Optimal Glucose and Stress-hyperglycaemia Ratio Cut-off Values for Predicting 1-year Mortality in Diabetic and Non-diabetic Acute Myocardial Infarction Patients

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Abstract

Background

Stress-induced hyperglycaemia at time of hospital admission has been linked to worse prognosis following acute myocardial infarction (AMI). The stress-hyperglycaemia ratio (SHR) index normalises the acute increase in blood glucose values to background glycaemic status. However, the optimal cut-off blood glucose and SHR values for predicting adverse outcomes post-AMI are unknown. As such, we determined the optimal blood glucose and SHR cut-offs for predicting 1-year all cause mortality in diabetic and non-diabetic non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) patients.

Methods

We undertook a national, registry-based study of patients with AMI from January 2008 to December 2015. We determined the optimal blood glucose and SHR cut-off values using the Youden's formula for 1-year all-cause mortality. We subsequently analyzed the sensitivity, specificity, positive and negative predictive values of the cut-offs in the diabetic and non-diabetic subgroups, stratified by the type of AMI.

Results

There were 5,841 STEMI and 4,105 NSTEMI in the study. In STEMI patients, both glucose and SHR were independent predictors of 1-year all-cause mortality [Glucose: OR 2.19 (95% CI 1.74–2.75); SHR: 2.19 (95% CI 1.73–2.78)]. However, in NSTEMI patients, glucose and SHR were not independently associated with 1-year all-cause mortality [Glucose: OR 1.37 (95% CI 1.00-1.89); SHR: 1.27 (95% CI 0.91–1.78)]. In STEMI patients, ROC analysis showed that SHR performed better than glucose (AUC for glucose 0.633 versus AUC for SHR 0.692, $P < 0.001$) in diabetic patients, whereas in non-diabetic patients, SHR and glucose performed equally well (AUC for glucose 0.720 versus AUC for SHR 0.717, $P < 0.664$). The optimal glucose cut-off values were 15.0mmol/L for diabetic STEMI patients and 11mmol/L for non-diabetic STEMI patients and the corresponding optimal cut-off values for SHR were 1.7 and 1.5, respectively.

Conclusions

Glucose on admission and SHR were independent predictors of 1-year all-cause mortality in STEMI, whereas this was not the case in NSTEMI patients. In STEMI setting, SHR performed better than admission glucose to predict 1-year all-cause mortality in diabetic patients, whereas in non-diabetic patients both SHR and glucose performed equally well.

Introduction

Stress-induced hyperglycaemia (SH) refers to the transient rise in blood glucose levels that occurs during an acute illness and has been linked to a worse prognosis in acute myocardial infarction (AMI) patients (1). Despite its potential role as a predictor for patient outcomes, guidelines are not consistent on the choice of optimal cut-off glucose level to define SH as the thresholds have been arbitrarily selected due to lack of scientific evidence. As such, the prognostic relevance of the blood glucose levels for defining SH are not clear and need to be better defined. The European Society of Cardiology and the American Heart Association recommend an admission blood glucose of $> 11\text{mmol/L}$ and $> 10\text{mmol/L}$ as cut-offs for defining SH, respectively, regardless of diabetic or chronic glycaemic status of patients (2, 3). Previous therapeutic trials for improving acute glucose control in AMI patients have been inconsistent in their definitions of glucose level that constitutes SH, which might account, in part, for the inconclusive results of these studies in terms of clinical outcomes (4–6).

This uncertainty in optimal cut-off values for glucose in AMI patients in predicting adverse events, may also differ between ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) patients, and there is also a need to account for the diabetic status of patients to avoid incorrect estimation of real prevalence of stress hyperglycaemia. Roberts et al (7) have devised a Stress Hyperglycaemia Ratio (SHR) index to normalise the acute increase in glucose values in relation to background glycaemic status, but the optimal SHR cut-off level for defining SH are not known.

As such, in this study, we evaluated and compared the optimal blood glucose and SHR cut-off values in both diabetic and non-diabetic STEMI and NSTEMI patients and their utility in predicting 1-year all-cause mortality.

Methods

This study utilised the Singapore Myocardial Infarction Registry (SMIR), a national registry managed by the ministry-funded National Registry of Diseases Office (NRDO). The local institutional review board granted an exemption for written consent from the participants for this study (SingHealth CIRB Reference No: 2016/2480) as this study involved analysis of a de-identified dataset. The research was conducted in accordance with the Declaration of Helsinki. The statistician had access to anonymised individual data points while the co-authors had access to analysed, aggregated data. The SMIR collects clinical and outcome data on all AMI patients in all hospitals in Singapore (8–11). Notification of AMI to the registry is mandated by law. Data was obtained from medical claims listings, hospital discharge summaries, laboratory results by dedicated registry coordinators, and merged with the national death register which captures all death outcomes in Singapore to obtain unique cases. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 410 was used to obtain AMI cases diagnosed prior to 2012 while ICD-10 (Australian Modification) codes I21 and I22 were used for those cases diagnosed in 2012. STEMI was defined by: 1) Typical chest pain of 20 minutes 2) Significant ST segment elevation (0.1 or 0.2 mV on 2 adjacent limb or precordial leads, respectively, or new left bundle-branch block) and 3) Confirmed later by a rise in biomarkers. The multinational monitoring of trends and determinants in cardiovascular disease (MONICA) criteria were used for defining episodes. Medication

use was based on documentation in the case notes. The outcome of interest was 1-year all-cause mortality, obtained from the SMIR. Annual data audits were performed on the data for accuracy and inter-rater reliability. Outlier and illogical data were flagged for review.

This study utilised STEMI and NSTEMI cases reported to the SMIR from January 2008 to December 2015 who received percutaneous coronary intervention (12). We excluded patients with a blood glucose level of < 3.9mmol/L, a first blood glucose level measured more than 24 hours after admission, patients with fasting glucose levels, patients managed outside the hospital and patients with missing glucose or HbA1c results (Fig. 1). The glucose values referred henceforth throughout the manuscript implies the admission random glucose within the first 24 hours. Diabetics were defined as patients with a previously documented history of diabetes or those with no documented history of diabetes but a HbA1c value of > 6.5% (13). Non-diabetics were defined as those without a history of diabetes and with a HbA1c value of ≤ 6.5%. The primary outcome of interest was 1-year all-cause mortality.

Statistical Analysis

Categorical variables of the patients' characteristics were expressed as frequency and percentages while continuous variables were expressed as median and interquartile range. The SHR, was calculated using the following formula:

$$SHR = \frac{\text{Acute glucose value (mmol/L)}}{[1.59 \times \text{HbA1c (\%)}] - 2.59}$$

The optimal cut-off value for each glucose and SHR metric were determined by the Youden's index (14). A 2 x 2 table was used to determine the sensitivity (Sn), specificity (Sp), positive (PPV) and negative predictive value (NPV) of the cut-off values. Receiver operating characteristic (ROC) curves were generated to compare the area-under-the-curves (AUC) of each metric. Missing data were excluded from the analyses through case deletion without imputation to maintain data in its original form. To determine if admission glucose and SHR were independent predictors of 1-year all-cause mortality, odd ratios with 95% confidence interval (95%CI) for 1-year all-cause mortality were adjusted for age, a history of ischemic heart disease, Killip class on admission, cardiac arrest on admission, and creatinine and hemoglobin on admission (factors found to be significant predictors of 1-year all-cause mortality in SMIR cohort of STEMI and NSTEMI cohort using multivariable stepwise logistic regression with backward elimination). Statistical analysis was performed using Stata (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP). All statistical tests were 2-tailed and statistical significance was set at $p < 0.05$.

Results

Baseline Characteristics

There were 5,841 STEMI and 4,105 NSTEMI patients available for analysis (Fig. 1). Patients were divided into the diabetic and non-diabetic subgroups. Baseline patient characteristics are displayed in Table 1. STEMI patients had a worse prognosis when compared to NSTEMI patients (**Supplementary Fig. 1A**). Diabetic patients were older, less likely to be male (Table 1) and were associated with a poorer prognosis (**Supplementary Fig. 1B**). There was a higher proportion of patients with a past medical history of hypertension, hyperlipidaemia, and ischaemic heart disease in the diabetic group, but fewer were current smokers. Median glucose levels were higher in the STEMI patients. Proportion of patients on goal-directed medical therapy was high for both STEMI and NSTEMI groups (Table 1). Moreover, the hazard ratios were higher as the glucose levels and SHR increased in both STEMI and NSTEMI patients (**Supplementary Figs. 2 and 3**). Among the patients analysed, 1-year all-cause mortality occurred in: 252 out of 2,820 (8.9%) STEMI diabetic; 202 out of 3,021 (6.7%) STEMI non-diabetic; 161 out of 2,338 (6.9%) NSTEMI diabetic; 56 out of 1,767 (3.2%) NSTEMI non-diabetic patients.

Table 1
Characteristics of acute myocardial infarction patients in the study

	STEMI		NSTEMI	
	Diabetic N = 2820	Non-diabetic N = 3021	Diabetic N = 2338	Non-diabetic N = 1767
Age in years, median (IQR)	58.6 (51.4–66.2)	57.0 (50.5–64.9)	61.2 (54.0–70.0)	58.4 (50.9–66.9)
Male, n (%)	2289 (81.2)	2644 (87.5)	1695 (72.5)	1498 (84.8)
Race, n (%)				
Chinese	1457 (51.7)	1997 (66.1)	1208 (51.7)	1202 (68.0)
Malay	714 (25.3)	574 (19.0)	550 (23.5)	305 (17.3)
Indian	601 (21.3)	400 (13.2)	540 (23.1)	230 (13.0)
Past medical history, n (%)				
Hypertension	1854 (65.7)	1266 (41.9)	1876 (80.2)	963 (54.5)
Diabetes	2142 (76.0)	NA	1994 (85.3)	NA
Not on treatment	451 (21.1)	NA	257 (12.9)	NA
Diet control	113 (5.3)	NA	102 (5.1)	NA
Oral medication	1391 (64.9)	NA	1264 (63.4)	NA
Insulin	64 (3.0)	NA	153 (7.7)	NA
Oral medication & insulin	123 (5.7)	NA	218 (10.9)	NA
Hyperlipidemia	1701 (60.4)	1070 (35.4)	1825 (78.1)	906 (51.3)
MI/PCI/CABG	499 (17.7)	319 (10.6)	963 (41.2)	337 (19.1)
Smoking, n (%)				
Current	1253 (44.9)	1602 (53.3)	750 (32.2)	806 (45.7)
Former	422 (15.1)	365 (12.1)	468 (20.1)	315 (17.9)
Never	1118 (40.0)	1039 (34.6)	1113 (47.7)	641 (36.4)
BMI in kg/m², median (IQR)	25.2 (22.9–27.9)	24.4 (22.2–27.0)	25.6 (23.1–28.9)	24.8 (22.6–27.5)

Abbreviations: ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CKMB, creatinine kinase-muscle brain; IHD, ischaemic heart disease; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; OHGA, oral hypoglycaemic agent; PCI, percutaneous coronary intervention; SHR, stress-hyperglycaemia ratio; STEMI, ST-segment elevation myocardial infarction

	STEMI		NSTEMI	
Glucose in mmol/L, median (IQR)	13.8 (10.5–18.4)	7.8 (6.8–9.4)	12.3 (9.0–16.4)	6.7 (5.8–8.0)
HbA1c in %, median (IQR)	8.0 (6.9–9.9)	5.7 (5.5–6.0)	7.7 (6.8–9.3)	5.7 (5.5–6.0)
Total cholesterol in mmol/L, median (IQR)	4.9 (4.0–5.9)	5.2 (4.5–6.1)	4.7 (3.8–5.7)	5.2 (4.4–6.0)
LDL-cholesterol in mmol/L, median (IQR)	3.1 (2.4–4.0)	3.5 (2.8–4.3)	2.8 (2.2–3.7)	3.5 (2.7–4.2)
HDL-cholesterol in mmol/L, median (IQR)	1.0 (0.8–1.2)	1.1 (0.9–1.3)	1.0 (0.8–1.2)	1.0 (0.9–1.2)
Triglyceride in mmol/L, median (IQR)	1.5 (1.1–2.3)	1.3 (1.0–1.8)	1.7 (1.2–2.5)	1.5 (1.1–2.1)
Haemoglobin in g/dL, median (IQR)	14.6 (13.2–15.7)	14.8 (13.7–15.8)	13.7 (12.1–15.0)	14.5 (13.4–15.4)
Creatinine in μ mol/L, median (IQR)	89 (74–112)	90 (77–105)	88 (72–116)	84 (73–97)
Killip class on admission, n (%)				
I	2261 (80.2)	2541 (84.1)	1790 (76.6)	1599 (90.5)
II	196 (6.9)	126 (4.2)	322 (13.8)	94 (5.3)
III	130 (4.6)	86 (2.9)	199 (8.5)	52 (2.9)
IV	233 (8.3)	267 (8.8)	26 (1.1)	21 (1.2)
In-patient medication, n (%)				
Aspirin	2733 (96.9)	2956 (97.9)	2298 (98.3)	1722 (97.5)
Beta-blocker	2457 (87.1)	2616 (86.6)	2121 (90.7)	1575 (89.1)
ACEI/ARB	2171 (77.0)	2221 (73.5)	1930 (82.6)	1265 (71.6)
Lipid lowering drug	2731 (96.8)	2955 (97.8)	2313 (98.9)	1755 (99.3)
P2Y12 inhibitor	2773 (98.3)	2982 (98.7)	2330 (99.7)	1760 (99.6)
Abbreviations: ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CKMB, creatinine kinase-muscle brain; IHD, ischaemic heart disease; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; OHGA, oral hypoglycaemic agent; PCI, percutaneous coronary intervention; SHR, stress-hyperglycaemia ratio; STEMI, ST-segment elevation myocardial infarction				

Optimal blood glucose cut-off values for predicting outcomes

The optimal glucose cut-off values for predicting all-cause mortality at 1 year are shown in Table 2. All cut-offs for both STEMI and NSTEMI patients, regardless of diabetic status showed excellent negative predictive value of > 94%. The optimal glucose cut-off values were 15.0mmol/L for diabetic STEMI patients and 11mmol/L for non-diabetic STEMI patients. In NSTEMI patients, the optimal cut-off values were lower, at 11.0mmol/L for diabetic patients and 8mmol/L for non-diabetic NSTEMI patients.

Table 2

Optimal glucose cut-offs for 1-year all-cause mortality in diabetic and non-diabetic ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction patients

	STEMI			NSTEMI		
	All	Diabetic	Non-diabetic	All	Diabetic	Non-diabetic
Statistical optimal glucose cut-off in mmol/L	12.9	15.0	10.6	10.2	10.7	8.1
Sensitivity in %	55.3	62.7	50.5	57.1	65.8	42.9
(95% CI)	(50.6–59.9)	(56.4–68.7)	(43.4–57.6)	(50.3–63.8)	(58.0–73.1)	(29.7–56.8)
Specificity in %	71.8	59.5	86.9	61.3	39.7	75.8
(95% CI)	(70.6–73.0)	(57.5–61.4)	(85.6–88.1)	(59.7–62.8)	(37.6–41.8)	(73.7–77.8)
Positive predictive value in %	14.2	13.2	21.6	7.6	7.5	5.5
(95% CI)	(13.1–15.4)	(12.0–14.4)	(18.9–24.6)	(6.8–8.5)	(6.7–8.3)	(4.1–7.4)
Negative predictive value in %	95.0	94.2	96.1	96.2	94.0	97.6
(95% CI)	(94.5–95.5)	(93.2–95.0)	(95.5–96.6)	(95.6–96.8)	(92.7–95.1)	(97.0–98.1)
Abbreviations: CI, confidence interval; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction						

Optimal SHR cut-off values for predicting outcomes

The optimal SHR cut-off values for predicting all-cause mortality at 1 year are shown in Table 3. The optimal cut-off values performed well with negative predictive values of > 94%. The SHR cut-off value for diabetic STEMI patients was 1.7, and was lower in non-diabetic STEMI patients at 1.5. For the NSTEMI group, the SHR values were lower being 1.5 in diabetics and 1.2 in non-diabetics.

Table 3

Performance statistics of the stress-hyperglycaemia ratio (SHR) in predicting 1-year all-cause mortality in diabetic and non-diabetic ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction patients

	STEMI			NSTEMI		
	All	Diabetic	Non-diabetic	All	Diabetic	Non-diabetic
Statistical optimal SHR cut-off	1.66	1.68	1.51	1.28	1.53	1.27
Sensitivity in %	48.7	50.4	55.0	52.1	35.4	44.6
(95% CI)	(44.0-53.4)	(44.1-56.7)	(47.8-61.9)	(45.2-58.9)	(28.0-43.3)	(31.3-58.5)
Specificity in %	85.8	83.2	82.2	67.4	78.3	79.0
(95% CI)	(84.9-86.8)	(81.7-84.6)	(80.7-83.6)	(65.9-68.9)	(76.5-80.0)	(77.0-80.9)
Positive predictive value in %	22.5	22.7	18.1	8.2	10.8	6.5
(95% CI)	(20.5-24.5)	(20.2-25.5)	(16.0-20.4)	(7.2-9.3)	(8.8-13.1)	(4.9-8.6)
Negative predictive value in %	95.2	94.5	96.2	96.2	94.2	97.8
(95% CI)	(94.8-95.6)	(93.8-95.1)	(95.6-96.7)	(95.6-96.7)	(93.6-94.9)	(97.2-98.2)

Comparison of optimal glucose and SHR cut-offs

In STEMI patients, ROC analysis (Fig. 2) showed that both glucose and SHR were good predictors of 1-year all-cause mortality. SHR performed better than glucose [AUC for glucose of 0.633 (95%CI 0.594–0.672) versus AUC for SHR of 0.692 (95%CI 0.653–0.732), $P < 0.001$] in diabetic patients, whereas in non-diabetic patients, SHR and glucose performed equally well [AUC for glucose of 0.720 (95%CI 0.677–0.763) versus AUC for SHR of 0.717 (95%CI 0.674–0.760), $P < 0.664$].

In diabetic NSTEMI patients, glucose performed worse than SHR as a predictor of 1-year all-cause mortality [AUC for glucose of 0.528 (95%CI 0.481–0.576) versus AUC for SHR of 0.588 (95%CI 0.540–0.635), $P < 0.001$]. However, in non-diabetic NSTEMI patients, both glucose and SHR performed equally well [AUC of glucose 0.620 (95%CI 0.540–0.700) versus AUC of SHR 0.606 (95%CI 0.522–0.690), $P < 0.404$].

Glucose and SHR as an independent predictor of 1-year all-cause mortality

Irrespective of diabetes status, in STEMI patients, both glucose and SHR were independent predictors of 1-year all-cause mortality [Glucose: OR 2.19 (95% CI 1.74–2.75); SHR: 2.19 (95% CI 1.73–2.78)], after adjusting for age, history of IHD, Killip Class on admission, cardiac arrest on admission, and creatinine and haemoglobin on admission (Tables 4 and 5). However, in NSTEMI patients, glucose and SHR were not independently associated with 1-year all-cause mortality [Glucose: OR 1.37 (95% CI 1.00-1.89); SHR: 1.27 (95% CI 0.91–1.78)] (Tables 4 and 5).

Table 4
SHR as an independent predictor of 1-year mortality

	STEMI			NSTEMI		
	OR	95% CI		OR	95% CI	
Age < 40 years	1.00	reference		1.00	reference	
Age 40–49 years	1.24	0.47	3.31	0.34	0.07	1.51
Age 50–59 years	1.45	0.56	3.75	0.44	0.11	1.70
Age 60–69 years	2.21	0.86	5.71	0.74	0.20	2.81
Age 70–79 years	3.89	1.49	10.16	1.21	0.32	4.59
Age 80–89 years	7.60	2.82	20.48	1.99	0.50	7.84
Age ≥ 90 years	10.60	2.54	44.30	12.00	1.25	115.55
SHR below proposed cutoff	1.00	reference		1.00	reference	
SHR above proposed cutoff	2.19	1.73	2.78	1.27	0.91	1.78
No history of MI/PCI/CABG	1.00	reference		1.00	reference	
History of MI/PCI/CABG	1.19	0.89	1.58	1.55	1.13	2.12
Killip class I on admission	1.00	reference		1.00	reference	
Killip class II on admission	1.48	0.95	2.30	2.88	1.96	4.25
Killip class III on admission	2.46	1.65	3.66	3.14	2.04	4.85
Killip class IV on admission	4.08	3.09	5.38	21.58	10.80	43.14
No CPR on arrival	1.00	reference		1.00	reference	
CPR on arrival	3.72	2.62	5.30	10.41	3.28	33.03
Creatinine < 35 µmol/L	not available			not available		
Creatinine 35–69 µmol/L	1.00	reference		1.00	reference	
Creatinine 70–105 µmol/L	0.72	0.49	1.04	0.69	0.42	1.13
Creatinine 106–140 µmol/L	1.55	1.06	2.27	1.32	0.77	2.26
Creatinine 141–176 µmol/L	2.06	1.28	3.31	1.20	0.61	2.35
Creatinine 177–353 µmol/L	2.40	1.45	3.98	1.21	0.58	2.55
Abbreviations: STEMI: ST-segment elevation myocardial infarction; NSTEMI: non ST-segment elevation myocardial infarction; IHD: ischaemic heart disease; SHR: stress hyperglycaemic ratio						
Odds ratio for Creatinine < 35 µmol/L was not available as there were insufficient number of patients and/or events.						

	STEMI			NSTEMI		
Creatinine ≥ 354 $\mu\text{mol/L}$	3.46	1.84	6.52	4.42	2.44	7.99
Haemoglobin < 10 g/dL	1.69	0.96	2.98	2.16	1.09	4.28
Haemoglobin 10–11 g/dL	2.14	1.50	3.06	2.85	1.68	4.81
Haemoglobin 12–13 g/dL	1.43	1.08	1.90	2.47	1.53	3.99
Haemoglobin 14–15 g/dL	1.00	reference		1.00	reference	
Haemoglobin ≥ 16 g/dL	1.21	0.86	1.72	0.95	0.40	2.28
Abbreviations: STEMI: ST-segment elevation myocardial infarction; NSTEMI: non ST-segment elevation myocardial infarction; IHD: ischaemic heart disease; SHR: stress hyperglycaemic ratio						
Odds ratio for Creatinine < 35 $\mu\text{mol/L}$ was not available as there were insufficient number of patients and/or events.						

Table 5
Glucose as an independent predictor of 1-year mortality

	STEMI			NSTEMI		
	OR	95% CI		OR	95% CI	
Age < 40 years	1.00	reference		1.00	reference	
Age 40–49 years	1.25	0.47	3.32	0.32	0.07	1.45
Age 50–59 years	1.47	0.57	3.78	0.42	0.11	1.63
Age 60–69 years	2.30	0.89	5.91	0.72	0.19	2.72
Age 70–79 years	4.17	1.60	10.89	1.19	0.31	4.52
Age 80–89 years	8.27	3.07	22.26	1.99	0.51	7.82
Age ≥ 90 years	11.36	2.71	47.61	10.32	1.06	100.35
Glucose below proposed cutoff	1.00	reference		1.00	reference	
Glucose above proposed cutoff	2.19	1.74	2.75	1.37	1.00	1.89
No history of MI/PCI/CABG	1.00	reference		1.00	reference	
History of MI/PCI/CABG	1.19	0.89	1.59	1.53	1.12	2.09
Killip class I on admission	1.00	reference		1.00	reference	
Killip class II on admission	1.45	0.94	2.26	2.81	1.91	4.14
Killip class III on admission	2.47	1.67	3.67	3.08	2.00	4.73
Killip class IV on admission	4.16	3.16	5.48	21.66	10.82	43.35
No CPR on arrival	1.00	reference		1.00	reference	
CPR on arrival	3.89	2.74	5.53	10.66	3.39	33.51
Creatinine < 35 µmol/L	not available			not available		
Creatinine 35–69 µmol/L	1.00	reference		1.00	reference	
Creatinine 70–105 µmol/L	0.79	0.55	1.14	0.70	0.42	1.15
Creatinine 106–140 µmol/L	1.73	1.18	2.52	1.34	0.78	2.28
Creatinine 141–176 µmol/L	2.27	1.41	3.64	1.19	0.61	2.34

Abbreviations: STEMI: ST-segment elevation myocardial infarction; NSTEMI: non ST-segment elevation myocardial infarction; IHD: ischaemic heart disease

Odds ratio for Creatinine < 35 µmol/L was not available as there were insufficient number of patients and/or events.

	STEMI			NSTEMI		
Creatinine 177–353 µmol/L	2.70	1.63	4.46	1.21	0.58	2.55
Creatinine >= 354 µmol/L	3.84	2.04	7.25	4.45	2.46	8.04
Haemoglobin < 10 g/dL	1.73	0.98	3.06	2.21	1.12	4.37
Haemoglobin 10–11 g/dL	2.13	1.49	3.04	2.88	1.70	4.86
Haemoglobin 12–13 g/dL	1.46	1.10	1.93	2.47	1.53	3.98
Haemoglobin 14–15 g/dL	1.00	reference		1.00	reference	
Haemoglobin >= 16 g/dL	1.19	0.84	1.68	0.94	0.39	2.26
Abbreviations: STEMI: ST-segment elevation myocardial infarction; NSTEMI: non ST-segment elevation myocardial infarction; IHD: ischaemic heart disease						
Odds ratio for Creatinine < 35 µmol/L was not available as there were insufficient number of patients and/or events.						

Discussion

This study utilised a national AMI database to investigate the optimal cut-offs for acute glucose values in predicting 1-year all-cause mortality. The main findings of our study were: glucose and SHR were independent predictors of 1-year all-cause mortality in STEMI, whereas in NSTEMI patients neither glucose nor SHR were independent predictors. ROC curve analysis showed that in diabetic STEMI patients SHR performed better than glucose to predict 1-year all-cause mortality, whereas in non-diabetic STEMI patients both SHR and glucose performed equally well. The optimal values for glucose and SHR were 15 and 1.7 in diabetic patients and 11 and 1.5 in non-diabetic patients, providing a negative predictive value of > 94%.

It is postulated that hyperglycaemia leads to poorer outcomes after MI events due to an acute increase in cortisol and catecholamine levels secondary to activation of the sympathetic nervous system as a physiological response to stress (15). Catecholamines suppress insulin release from the pancreatic β -cells and promote hepatic and muscular glycogenolysis. This decreases glucose uptake into the heart and causes hyperglycaemia. Cortisol reduces glucose transporter translocation in the peripheral tissues and increases liver gluconeogenesis and hence hyperglycaemia (16–18). It is speculated that the hyperglycaemia causes a poor outcome as it induces oxidative stress (19), increases endothelial dysfunction (20) and reduces the cardioprotective effect of ischaemic preconditioning (21).

We found that the glucose and SHR were independent predictors of all-cause mortality at 1-year. Therefore, glucose and SHR may improve the risk-stratification of STEMI patients. Clinicians can use this information to follow selected patients up more closely and be more aggressive in up-titrating goal-directed medical therapy and controlling their cardiovascular risk factors aggressively. The TIMI and

GRACE risk scores have traditionally been used in prognosticating patients after acute myocardial infarction (22, 23). Whether glucose or SHR values add independent prognostic value above the TIMI and GRACE risk scores needs to be validated in future studies.

Current guidelines provide a single glucose reading as a cut-off to define SH (2, 3). There has also not been any clear protocol to date for the management of acute hyperglycaemia in AMI patients, with studies having conflicting results at best. Except for the DIGAMI-1 trial, results of subsequent larger randomized controlled trials with glucose-insulin-potassium infusions have been neutral or even causing increased hypoglycaemia rates (24–26). One factor contributing to these results is that a single glucose cut-off was used. It may be worth considering recruiting patients based on the optimal glucose cut-offs or targeting the therapy to see if this would optimize outcomes in acutely hyperglycaemic patients. Our study support the findings by Hao et al demonstrating that there are different cut-offs for acute glucose values for predicting adverse events at day 30 and year 3 depending on diabetic status (27). Our study builds on the work by Hao et al by studying 1-year all-cause mortality as a hard end-point, supporting the need for optimal glucose cut-offs separately for diabetic and non-diabetic STEMI patients.

Previously, Roberts et al showed that SHR was an independent predictor of death or intensive care admission while glucose alone was not. A similar formula (random serum glucose / HbA1c) has subsequently been studied in a Korean post-AMI population of 4,362 subjects from the COACT registry (28) and it showed that SHR predicted mortality, MI and stroke in the non-diabetic STEMI population. An alternative method of calculating relative hyperglycaemia has been termed the glycaemic gap. This is calculated by subtracting the estimated average glucose levels over 3 months from the admission glucose (29). Like the SHR, the glycaemic gap performs better than either admission glucose or HbA1c alone at predicting the risk of moderate-to-severe stroke (30). Two recent publications have shown that using SHR as a biomarker showed increased mortality risks in diabetic Australian and Italian AMI patients (31, 32). The former study was done on 192 patients in the HI-5 trial showing that relative but not absolute glycaemia during insulin treatment was associated with complications post-AMI (31). The latter study consisted of 1,553 consecutive AMI patients, and the study utilised a formula termed the acute-to-chronic glycemic ratio. Both studies showed that in AMI patients with diabetes, the glycemic ratio was a better predictor of in-hospital mortality than admission glycaemia (32). Our study corroborates these findings that a metric adjusted for background glycemic control performs better in risk prediction. Further efforts are needed to standardize the use of a common metric of stress hyperglycaemia considering background glycemic control so that studies can be directly comparable and common definitions can be developed for future therapeutic studies.

The strength of this study is that it used a large national registry-level database to examine outcomes in AMI patients across a range of outcomes at various time points, including national-level rehospitalization data, which allowed comprehensive and accurate case capture. The use of the national death registry to track death outcomes meant that there was comprehensive follow-up. However, we acknowledge several weaknesses of this study. We could not exclude the possibility of selection bias given that more than half the patients in the database were excluded from the analysis due to missing data. As this was a

retrospective study, causality cannot be determined in this study. We also could not standardize the time in which the acute glucose levels were measured in hospital within the first 24 hours of presentation as we were using retrospective data, although this does reflect real-world practice. We did not have GRACE and TIMI risk scores in our cohort and therefore we could not assess whether glucose or SHR provided additive prognostic value over those existing scores. However, we did adjust for prognostic factors from the SMIR cohort.

Conclusion

In summary, in this national registry of a south-east Asian cohort of AMI patients treated by PCI, glucose on admission and SHR were independent predictors of 1-year all-cause mortality in STEMI, whereas this was not the case in NSTEMI patients. The reason for this is not clear but may relate to the timing of the admission glucose being closer to the acute presentation in STEMI compared to NSTEMI. In STEMI setting, SHR performed better than admission glucose to predict 1-year all-cause mortality in diabetic patients, whereas in non-diabetic patients both SHR and glucose performed equally well. The optimal cut-off values for glucose were 15 in diabetic patients and 11 in non-diabetic patients and the optimal cut-off values for SHR was 1.7 in diabetic patients and 1.5 in non-diabetic patients. Our findings need to be validated in future studies.

Declarations

Ethics approval and consent to participate

Ethics approval and consent to participate were approved and waived respectively as written in the methods section.

Consent for publication

Consent for publication was not applicable for this publication as the dataset do not include individual person's database and contained de-identified values.

Availability of data and materials

Material and dataset may be available upon request and the corresponding author's approval.

Competing interests

The author(s) declare no competing interests.

Contributions

C.H.S., M.H.C., H.B., and D.J.H. designed this study; H.Z. contributed to this study by obtaining and analyzing the data of SMIR; C.H.S., M.H.C, J.K., H.B., and D.J.H. contributed to interpreting the data. J.K.,

C.H.S., M.H.C, H.B, H.Z., D.J.H wrote the manuscripts. A.F.H., J.C., D.F., L.F., P.Z.L., B.W.L., P.C., T.Y., H.T., T.C., M.Y.C., and J.W.C.T. contributed to this paper by providing constructive comments and insights. D.J.H. and H.B. supervised and provided critical review of the manuscript.

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Figures

Figure 1

Flow Chart of Inclusion and Exclusion Criteria. 67,887 patients were initially included in the SMIR database for this study (19,724 for STEMI and 48,163 for NSTEMI). The patients with the following criteria were excluded from the pool; no PCI treatment, no admission, in-hospital STEMI or NSTEMI, no data on glucose or HbA1C, delayed measurement of glucose (longer than 24 hours after admission), and extremely low glucose levels (less than 3.9mmol/L). Abbreviations: NSTEMI, non-ST-segment elevation myocardial infarction; PPCI, primary percutaneous coronary intervention; SMIR, Singapore Myocardial Infarction Registry; STEMI, ST-segment elevation myocardial infarction

Figure 2

Area Under the Curve (AUC) Analysis for Glucose Levels and Stress-hyperglycemia Ratio (SHR). The area under the curves (AUC) were plotted to compare the use of glucose levels and the stress-hyperglycaemia ratio (SHR) to predict 1-year all-cause mortality for ST-segment elevation and non-ST-segment elevation myocardial infarction patients with and without diabetes mellitus. Abbreviations: AUC, area under the

curve; NSTEMI, non-ST-segment elevation myocardial infarction; SHR, stress-hyperglycaemia ratio; STEMI, ST-segment elevation myocardial infarction

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