<0.001
Hypertension	891 (61.3%)	7270 (57.2%)	0.002
Hyperlipidaemia	372 (32.1%)	3754 (35.3%)	0.030
Family history	158 (9.0%)	1658 (11.2%)	<0.001
Premorbids			
Cerebrovascular	49 (3.4%)	386 (3.1%)	0.422

Previous MI	208 (15.1%)	1553 (12.6%)	0.009
Peripheral vascular disease	10 (0.7%)	35 (0.3%)	0.007
Chronic kidney disease	100 (7.1%)	461 (3.7%)	<0.001
Chronic lung disease	58 (4.1%)	285 (2.3%)	<0.001
Myocardial infarct type			
Inferior infarct	732 (41.8%)	5310 (36.0%)	<0.001
Anterior infarct	743 (42.4%)	6772 (45.9%)	0.001

MI=Myocardial Infarction, CS = Cardiogenic Shock, Non-CS = Non-Cardiogenic Shock

Table II: Coronary reperfusion and revascularisation therapy in STEMI patients who have CS and do not have CS.

	CS STEMI	Non-CS STEMI	p-value
Thrombolysis			
Given	1216 (71.4%)	10885 (75.2%)	
Not given – proceeded to primary angioplasty	199 (11.7%)	1451 (10.0%)	<0.001
Not given – missed	129 (7.6%)	1690 (11.7%)	
Not given – patient refusal	4 (0.2%)	49 (0.3%)	
Not given – contraindicated	156(9.2%)	391 (2.7%)	
In-Hospital PCI*	537 (33.6%)	4083 (29.5%)	0.001
Door to needle time for thrombolysis (minutes)	45.0	60.0	<0.001
Symptom to door time (minutes)	249.98 +/- 224.74	239.34 +/- 215.37	0.074

PCI= percutaneous coronary intervention, CS=Cardiogenic Shock, STEMI=ST Elevation Myocardial Infarction. In-Hospital PCI= Defined as PCI done during index admission that was not Primary Angioplasty – includes rescue PCI, pharmacoinvasive PCI and early routine PCI.*

Table III: In hospital pharmacotherapy

Medications	CS STEMI (n= 1753)	Non-CS STEMI (n= 14764)	p-value
Aspirin	1024 (75.7%)	12470 (93.3%)	<0.001
ADP-antagonist	632 (67.8%)	8346 (81.4%)	<0.001
ACE-I/ARB	529 (30.3%)	8128 (55.8%)	<0.001
Beta Blocker	659 (51.1%)	9185 (71.5%)	<0.001
Statin	957 (70.9%)	12024 (90.5%)	<0.001

ADP= Adenosine diphosphate, ACE-I=angiotensin converting enzyme inhibitor, ARB= Angiotensin Receptor Blocker, CS=Cardiogenic Shock, STEMI=ST Elevation Myocardial Infarction

Table IV: In-hospital and 30-day mortality rates.

	No of patients	Death (%)	Unadjusted risk ratio	Adjusted risk ratio	P-value
In-hospital					

mortality:					
CS	1753	598 (34.1%)	6.827 (6.104, 7.954)	7.143 (6.365, 8.017)	<0.001
Non-CS	14764	821 (5.6%)	1	1	
30-day mortality:					
CS	1753	634 (36.2%)	7.587 (7.002, 9.552)	8.863 (7.848, 10.009)	<0.001
Non-CS	14764	1085 (7.3%)	1	1	

CS=Cardiogenic Shock, STEMI=ST Elevation Myocardial

Table V: Comparison of Mortality Rates between Cardiogenic Shock with or without PCI

In Hospital mortality	No. of patients	Death (%)	Unadjusted risk ratio	Adjusted risk ratio	P values
PCI done	537	145 (27%)	0.535 (0.428, 0.670)	0.600 (0.513,0.700)	P<0.001
PCI not done	1063	414 (38.9%)	1	1	

PCI= percutaneous coronary intervention

Table VI: Comparison of Clinical Factors Between Survivors and Non-survivors of Cardiogenic Shock.

	Survivors (n=1126)	Non-survivors (n=598)	P value
Age >65	226 (20.8%)	253 (43.1%)	<0.001
Diabetes	429 (47.5%)	295 (58.2%)	<0.001
Hypertension	520 (56.5%)	361 (70.4%)	<0.001
Smoking status Active/Ex Smokers Non Smokers	 607 (67.0%) 299 (33.0%)	 219 (48.6%) 232 (51.4%)	 <0.001
Dyslipidaemia	224 (30.3%)	143 (35.3%)	0.083
Previous MI	126 (14.0%)	82 (17.8%)	0.061
Chronic Lung Disease	25 (2.7%)	32 (6.6%)	0.001
Cerebrovascular Disease	27 (2.9%)	21 (4.4%)	0.161
Peripheral Vascular Disease	8 (0.9%)	2 (0.4%)	0.337
Chronic Renal Disease	46 (5.0%)	54 (11.2%)	<0.001

PCI=percutaneous coronary intervention, MI=myocardial infarction

Table VII: Logistic Regression of Predictors for In-Hospital Mortality in Cardiogenic Shock.

	P Values	Risk Ratios	95% C.I.for EXP(B) Lower	Upper
Age >65	**0.000**	**2.470****	**2.073**	**2.944**
Dyslipidaemia	0.040	0.828	.691	.992
Hypertension	**0.000**	**1.427****	**1.180**	**1.726**
Diabetes Mellitus	**0.000**	**1.600****	**1.343**	**1.907**
Smoking status	0.000	0.675	.567	.804
Previous MI	0.175	1.177	.930	1.490
Chronic Lung Disease	**0.032**	**1.744****	**1.048**	**2.903**
Chronic Renal Disease	**0.000**	**2.853****	**2.079**	**3.915**
Cerebrovascular disease	0.922	1.023	.648	1.615
Peripheral vascular disease	0.256	0.410	.088	1.909
Constant	0.000	0.052		

** statistically significant predictors of mortality , *MI=myocardial infarction*

Table VIII: Length of Stay of CS vs non-CS Patients

Total day stay	Cardiogenic shock	Non-cardiogenic shock	p-value
Mean	8.17 (7.53, 8.82)	5.21 (5.12, 5.29)	
Standard deviation	11.561	5.102	0.014

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The in-hospital mortality of cardiogenic shock complicating ST-elevation myocardial infarction in Malaysia: A retrospective analysis of the Malaysian National Cardiovascular Database (NCVD) registry.

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Cardiogenic shock complicating ST-elevation myocardial infarction in Malaysia

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Abstract

Objectives:

Cardiogenic shock (CS) complicating ST-elevation myocardial infarction (STEMI) carries an extremely high mortality. The clinical pattern of this life threatening complication has never been described in Malaysian setting. This study is to investigate the incidence, clinical characteristics and outcome of STEMI patients with CS in our population

Design:

A retrospective analysis of STEMI patients from 18 hospitals across Malaysia contributing to the Malaysian National Cardiovascular Database (Acute coronary syndrome) registry (NCVD-ACS) year 2006 to 2013

Participants:

16,517 patients diagnosed of STEMI from 18 hospitals in Malaysia from the year 2006 to 2013.

Primary Outcome Measures:

In-hospital and 30-day post discharge mortality

Results:

CS complicates 10.6% of all STEMIs in this study. They had unfavorable premorbid conditions and poor outcomes. The in-hospital mortality rate was 34.1% which translates into a 7.14 times mortality risk increment compared to STEMI without cardiogenic shock. Intravenous thrombolysis remained as the main urgent reperfusion modality. Percutaneous

coronary interventions (PCI) in CS conferred a 40% risk reduction over non-invasive therapy but were only done in 33.6% of cases. Age over 65, diabetes mellitus, hypertension, chronic lung and kidney disease conferred higher risk of mortality.

Conclusion:

Mortality rates of CS complicating STEMI in Malaysia are high. In-hospital PCI confers a 40% mortality risk reduction but the rate of PCI among our patients with CS complicating STEMI is still low. Efforts are being made to increase access to invasive therapy for these patients.

Keywords: Cardiogenic shock; myocardial infarction; percutaneous coronary intervention; mortality; acute coronary syndrome

STRENGTHS AND LIMITATIONS

- To our knowledge, this is the first study to describe the outcome of cardiogenic shock complicating STEMI in Malaysia
- The analysis was done on a large data consisting 16517 patients from 18 hospitals across Malaysia. Hence it is so far the most representative of Malaysian population in general.
- Patients were from multi-racial background representing the major racial groups in Asia ie Chinese, Indian and Malay
- Confounding factors and inter-centre variations in terms of treatment and outcome from this retrospective study cannot be eliminated

- This study focuses on in-hospital mortality only. The long term outcome was not analyzed due to insufficient follow up data

INTRODUCTION

Cardiogenic shock (CS) is an important cause of death in acute ST elevation myocardial infarction (STEMI) (1-3). Left ventricular dysfunction is the most common underlying aetiology in cardiogenic shock accounting for about 74.5% of cases (4,5). There is correlation with the severity of coronary artery disease whereby CS is strongly associated with triple vessel or left main stem coronary involvement (6)

Despite the advancement in reperfusion therapy with invasive percutaneous coronary intervention (PCI), the mortality rate remains high. The in-hospital mortality rate even after successful PCI is reported to be as high as 40% (7-9). Although the incidence of CS complicating myocardial infarctions is only around 4% to 10% (1,10), it remains a big challenge in terms of clinical management.

Due to various limitations locally, the rate of coronary reperfusion with primary PCI in STEMI is only about 7% in Malaysia (11). Given the restriction in delivering the preferred revascularization therapy (primary PCI), the outcome of CS complicating myocardial infarctions in our population has yet been fully described and no comparison ever made with other studies. Hence, we utilize data from the Malaysian National Cardiovascular Database – Acute coronary syndrome 2006 to 2013 (NCVD-ACS 2006 to 2013) to investigate the characteristics and outcome of CS complicating STEMIs in Malaysia.

METHODS:

Patient population

A total of 16,517 patients diagnosed with STEMI were identified from the Malaysian National Cardiovascular Database- Acute coronary syndrome (NCVD-ACS) from year 2006 to 2013. The NCVD is a national registry involving 18 hospitals nationally. It captures clinical data on all patients admitted with acute coronary syndromes. The Ministry of Health (MOH) Malaysia and the National Heart Association of Malaysia (NHAM) sponsor the registry. Data is collected upon admission and throughout the patient stay using a standardized case reporting form. A unique national identification number is given to each patient to avoid duplication. Parameters recorded include baseline characteristics and clinical presentation, in-hospital treatment, procedural details and clinical outcome.

STEMI is defined as a persistent ST-segment elevation of ≥1 mm in two contiguous electrocardiographic leads or the presence of a new left bundle branch block in the setting of positive cardiac markers and/or typical cardiac pain. Patients were divided into 2 groups based on their Killip class on presentation. Those in Killip class IV were grouped under 'cardiogenic shock' (n=1753) while those in Killip class I, II and III were grouped under 'non-cardiogenic shock' (n=14764). The 2 groups were compared in terms of clinical characteristics, in-hospital invasive treatment, pharmacotherapy and all cause in-hospital mortality. A cross check with the national death registry was also done to verify the patients' mortality status.

The results of the study will be made public in National Heart Association of Malaysia website through the National Cardiovascular Disease Database (NCVD) annual

reports in interest for the view of the participants. In this study we use retrospective cohort studies looking at data that has already been existing.

Definition of Killip class

Killip class IV is defined as the presence of hypotension with a systolic BP lower than 90mmHg and evidence of peripheral vasoconstriction. Below are the definitions of the other Killip classes:

Killip I: No clinical signs of heart failure,

Killip II: Presence of rales or crepitation in the lungs bases only or a third heart sound (S3),

Killip III: Presence of frank acute pulmonary oedema

Killip IV: Cardiogenic shock or hypotension (measured as systolic blood pressure < 90 mmHg), and evidence of peripheral vasoconstriction

Statictical analysis

Categorical variables were described as numbers and percentages. The differences were analysed by chi-square test or Fisher exact test. Continuous variables were expressed as median and differences were analysed using t-test. To avert biases in the estimates and loss of power, missing data for explanatory variables were assumed to be missing at random. A generalized linear model with a log link, binomial distribution, and a robust variance estimator was used to estimate the risk ratios. The risk ratios represent the relative risk for mortality of the non-cardiogenic shock group compared to the cardiogenic shock group. Subsequently, risk ratios of CS patients with PCI done and without PCI were also compared. Variables that were statistically significantly different (a 2-sided P value of less than 0.05) between the CS and non-CS patients, that were of clinical importance, and that had sufficient outcomes in the respective subcategories were adjusted for. Finally, binary logistics regression was executed to determine the independent predictors of in-hospital mortality

among CS patients. All analyses were conducted using SPSS statistical software (version 21, IBM SPSS Statistics, USA).

Patient and public involvement

There is no patient or public involvement in the development of this study's research question and outcome. All data was obtained retrospectively from the Malaysian National Cardiovascular Database Registry – Acute Coronary Syndrome (NCVD-ACS).

RESULTS:

Table I illustrates the comparison in baseline characteristics between the CS and non-CS group. A total of 1753 out of 16517 patients (10.6%) presented with CS. Demographically, the CS group contained more patients over the age of 65 (28.6% Vs 22.6% P<0.001). Females and Malay ethnic groups were also seen to be significantly more prevalent in the cardiogenic shock group. In terms of cardiovascular risk factors, they had higher rate of diabetes and hypertension but unexpectedly lower rate of smoking, hyperlipidaemia and premature family history. Other related premorbid conditions were unfavourable to the CS group where they had higher rate of previous MI, cerebrovascular, peripheral vascular, chronic kidney and chronic lung diseases.

Table II compares the revascularisation treatment between the 2 groups. Intravenous thrombolysis remained the main emergency reperfusion therapy for both CS and non-CS patients. Although there was no significant difference of symptom to door times between the 2 groups, the door to needle time was significantly shorter for CS patients (45 minutes vs. 60 minutes P <0.001). The difference in the rate of primary PCIs between the 2 groups was small (11.7% CS vs. 10.0% non-CS). Total rate of in-hospital PCIs (inclusive of primary PCIs) was however significantly higher in CS patients (33.6% vs. 29.5% P=0.001). Table III

shows the administrative rate of evidence-based pharmacotherapy during the admission, which favoured the non-CS patients across all class of medications especially antihypertensives.

Table IV compares the all cause in-hospital mortality rate between patients with CS and non-CS. The mortality rate was different between the 2 groups (34.1% CS vs. 5.6% non-CS, P value <0.001) After multivariate adjustment of confounding factors, we found that the CS group had 7.14 times higher mortality risk compared to the non-CS group.

Mortality data was obtained from official records from the National Registration Department of Malaysia and cross-referenced to patients, however we were unable to get information for 29 patients (0.017%) in the CS group for undetermined reasons. Table V sub-analyses the in-hospital mortality rates among CS patients. Those who had PCI done during the admission had a lower rate of in-hospital mortality (27.0% vs. 38.9%) compared to those who did not. Adjusted mortality risk ratio showed that there was a 40% mortality risk reduction in those with PCI done.

Table VI shows univariate analysis of clinical variables related to mortality in the CS group. All variables that were statistically significant from this table were then grouped into a multivariate logistic regression to determine the independent predictors of in-hospital mortality within the CS group. The result of the multivariate logistic regression is tabulated in Table VII. We found that the presence of hypertension, diabetes mellitus, chronic lung and kidney diseases, and age of over 65 carried statistically significantly higher mortality risks and hence they seem to be independent predictors of in-hospital mortality. Table VIII shows

the length of stay between the two groups. Patients with CS have significantly longer duration of inpatient stay compared to non-CS.

DISCUSSION:

Cardiogenic shock (CS) is a clinical state where cardiac dysfunction results in inadequate tissue perfusion. CS is characterised by a state of haemodynamic insufficiency that may involve hypotension (systolic blood pressure <90 mmHg), significant decrease in mean arterial pressure (MAP) from baseline, and reduced cardiac index. CS can be multifactorial but most commonly occurs secondary to myocardial infarction (MI).

CS complicating a myocardial infarction more commonly occurs in ST elevation myocardial infarctions compared to non-ST elevation myocardial infarctions and is a predictor of poor prognosis. Data from our NCVD registry showed in-hospital mortality rates of 34.1%. This figure is lower than other MI registries and trials such as the SHOCK trial, which reported in hospital mortality rates of at least 48%. Reasons for the lower figures are unclear, but may be contributed to by a common practice of early hospital discharging of STEMI patients, which may not capture data on patients who died at home early after discharge that would be reflected in 30-day outcomes if this data was available.

Preexisting conditions including hypertension, diabetes mellitus, chronic kidney and lung disease conferred a higher risk of death in our patients, which may reflect poor pre-hospital reserve that is ill prepared to cope with a major stressor such as cardiogenic shock. Increasing age was also a predictor of mortality in our cohort with adults over 65 years of age more than twice more likely to die in hospital if they had CS complicating a STEMI. Age was

also found in another study to be the parameter most strongly associated with developing cardiogenic shock after a myocardial infarction with every 10-year increase in age the risk of developing shock was greater by 47%(12). We observed an interesting finding of significantly lower rates of smoking, family history and dyslipidaemia in the CS group. It is not clear whether this represents under-reporting or under-diagnosis of risk factors or these are paradoxical risk factors for developing CS in STEMI in our population. Nonetheless, further studies would be appropriate to investigate this further, perhaps with future data from NCVD.

Data shows that cardiogenic shock patients in the setting of acute myocardial infarction who were treated non-invasively had poorer outcome and primary PCI is superior to thrombolytic therapy (12-16). Similar to other registries and studies, our data showed improved survival for patients who underwent in-hospital PCI including primary PCI (12). The adjusted risk of death was reduced by 40% for patients who received PCI during the index admission compared to those who did not. Intravenous thrombolysis remains the most frequent mode of achieving reperfusion in Malaysia due to several factors. PCI in Malaysia is more costly than thrombolysis and primary or urgent PCI services are limited to patients presenting to one of several PCI centres or their network hospitals, which explains why around only 10% of patients received primary PCI. Nonetheless, in the SHOCK trial, thrombolysis was superior to medical therapy only and is recommended in many guidelines as a reperfusion strategy when PCI is not possible or delayed, particularly when patients present within 3 hours of symptoms (17). We did not have any data on intra-aortic balloon pump or assist devices in our patients in this registry. Our data showed a shorter door to needle time in patients presenting with CS compared to non-CS. We postulate several factors - CS patients would be appear more ill during initial assessment and the presence of

hypotension would likely push for more urgent and swift diagnostic and management steps. In our personal experience, patients with non-CS STEMI may also present in atypical ways that may delay or make assessment less urgent, hence explain the longer door to needle time. Ideally we would have included the door to balloon data for comparison, however that data is contained in a separate registry called the NCVD-PCI registry, which we did not have access to.

Efforts are being made to increase coverage of primary PCI through the development of a hub and spoke model for ST elevation myocardial infarctions called the MySTEMI Network. Non-PCI centres (hub) are paired with a PCI capable centre (spoke) whereby patients presenting to a non-PCI hospital with a STEMI are transferred to a PCI centre for primary PCI (18). We hope that with the rolling out of this MySTEMI Network nationally, we are able to offer PCI as the main reperfusion modality for STEMI patients. Efforts are also being made to improve prescribing rates of evidence-based therapy through clinical audits and CME sessions. There was a low rate of antiplatelet prescription particularly in the CS group, which has been noted in other local studies (11,19). Although the exact reasons to explain the low prescription rates in our population were not detailed in the NCVD registry, one factor could be the increased bleeding rates in patients with CS (20). We recognise that although our findings are based on the NCVD data, these may not be truly representative of the current situation. The current NCVD is incomplete as there are still several hospitals that are not yet fully contributing towards NCVD data; efforts are however being taken to improve this. Increased reporting will only improve the accuracy of future studies and allow better allocation of resources in improving outcomes.

CONCLUSION:

CS complicated STEMI in about 10.6% of our patients. The in-hospital mortality was high (34.1%) and invasive coronary revascularisation lowered the mortality rate substantially. Similar to other studies, multiple comorbidities including increased age were predictors of poor prognosis. Greater effort is needed to improve outcomes and increased effort is being made to improve the rate of primary and in-hospital PCI.

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CONTRIBUTORS

Original idea of the study originated from ASMZ. PV, YZZ and ASMZ designed the study. WAWA, MIAH, MFH and MDI wrote the initial draft of the manuscript. PV, MIAH, MFH, YZZ, WAWA and MDI analysed the data and revised the manuscript. All authors interpreted the data analysis and scrutinized the final manuscript.

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COMPETING INTERESTS

None declared.

PATIENT CONSENT

Not required.

ETHICS APPROVAL

The NCVD registry study was approved by the Medical Review & Ethics Committee (MREC), Ministry Of Health (MOH) Malaysia in 2007 (Approval Code: NMRR-07-20-250). MREC waived informed consent for NCVD.

DATA AVAILABILITY STATEMENT

No data are available

PROVENANCE AND PEER REVIEW

Not commissioned; externally reviewed.

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TABLES

Table I: Baseline Characteristics of Patients with ST-Elevation Myocardial Infarction

	CS (Killip IV) (n= 1753)	Non-CS (Killip I to III) (n=14764)	P – value
Age: 64 years or less >65	 1214 (71.4%) 486 (28.6%)	 11141 (77.4%) 3252 (22.6%)	 <0.001
Gender Male Female	 1455 (83.0%) 298 (17.0%)	 12687 (85.9%) 2077 (14.1%)	 0.001
Ethnicity Malay Chinese Indian Others	 1113 (63.5%) 285 (16.3%) 247 (14.1%) 108 (6.2%)	 8631 (58.5%) 2632 (17.8%) 2466 (16.7%) 1035 (7.0%)	 0.001
Risk Factors Smoking (active/ex) Diabetes Hypertension Hyperlipidaemia Family history	 1109 (67.4%) 732 (51.3%) 891 (61.3%) 372 (32.1%) 158 (9.0%)	 10020 (70.0%) 5257 (42.3%) 7270 (57.2%) 3754 (35.3%) 1658 (11.2%)	 0.028 <0.001 0.002 0.030 <0.001
Premorbids Cerebrovascular Previous MI Peripheral vascular disease	 49 (3.4%) 208 (15.1%) 10 (0.7%)	 386 (3.1%) 1553 (12.6%) 35 (0.3%)	 0.422 0.009 0.007

Chronic kidney disease	100 (7.1%)	461 (3.7%)	<0.001
Chronic lung disease	58 (4.1%)	285 (2.3%)	<0.001
Myocardial infarct type			
Inferior infarct	732 (41.8%)	5310 (36.0%)	<0.001
Anterior infarct	743 (42.4%)	6772 (45.9%)	0.001
Left ventricular ejection fraction (LVEF) mean +/- SD	38.7 +/- 12.2	46.1 +/- 11.1	0.025

MI=Myocardial Infarction, CS = Cardiogenic Shock, Non-CS = Non-Cardiogenic Shock

Table II: Coronary reperfusion and revascularisation therapy in STEMI patients who have CS and do not have CS.

	CS STEMI	Non-CS STEMI	p-value
Thrombolysis			
Given	1216 (71.4%)	10885 (75.2%)	
Not given – proceeded to primary angioplasty	199 (11.7%)	1451 (10.0%)	<0.001
Not given – missed	129 (7.6%)	1690 (11.7%)	
Not given – patient refusal	4 (0.2%)	49 (0.3%)	
Not given – contraindicated	156(9.2%)	391 (2.7%)	
In-Hospital PCI*	537 (33.6%)	4083 (29.5%)	0.001
Door to needle time for thrombolysis (minutes)	45.0	60.0	<0.001
Symptom to door time (minutes)	249.98 +/- 224.74	239.34 +/- 215.37	0.074

PCI= percutaneous coronary intervention, CS=Cardiogenic Shock, STEMI=ST Elevation Myocardial Infarction. In-Hospital PCI= Defined as PCI done during index admission that was not Primary Angioplasty – includes rescue PCI, pharmacoinvasive PCI and early routine PCI.*

Table III: In hospital pharmacotherapy

Medications	CS STEMI (n= 1753)	Non-CS STEMI (n= 14764)	p-value
Aspirin	1024 (75.7%)	12470 (93.3%)	<0.001
ADP-antagonist	632 (67.8%)	8346 (81.4%)	<0.001
ACE-I/ARB	529 (30.3%)	8128 (55.8%)	<0.001
Beta Blocker	659 (51.1%)	9185 (71.5%)	<0.001
Statin	957 (70.9%)	12024 (90.5%)	<0.001

ADP= Adenosine diphosphate, ACE-I=angiotensin converting enzyme inhibitor, ARB= Angiotensin Receptor Blocker, CS=Cardiogenic Shock, STEMI=ST Elevation Myocardial Infarction

Table IV: In-hospital and 30-day mortality rates.

	No of patients	Death (%)	Unadjusted risk ratio	Adjusted risk ratio	P-value
In-hospital mortality:					
CS	1753	598 (34.1%)	6.827 (6.104, 7.954)	7.143 (6.365, 8.017)	<0.001
Non-CS	14764	821 (5.6%)	1	1	
30-day mortality:					
CS	1753	634 (36.2%)	7.587 (7.002, 9.552)	8.863 (7.848, 10.009)	<0.001
Non-CS	14764	1085 (7.3%)	1	1	

CS=Cardiogenic Shock, STEMI=ST Elevation Myocardial

Table V: Comparison of Mortality Rates between Cardiogenic Shock with or without PCI

In Hospital mortality	No. of patients	Death (%)	Unadjusted risk ratio	Adjusted risk ratio	P values
PCI done	537	145 (27%)	0.535 (0.428, 0.670)	0.600 (0.513,0.700)	P<0.001
PCI not done	1063	414 (38.9%)	1	1	

PCI= percutaneous coronary intervention

Table VI: Comparison of Clinical Factors between Survivors and Non-survivors of Cardiogenic Shock.

	Survivors (n=1126)	Non-survivors (n=598)	P value
Age >65	226 (20.8%)	253 (43.1%)	<0.001
Diabetes	429 (47.5%)	295 (58.2%)	<0.001
Hypertension	520 (56.5%)	361 (70.4%)	<0.001
Smoking status			
Active/Ex Smokers	607 (67.0%)	219 (48.6%)	<0.001
Non Smokers	299 (33.0%)	232 (51.4%)	
Dyslipidaemia	224 (30.3%)	143 (35.3%)	0.083
Previous MI	126 (14.0%)	82 (17.8%)	0.061
Chronic Lung Disease	25 (2.7%)	32 (6.6%)	0.001
Cerebrovascular Disease	27 (2.9%)	21 (4.4%)	0.161
Peripheral Vascular Disease	8 (0.9%)	2 (0.4%)	0.337
Chronic Renal Disease	46 (5.0%)	54 (11.2%)	<0.001

PCI=percutaneous coronary intervention, MI=myocardial infarction

Table VII: Logistic Regression of Predictors for In-Hospital Mortality in Cardiogenic Shock.

	P Values	Risk Ratios	95% C.I.for EXP(B) Lower	Upper
Age >65	**0.000**	**2.470****	**2.073**	**2.944**
Dyslipidaemia	0.040	0.828	.691	.992
Hypertension	**0.000**	**1.427****	**1.180**	**1.726**
Diabetes Mellitus	**0.000**	**1.600****	**1.343**	**1.907**
Smoking status	0.000	0.675	.567	.804
Previous MI	0.175	1.177	.930	1.490
Chronic Lung Disease	**0.032**	**1.744****	**1.048**	**2.903**
Chronic Renal Disease	**0.000**	**2.853****	**2.079**	**3.915**
Cerebrovascular disease	0.922	1.023	.648	1.615
Peripheral vascular disease	0.256	0.410	.088	1.909
Constant	0.000	0.052		

** statistically significant predictors of mortality , *MI=myocardial infarction*

Table VIII: Length of Stay of CS vs non-CS Patients

Total day stay	Cardiogenic shock	Non-cardiogenic shock	p-value
Mean	8.17 (7.53, 8.82)	5.21 (5.12, 5.29)	
Standard deviation	11.561	5.102	0.014

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Retrospective analysis of a registry data (Page 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Done – refer abstract (Page 2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Cardiogenic shock carries the worse prognosis in STEMI and has never been fully described in the setting of Malaysian population. (Page 4)
Objectives	3	State specific objectives, including any prespecified hypotheses To investigate the mortality of cardiogenic shock complicating STEMI in Malaysian setting where the utility of percutaneous coronary intervention is still sub optimal (page 4)
Methods		
Study design	4	Present key elements of study design early in the paper Retrospective analysis of Malaysian National Cardiovascular Database – Acute coronary syndrome 2006 to 2013 (NCVD-ACS). Observational study. (page 5)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection We include all patients diagnosed of STEMI in 18 hospitals across Malaysia from the year 2006 to 2013. Patients were followed up for 30-days post discharge (page 5)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Anonymous patients' data from the NCVD-ACS registry from 18 hospitals in Malaysia. Follow up on all-cause mortality done via telephone calls and cross-checked with the national death register of Malaysia. (page 5) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed Done (page 5) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable We analysed in-hospital mortality and 30-day mortality of patients presented with STEMI with and without cardiogenic shock. Clinical baseline characteristics and in-hospital treatment were analysed and adjusted for towards the outcome (mortality) (page 5)

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Clinical variables were extracted from the NCVD-ACS registry (page 5)
Bias	9	Describe any efforts to address potential sources of bias Data obtained from 18 hospitals across Malaysia. These hospital are evenly distributed geographically to best represent Malaysian population in general (page 5)
Study size	10	Explain how the study size was arrived at All-comers from the NCVD-ACS registry included (page 5)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why The patients were divided into 2 groups: STEMI with cardiogenic shock and STEMI without cardiogenic shock. This division is to compare the increase in mortality rate from the cardiogenic shock group in relation to the non-cardiogenic shock (page 5)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses Categorical variables were described as numbers and percentages. The differences were analysed by chi-square test or Fisher exact test. Continuous variables were expressed as median and differences were analysed using t-test. To avert biases in the estimates and loss of power, missing data for explanatory variables were assumed to be missing at random. A generalized linear model with a log link, binomial distribution, and a robust variance estimator was used to estimate the risk ratios. The risk ratios represent the relative risk for mortality of the non-cardiogenic shock group compared to the cardiogenic shock group. Subsequently, risk ratios of CS patients with PCI done and without PCI were also compared. Variables that were statistically significantly different (a 2-sided P value of less than 0.05) between the CS and non-CS patients, that were of clinical importance, and that had sufficient outcomes in the respective subcategories were adjusted for. Finally, binary logistics regression was executed to determine the independent predictors of in-hospital mortality among CS patients. All analyses were conducted using SPSS statistical software (version 21, IBM SPSS Statistics, USA). (page 6)

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed A total of 16517 STEMI patients analysed (page 7)
		(b) Give reasons for non-participation at each stage N/A
		(c) Consider use of a flow diagram N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders 16,517 STEMI patients from Malaysian NCVD-ACS registry year 2006 to 2013 (page 7)
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) In-hospital and 30-day follow up (page 7 and 8)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time Refer tables IV and V in the manuscript (page 18)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Refer tables IV and V in the manuscript (page 18)
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses N/A
Discussion		
Key results	18	Summarise key results with reference to study objectives Done. Refer discussion and summary sections in the manuscript (page 12 –conclusion)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias We have listed the limitations and strengths of this study in the manuscript (page 3 and 4)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Done in the discussion section (page 9-11)
Generalisability	21	Discuss the generalisability (external validity) of the study results Done in the discussion section (page 9-11)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based The NCVD is sponsored by the Ministry of Health Malaysia and co-sponsored by National Heart Association of Malaysia (NHAM). The Clinical Research Centre (CRC) is providing the technical support in the form of clinical epidemiology expertise, biostatistics and Information and Communication Technology (ICT) services. (page 5 – methods)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.