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Impact of COVID-19 pandemic on STEMI thrombolysis and Emergency Department's performance in a non-PCI capable tertiary hospital

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ARTICLE INFO

Article history:

Received 19 April 2022

Received in revised form 7 July 2022

Accepted 9 July 2022

Keywords:

COVID-19

STEMI

Thrombolysis

Streptokinase

Tenecteplase

Asian

Emergency Department

ABSTRACT

Introduction: Some guidelines had recommended “thrombolysis first” in ST-elevated myocardial infarction (STEMI) during the Coronavirus Disease 2019 (COVID-19) outbreak. The impact of COVID-19 solely on STEMI thrombolysis is lacking as most studies reported outcomes related to percutaneous coronary intervention (PCI) setting. Thus, this study aimed to assess the impact of the COVID-19 pandemic on STEMI thrombolysis outcomes and the Emergency Department's performance in a non-PCI capable centre.

Methods: This single-centre retrospective study analysed data on consecutive STEMI patients who received thrombolytic therapy from May 2019 to December 2020 (20 months) in a non-PCI capable tertiary hospital. Total population sampling was used in this study. We compared all patients' characteristics and outcomes ten months before and during the pandemic. Regression models were used to assess the impact of COVID-19 pandemic on door-to-needle time (DNT), mortality, bleeding events, and the number of overnight stays.

Results and discussion: We analysed 323 patients with a mean age of 52.9 ± 12.9 years and were predominantly male ($n = 280, 88.9\%$). There was a 12.5% reduction in thrombolysis performed during the pandemic. No significant difference in timing from symptoms onset to thrombolysis and DNT was observed. In-hospital mortality was significantly higher during the pandemic (OR 2.02, 95% CI 1.02–4.00, $p = 0.044$). Bleeding events post thrombolysis remained stable and there was no significant difference in the number of overnight stays during the pandemic.

Conclusion: STEMI thrombolysis cases were reduced during the COVID-19 pandemic, with an inverse increase in mortality despite the preserved Emergency Department performance in timely thrombolysis.

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1. Introduction

The Coronavirus Disease-2019 (COVID-19) pandemic has remained the primary global health threat for more than two years since its outbreak. This pandemic has caused crisis and collateral burden to the whole healthcare system, including the Cardiology services for ST-elevation myocardial infarction (STEMI) [1,2]. The healthcare system, including the Emergency Department (ED), has been reorganized to cope with the enormous surge of critically ill patients and prevent nosocomial COVID-19 transmission [2,3]. For instance, several tertiary

public hospitals in Malaysia have been converted into hybrid hospitals that manage COVID-19 and non-COVID-19 patients.

Ischemic heart disease is the principal global cause of mortality despite the evolution of coronary reperfusion over 40 years [4]. In STEMI, immediate reperfusion intervention is needed as “time is myocardium” [5]. There were different recommendations on acute STEMI management during the COVID-19 pandemic. Several Asian countries, including Malaysia, had recommended “thrombolytic first” in STEMI patients presented with unconfirmed COVID-19 status, while Western guidelines maintained the primary PCI protocols as the preferred reperfusion strategy [6,7].

A recent meta-analysis had reported the pandemic's impact on STEMI, but the included studies mainly originated from developed countries with PCI-capable settings [8]. A significant reduction in STEMI admission, similar time from symptoms onset to first medical contact, and significantly prolonged door-to-balloon time were

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¹ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

observed during the pandemic [8]. The in-hospital mortality remained stable as most countries were able to maintain timely acute STEMI management during the pandemic [8]. However, a higher mortality rate was reported in Hubei Province, the epicenter in China. China is the only Asian country included in the meta-analysis that advocated “thrombolysis first” in STEMI during the pandemic [6].

The superiority of primary PCI over thrombolysis is well established and is the primary reperfusion therapy performed in developed countries with high accessibility to PCI-capable facilities, i.e. >90% in the United States and >70% in European countries [9–11]. In these countries, thrombolysis (alone or as part of pharmacoinvasive therapy) is used only when primary PCI cannot be performed in a timely manner [10]. However, pharmacological thrombolysis remains the primary STEMI reperfusion strategy in many low to medium-income countries, including Malaysia (>70%), due to the limited PCI-capable facilities [5,12–14]. To date, data on the impact of COVID-19 pandemic on STEMI thrombolysis in the non-PCI-capable centre is lacking. Additionally, the recent meta-analysis included only studies that examined the impact of the pandemic in a short duration (3 months or lesser) [8]. Thus, this study aimed to assess the impact of the COVID-19 pandemic on STEMI thrombolysis outcomes and the ED's performance in a non-PCI-capable centre of a developing country. Also, this study provided insights into the patients' and public healthcare response to acute myocardial infarction during the COVID-19 pandemic in Malaysia, a country that provides subsidized healthcare.

2. Materials and methods

2.1. Design, setting, and population

This single-centre retrospective observational study was conducted at Hospital Kuala Lumpur (HKL), the largest tertiary care hospital with 2300 beds under the Ministry of Health Malaysia and one of the biggest hospitals in Asia. Emergency Department (ED) HKL has >250,000 patient attendances annually. During the COVID-19 pandemic, HKL was converted into a hybrid hospital treating both COVID-19 and non-COVID-19 patients. During the early days of the COVID-19 outbreak (the study period), there was about a 30% reduction in the total ED attendance, but mainly in the Green (non-critical) Zone, possibly due to the strict movement control orders implemented by the federal government of Malaysia. However, the ED workload was rising during the outbreak due to additional steps during triaging, restructuring of ED zones, extensive COVID-19 screening, the requirement to comply with more standard operating procedures, and more complicated and meticulous management of COVID-19 patients.

HKL is a non-PCI-capable hospital but performs the highest number of STEMI thrombolysis cases in Malaysia. The dose of streptokinase was 1.5 million units, given over 1 h. Tenecteplase was dosed according to the patient's body weight as per the Metalyse® product insert and given as a bolus. All STEMI patients who received the fibrinolytic agent were given dual-antiplatelets (clopidogrel plus acetylsalicylic acid) and fondaparinux (majority) as part of acute STEMI management. Enoxaparin was used only in patients with creatinine clearance of below 30 ml/min. This study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-20-2630-57346). Informed consent was waived due to the retrospective nature of the study. The study conformed to the principles outlined in the Declaration of Helsinki.

2.2. Inclusion and exclusion criteria

This study included adult patients aged ≥ 18 years diagnosed with STEMI upon admission to the ED from May 2019 to December 2020 (20 months) and who received a thrombolytic agent. Patients with a final diagnosis revised to other than STEMI after Cardiologist's review were excluded from this study.

2.3. Data collection

Total population sampling was used in this study. Medical records of all STEMI patients were screened based on eligibility criteria. Pertinent data obtained from the patients' medical records include (A) patients' socio-demographic, (B) comorbidities, (C) STEMI diagnosis, (D) fibrinolysis therapy, (E) efficacy outcomes (ST-segment resolution, in-hospital mortality), and (F) in-hospital safety outcomes, including stroke, bleeding, cardiac events and other complications.

2.4. Definitions

In Malaysia, the second wave of COVID-19 began in late February 2020, and the movement control order (social containment) was started in March 2020 [15]. Thus, this study defined pre-covid outbreak (PCovO) duration from 01 May 2019 to 29 February 2020 (10 months), and COVID-19 outbreak (CovO) duration was from 01 March 2020 to 31 December 2020 (10 months). During the early days of the outbreak (the study period), the real-time reverse transcription-polymerase chain reaction (rRT-PCR) assay was the standard test for laboratory diagnosis of COVID-19 infection. In ED, only patients with a severe acute respiratory infection (SARI), acute respiratory illness (ARI), and/or epidemiological link to the active COVID-19 clusters were actively tested. These patients with suspected COVID-19 may be admitted to “person under investigation” (PUI) or SARI wards before the availability of rRT-PCR results [16].

The diagnosis of STEMI followed both international and local guidelines, i.e., the 2017 European Society of Cardiology (ESC) STEMI guidelines and the Malaysian Clinical Practice Guidelines on STEMI management [5,10]. All included STEMI cases were reviewed and confirmed by the Cardiologist. Door-to-needle time (DNT) was defined as the time STEMI patient presented with symptoms at the ED to the start of the thrombolytic agent.

2.5. Data analysis and sample size

Data analysis was performed using the statistical package for social sciences (SPSS) for Windows version 26 (IBM Corp., Armonk, N.Y., USA). Kolmogorov–Smirnov equation was used to test for normality for all continuous variables. Descriptive analysis used to describe continuous data was expressed as mean and standard deviations (SD) or median and interquartile range (IQR) depending on normality distribution, whereas categorical data were reported as counts and percentages. Relevant dichotomous data were analysed using the Chi-square test or Fisher's Exact test where appropriate. Multivariate regression models (linear regression models for continuous outcome variables and logistic regression models for dichotomous outcome variables) with age and gender as control variables were used to analyze the association of COVID-19 pandemic with time symptoms onset to thrombolysis, DNT, mortality, bleeding events and number of overnight stays.

3. Results

3.1. Subjects' demographics

A total of 323 STEMI patients received thrombolysis from May 2019 to December 2020. After screening, 168 and 147 patients from PCovO and CovO groups, respectively, were included in the final analyses (Fig. 1).

The majority of the patients were male ($n = 280$, 88.9%), current smoker ($n = 215$, 68.3%) with a mean age of 52.9 (± 12.9) years. Hypertension was the highest pre-existing comorbid presented in the population ($n = 155$, 49.2%). Most STEMI cases involved the anterior location ($n = 177$, 56.2%) and almost half of the patients were presented to ED with Killip II and above ($n = 161$, 51.1%) (Table 1). The majority of the baseline characteristics between PCovO and CovO groups were similar except for heart rate (HR) below 60 beats per min (bpm). Besides,

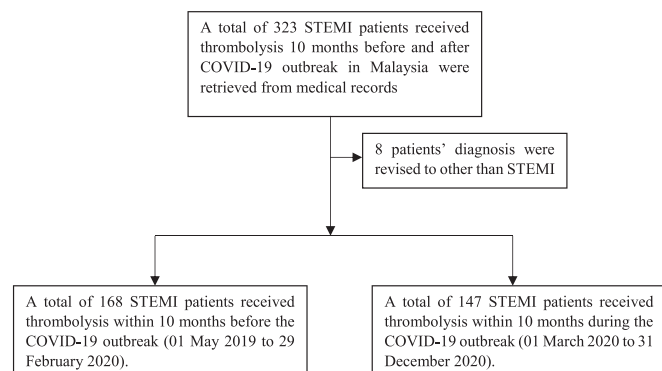


Fig. 1. Study profile.

most (99.3%) STEMI patients in the CovO group were not diagnosed with COVID-19 (Table 1).

3.2. Number of thrombolysis performed

There was a 12.5% reduction in STEMI thrombolysis during CovO as the absolute number of STEMI patients presented to our ED was reduced compared to PCovO for the same duration. Fig. 2 shows the pattern of thrombolysis cases performed nine months before and during the COVID-19 outbreak.

3.3. Impact of COVID-19 outbreak on patient's presentation and ED performance

There was no difference in time from symptoms onset to thrombolysis and DNT before and during the pandemic. There was an increment in

Table 1
Subjects' baseline demographics and clinical characteristics.

Parameters	Frequency, n (%)			P-value, (χ^2)*
	Total (N = 315)	PCovO (N = 168)	CovO (N = 147)	
COVID-19 positive	1 (0.3)	0 (0.0)	1 (0.7)	–
Age				
Mean (\pm SD), in years	52.9 (\pm 12.9)	52.9 (\pm 12.9)	52.9 (\pm 13.0)	0.993 ^a
Range	22–92	22–86	26–92	–
\geq 65 years old	56 (17.8)	32 (19.0)	24 (16.3)	0.529
Male gender	280 (88.9)	147 (87.5)	133 (90.5)	
Race				
Malay	92 (29.2)	47 (28.0)	45 (30.6)	0.608
Chinese	25 (7.9)	12 (7.1)	13 (8.8)	0.577
Indian	59 (18.7)	32 (19.0)	27 (18.4)	0.877
Others Malaysian	6 (1.9)	4 (2.4)	2 (1.4)	0.689 ^b
Permanent residents	37 (11.7)	22 (13.1)	15 (10.2)	0.427
Foreigners	96 (30.5)	51 (30.4)	45 (30.6)	0.961
Current smoker	215 (68.3)	109 (64.9)	106 (72.1)	0.169
Positive family history of IHD	52 (16.5)	25 (14.9)	27 (18.4)	0.406
Comorbidities				
Hypertension	155 (49.2)	86 (51.2)	69 (46.9)	0.451
Diabetes	143 (45.4)	72 (42.9)	71 (48.3)	0.333
IHD	48 (15.2)	26 (15.5)	22 (15.0)	0.9
History of PCI/CABG	10 (3.2)	6 (3.6)	4 (2.7)	0.756 ^b
Heart failure	7 (2.2)	4 (2.4)	3 (2.0)	1.000 ^b
Stroke	6 (1.9)	4 (2.4)	2 (1.4)	0.689 ^b
Dyslipidemia	71 (22.5)	42 (25.0)	29 (19.7)	0.264
Thrombolytic agent				
streptokinase	163 (51.7)	96 (57.1)	67 (45.6)	0.04
tenecteplase	152 (48.3)	72 (42.9)	80 (54.4)	
Anterior involvement MI	177 (56.2)	86 (51.2)	91 (61.9)	0.056
Killip class				
I	154 (48.9)	80 (47.6)	74 (50.3)	0.63
II	72 (22.9)	42 (25.0)	30 (20.4)	0.333
III	20 (6.3)	10 (6.0)	10 (6.8)	0.757
IV	69 (21.9)	36 (24.4)	33 (22.4)	0.827
Cardiac arrest before Thrombolysis	8 (2.5)	4 (2.4)	4 (2.7)	1.000 ^b
Door to needle time				
Median (IQR), minutes	24.0 (15.0–35.0)	20.0 (15.0–30.0)	25.0 (15.0–40.0)	0.151 ^c
\leq 30 min	230 (73.0)	128 (76.2)	102 (69.4)	0.175
Time symptoms onset to thrombolysis (n = 305)				
Median (IQR), minutes	195.0 (130.0–300.0)	196.00 (129.5–285.0)	195.0 (130.0–300.0)	0.892 ^c
$>$ 4 h	110 (36.1)	60 (37.0)	50 (35.0)	0.707
SBP on presentation				
Mean \pm SD, mmHg	129.4 (\pm 24.5)	129.9 (\pm 23.7)	128.7 (\pm 25.4)	0.676 ^a
$<$ 100 mmHg	35 (11.1)	15 (8.9)	20 (13.6)	0.188
Heart rate on presentation				
Mean \pm SD, bpm	83.0 (\pm 21.0)	83.9 (\pm 20.8)	82.0 (\pm 21.3)	0.427 ^a
$<$ 60 bpm	40 (12.7)	15 (8.9)	25 (17.0)	0.032
\geq 100 bpm	61 (19.4)	36 (21.4)	25 (17.0)	0.322

bpm beats per minute; CABG coronary artery bypass graph; CovO COVID-19 outbreak; IHD ischemic heart disease; IQR interquartile range; MI myocardial infarction; PCovO pre-COVID-19 outbreak; SBP systolic blood pressure; SD standard deviation; PCI percutaneous coronary intervention.

* PCovO vs CovO.

^a Independent t-test.

^b Fisher exact.

^c Mann-Whitney U test.

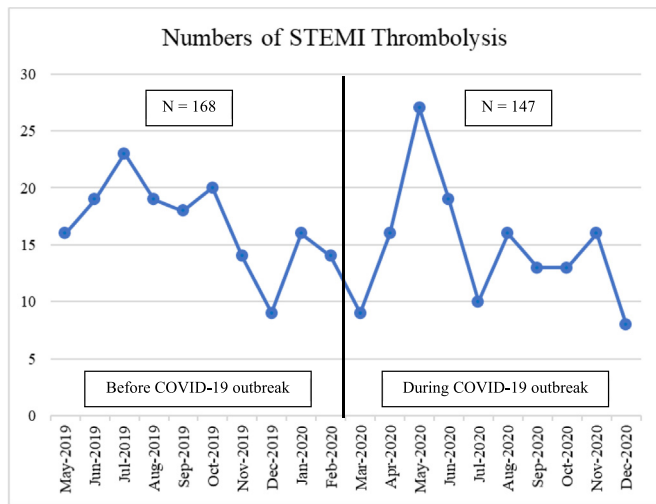


Fig. 2. Numbers of STEMI thrombolysis before and after the COVID-19 outbreak.

tenecteplase usage, but it was not statistically significant in multivariate logistic regression (Table 1 and Table 3).

3.4. Impact of COVID-19 outbreak on thrombolysis outcomes

During the COVID-19 pandemic, in-hospital mortality in STEMI patients who received thrombolysis was higher than pre-pandemic with the same duration (OR 2.02, 95% CI 1.02–4.00, $p = 0.044$). There was no significant difference in bleeding events and the number of overnight stays before and during the pandemic (Table 2 and Table 3).

4. Discussion

To our knowledge, this is the first study that assessed the impact of the COVID-19 pandemic on STEMI thrombolysis outcomes and ED performance in a non-PCI facility of an Asian country that mainly relies on thrombolysis. Interrogation of these data offers the opportunity to evaluate the strengths and weaknesses in STEMI management of a non-PCI-capable centre during the current pandemic, identify the gap to improvise Emergency and Cardiology services and prepare for future major health crises.

This study demonstrated a decrease in STEMI presentation during the CovO period, similar to findings in PCI-capable facilities of several Western countries, China and Singapore, as reported in a meta-analysis and a retrospective cohort study [8]. Several studies have postulated the fear of COVID-19 exposure and lower physical stress during social containment as the reasons for the reduction in myocardial infarction attendance [17–20].

Patients' baseline demographics and clinical characteristics during the presentation to ED were mostly comparable during PCovO and CovO periods, similar to a meta-analysis that reported the effect of the COVID-19 pandemic on mortality of patients with STEMI that included mainly PCI-capable facilities [8]. Surprisingly, the vast majority of patients presented during CovO were tested negative for COVID-19, possibly due to the nationwide strict movement control orders during the study period. However, our study reported a numerically higher number of anterior involvement STEMI and a significantly higher rate of bradycardia (at presentation) during the CovO period. Additionally, we found a worrisome trend of STEMI occurring at a younger age in Malaysia. Our patients were much younger than as reported in similar literature on STEMI outcomes during the pandemic, possibly contributed by the much high prevalence of active smokers in our population [8,20]. Also, our STEMI patients were more ill and had a higher risk of 30-day mortality at presentation as most were presented with anterior involvement STEMI and higher Killip class [21–23].

Table 2
Outcomes following STEMI thrombolysis.

Outcomes	Frequency, n (%)			P-value, (χ^2)*
	Total (N = 315)	PCovO (N = 168)	CovO (N = 147)	
Failed thrombolysis	33 (10.5)	18 (10.7)	15 (10.2)	0.883
All-cause mortality				
In-hospital	41 (13.0)	16 (9.5)	25 (17.0)	0.049
In-hospital strokes				
Ischemic	2 (0.6)	0 (0.0)	2 (1.4)	0.217 ^b
TIMI Bleeding				
Major	0 (0.0)	0 (0.0)	0 (0.0)	–
Minor/Minimal	41 (13.0)	26 (15.5)	15 (10.2)	0.165
Number of overnights stays, days				
Median (IQR)	4.0 (4.0–5.0)	4.0 (4.0–5.0)	4.0 (4.0–6.0)	0.768 ^a
Cardiac events post fibrinolysis (in-hospital)				
Reinfarction	8 (2.5)	7 (4.2)	1 (0.7)	0.072 ^b
Hypotension	56 (17.8)	32 (19.0)	24 (16.3)	0.529
Bradycardia	28 (8.9)	15 (8.9)	13 (8.8)	0.979
Second- and third-degree AV block	2 (0.6)	1 (0.6)	1 (0.7)	1.000 ^b
Congestive heart failure	5 (1.6)	3 (1.8)	2 (1.4)	1.000 ^b
Cardiogenic shock	4 (1.3)	2 (1.2)	2 (1.4)	1.000 ^b
VF/VT	48 (5.2)	32 (19.0)	16 (10.9)	0.044
AF	9 (2.9)	7 (4.2)	2 (1.4)	0.182 ^b
Stent placement	51 (16.2)	24 (14.3)	27 (18.4)	0.327
Anaphylaxis and allergic reaction	11 (3.5)	4 (2.4)	7 (4.8)	0.251

AF atrial fibrillation/flutter; AV atrioventricular; CovO COVID-19 outbreak; IQR interquartile range; PCovO pre-COVID-19 outbreak; PEA pulseless electrical activity; SVT supra-ventricular tachycardia; TIMI thrombolysis in myocardial infarction; VF/VT ventricular fibrillation/ tachycardia.

* PCovO vs CovO.

^a Mann-Whitney U test.

^b Fisher exact.

Despite the pandemic, the insignificant difference in symptoms onset to thrombolysis time may suggest an insignificant delay in patients seeking treatment at the ED. Nevertheless, the overall proportion of STEMI patients who received thrombolytic therapy within 4 h from the onset of the ischemic symptoms was far higher than 23.2% as reported in a major clinical trial on STEMI thrombolysis [24]. This finding showed that most of our STEMI patients attended the ED late to seek treatment, even before the pandemic. Time from ischemic symptoms to treatment is among the risk factors affecting STEMI mortality [25]. Thus, it is crucial to equip the public with awareness of myocardial infarction symptoms where they should attend the hospital in the event of a medical emergency.

The ED performance on acute STEMI management was evaluated based on the achievement of DNT ≤ 30 min. The achievement of DNT ≤ 30 min is one of the key performance indicators for ED under the Ministry of Health Malaysia. The insignificant difference in DNT achievement indicated our ED could maintain its high-quality performance, although there was a minimal insignificant delay of DNT during the pandemic. The binary system adapted by ED HKL since the early COVID-19 outbreak probably contributed to the preserved

Table 3
Results of multivariate regression models.

Model (n = 315)	Outcome variable	OR (95% CI)	P-value
1 ^a	Time symptoms onset to thrombolysis, hour	12.95 (–19.65–45.56)	0.435
2 ^a	Door-to-needle time, minute	–5.23 (–15.42–4.97)	0.314
3 ^b	Tenecteplase use	1.57 (0.99–2.49)	0.055
4 ^b	In-hospital mortality	2.02 (1.02–4.00)	0.044
5 ^b	Bleeding event	0.63 (0.32–1.25)	0.168
6 ^a	Number of overnight stay	2.05 (–0.04–4.14)	0.054

^a Linear regression.

^b Logistic regression; control variables = age and gender.

performance. Under the binary system, ED treatment zones were categorized into 'clean' and 'dirty' zones. The 'clean' zones catered for patients who presented without any symptoms of infectious diseases, and vice versa for 'dirty' zones. Each of these 'clean' and 'dirty' zones has red, yellow, and green segments that cater for patients based on illness severity [3]. This binary system can efficiently triage patients based on their symptoms at presentation and reduce the healthcare workers' exposure to COVID-19 [3]. On top of that, we observed numerically higher usage of tenecteplase during the pandemic. Tenecteplase offers the benefits of ease of administration, high fibrin-specificity, and fewer adverse events (especially hypotension and allergic reaction), although it requires accurate weight-based dosing and is more costly than streptokinase [5,26].

Higher mortality following STEMI thrombolysis during the pandemic was observed despite the preserved ED performance on DNT and increased use of the fibrin-specific thrombolytic agent. However, the numerically higher numbers of patients with anterior involvement STEMI probably partially contributed to the mortality rates. Anterior STEMI occurs following the occlusion of the left anterior descending (LAD) artery and carries the poorest prognosis than other infarct locations as it causes a larger infarct area of the myocardium [27]. The lack of dedicated Cardiology wards (Coronary Care Unit and Cardiac Rehabilitation Ward were converted to general SARI wards) and the requirement of healthcare workers to be equipped with personal protective equipment (PPE) before conducting CPR in cardiorespiratory arrest patients (CPR involves numerous aerosol-generating procedures) may also be attributed to the higher mortality during CovO period. Additionally, there were two cases of ischemic stroke post thrombolysis during the pandemic with 100% mortality.

Our mortality finding was in agreement with a Chinese study that advocated "thrombolysis first" during the pandemic, where STEMI mortality increased simultaneously following the increment in STEMI thrombolysis and reduction in PCI performed, specifically at the epicenter (Hubei Province) [6]. However, our mortality finding was in contrast with the finding of a meta-analysis that included most studies that reported PCI-related outcomes [8]. Before the COVID-19 pandemic, Malaysian National Cardiovascular Disease (NCVD) Registry had reported 2.0% of in-hospital mortality (for 2015–2016) following primary PCI, far lower than 17% reported during the first ten months of the pandemic [28]. Our findings suggest that PCI remains a better option for STEMI despite the pandemic, and PCI-capable facilities should maintain the PCI service for eligible patients presented to their centre.

We acknowledged several limitations in this study. The retrospective observational nature of this study may affect the data quality primarily due to recall bias in the documentation and missing data. However, missing data was minimized as the reporting of STEMI cases is the key performance indicator for the ED, and the Cardiology Unit is the source data provider for the Malaysian NCVD Registry. Nevertheless, this study provided the "real world" data with consecutive STEMI patients over 20 months despite the retrospective design.

Secondly, the sample size of this present study was not powered to assess differences in the endpoint. Thus, the observed data on clinical outcomes should be considered exploratory only. We assessed only short-term STEMI outcomes limited to the index hospital stay, as long-term follow-up data are currently unavailable and the COVID-19 pandemic is still not under control. Lastly, this study was a single-centre study conducted in a tertiary hospital in the urban capital city of Malaysia. Hence, the results obtained in this study may not represent all hospitals in Malaysia.

5. Conclusion

STEMI thrombolysis cases were reduced during the COVID-19 pandemic, with an inverse increase in mortality despite the preserved Emergency Department performance in timely thrombolysis.

Funding

This study was a self-funded work.

Data availability

Raw data are not attached.

Ethics approval

This study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-20-2630-57346).

Credit authorship contribution statement

Hock Peng Koh: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Adyani Md Redzuan:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Shamin Mohd Saffian:** Writing – review & editing, Validation, Supervision. **Jivanraj R. Nagarajah:** Investigation, Writing – review & editing. **Noel Thomas Ross:** Investigation, Writing – review & editing. **Hasnita Hassan:** Investigation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgement

We would like to thank the Director-General of Health, Ministry of Health Malaysia for his permission to publish this article.

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