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ORIGINAL RESEARCH

The difficulty in distinguishing the type of occlusive coronary artery disease among patients with sepsis in the emergency department: a multicenter retrospective cohort study

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Abstract

Purpose: Distinguishing true obstructive coronary artery disease (OCAD) from myocardial infarction (MI) resulting from a mismatch between oxygen supply and demand (T2MI) in patients with sepsis is difficult. This study aimed to assess the clinical presentation and laboratory biomarkers of OCAD in patients with sepsis in the emergency department.

Materials and Methods: This was a multicenter retrospective cohort study. We included patients diagnosed with sepsis or septic shock in the emergency department between January 2010 and December 2017 and who underwent coronary angiography in the emergency department for suspected concomitant MI. The patients were categorized into the mixed MI group, for those who had significant coronary occlusion superimposed on type 2 MI or the pure type 2 MI (T2MI) group.

Results: A total of 71 patients were included after exclusion. Forty patients (56.3%) had OCAD (mixed MI). Fever (25% vs. 15%) and high scores of quick sequential organ failure assessment (qSOFA score) (35.5% vs. 27.5%) were more frequent in the T2MI group, and the troponin-I level was more elevated in the mixed MI group, but the difference was not significant. The most common focus of infection was pulmonary. Sepsis patients with OCAD tended to have longer admissions in the intensive care unit and ward admission days. However, the proportion of mortality and shock events was similar to T2MI group after percutaneous coronary artery intervention (PCI) treatment.

Conclusions: Differentiating between mixed MI from pure T2MI through clinical presentation or laboratory results in patients with sepsis with suspected myocardial infarctions remains difficult. Lowering the threshold of coronary artery angiography may play a critical role in differentiating OCAD from T2MI.

Keywords

Sepsis; Obstructive coronary artery disease; Myocardial infarction; Coronary angiography; Type 2 MI

1. Introduction

Acute coronary artery syndrome (ACS) remains a fetal disease in the emergency department (ED). It results in significant disability and mortality and accounts for up to 10% of all ED admissions in the US [1]. The Diagnosis of acute coronary artery syndrome is a major task for emergency physicians. In 2007, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Society of Cardiology, and the World Heart Federation proposed the first universal definition of myocardial infarction (MI), categorizing MI into five subgroups [2]. The latest update was published in 2018 after years of practice and remodification. The fourth universal definition of myocardial infarction states that type 1 MI is that caused by atherothrombotic coronary artery disease (CAD) and is usually precipitated by atherosclerotic plaque disruption. On the other hand, type 2 MI refers to a pathophysiological mechanism leading to ischemic myocardial injury in the context of a mismatch between oxygen supply and demand. This mismatch could be caused by acute stress, sustained tachyarrhythmia, severe anemia, hypotension, or other chronic diseases [3]. The prevalence of type 2 MI reported in the literature varies from 1.6% to 29% [4–6].

The treatment for different types of MI could be different. Type 1 myocardial infarction should be treated with early revascularization, percutaneous coronary artery intervention,

dual-antiplatelet therapy (DAPT), and high-dose statins. These treatments have been shown to improve patient outcomes and mortality and morbidity rates and are recommended in current clinical guidelines [7]. In contrast, there is a lack of evidence-based recommendations for the treatment of T2MI. This could be due to the variability and complexity of the underlying conditions [8]. It is crucial to differentiate between these two types of MI patients in the early stages for treatment purposes from a clinical perspective. Unfortunately, distinguishing T2MI from T1MI is difficult in practice.

Among several acute stressors, sepsis has long been one of the most important fatal diseases in the ED. Although not specified as a pathophysiological factor by the third universal MI definition of T2MI, sepsis was listed as a systemic condition causing myocardial injury and cardiac troponin elevation in the fourth universal definition. Distinguishing T1MI from T2MI in patients with sepsis could be challenging. The troponin-I level is frequently used as a reference. Serum troponin concentrations have been associated with increased mortality in almost every clinical setting they have been examined, including sepsis. Non-thrombotic troponin elevation is probably multifactorial and a common finding among critically ill patients with sepsis [9]. High troponin elevation was reported to be more frequent in T1MI, whereas marked elevation of C-reactive protein (CRP) level was associated with T2MI. However, the suggested cut-off value for troponin or CRP levels is still unknown [10].

Despite increasing attention on T2MI over the last decade, there is still uncertainty regarding its true incidence, diagnostic criteria, management, and prognosis. In a previous study, concomitant occlusive coronary artery disease was identified as a poor prognostic factor for patients hospitalized for severe sepsis or septic shock, which was defined as a mixture of T1MI and T2MI [11]. Rapid and accurate diagnosis of sepsis patients with either a mixed MI or pure T2MI may influence treatment planning and, ultimately, a patient's prognosis. However, differentiating the above two conditions is difficult, and research on this topic is scarce [12]. This study aimed to investigate sepsis patients with suspected occlusive coronary artery disease by assessing clinical features, laboratory data, and angiography results taken from the emergency department.

2. Methods

2.1 Study design

This retrospective cohort analysis was conducted at multiple medical centers in Taiwan. The study site included two medical centers, one of which is the largest medical facility in Taiwan, and two regional hospitals. The largest site consists of 3700 primary beds and 206,657 annual ED visits. All study sites used the Chang Gung electronic medical record system for regular data collection. Electronic medical records throughout 8 years (2010–2017) were collected and analyzed. This study was approved by the Chang Gung Medical Foundation Institutional Review Board (IRB No. 202100420B0) and was qualified for a waiver of informed consent. This study was prepared with adherence to the STROBE guidelines.

2.2 Patient population and definition

All patients diagnosed with sepsis and believed to have acute coronary syndrome who underwent coronary angiography from 2010–2017 were included. Sepsis or acute infection was diagnosed using the implicit ICD-9 or ICD-10 codes of sepsis or septic shock. Acute myocardial infarction was defined according to the fourth universal definition of MI. All patients underwent coronary angiography after consultation with an emergency cardiologist. Patients who did not undergo blood tests or who refused coronary angiography were excluded.

A type I Myocardial infarction (T1MI) was defined as the detection of a rise in cardiac troponin values with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: symptoms of acute myocardial ischemia, new ischemic electrocardiogram (ECG) changes; development of pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology, or identification of a coronary thrombus by angiography including intracoronary imaging or autopsy. T1MI is often related to ischemia due to a primary coronary event such as spontaneous plaque erosion or rupture and intraluminal thrombus.

A type II myocardial infarction (T2MI) was defined as the detection of a rise or fall in cardiac troponin values with at least one value above the 99th percentile URL and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following: symptoms of acute myocardial ischemia; new ischemic ECG changes; development of pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology. We also included patients with normal cardiac troponin level and ischemic ECG changes, and those who presented with typical chest pain or exertional dyspnea due to suspected acute myocardial infarction. T2MI was defined as the absence of evidence of plaque rupture on coronary angiography, with the presence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, which in our study was sepsis and acute infection.

2.3 Data collection

Patients' basic information and information regarding underlying diseases such as end-stage renal disease, cardiovascular disease, hypertension, diabetes mellitus, and other diseases were collected. Initial vital signs and scores on Glasgow coma scale and quick sequential organ failure assessment (qSOFA) at the ED were documented. Laboratory data recorded included C-reactive protein, troponin-I, blood culture, hemoglobin, serum creatinine, ECG at present, and the subsequent ECG. Patients' formal coronary artery angiography reports or percutaneous coronary artery intervention notes were also reviewed to verify whether occlusive myocardial infarction or non-obstructive coronary artery was concluded. The authors also documented whether coronary artery intervention such as plain old balloon angioplasty (POBA), coronary artery stenting, or intra-aortic balloon pump (IABP), were used.

TABLE 1. Patient demographics.

	Mixed MI (40)	Type II MI (31)	*p*-value
Age [years (mean ± SD)]	68.70 ± 12.23	66.74 ± 15.85	0.279
Gender male (n, %)	21 (52.5%)	20 (64.5%)	0.088
Diabetes mellitus	17 (42.5%)	9 (29.0%)	0.243
Hypertension	21 (52.5%)	16 (51.6%)	0.974
ESRD	5 (12.5%)	2 (6.45%)	0.396
Previous CAD	10 (25%)	4 (12.9%)	0.204
Cancer	2 (5%)	3 (9.68%)	0.445

MI, myocardial infarction; ESRD, end-stage renal disease; CAD, coronary artery disease.

2.4 Statistical analysis

Continuous variables are expressed as mean (standard deviation, SD), whereas categorical variables are indicated as frequency (%). We used Student's *t*-test for the comparison of continuous variables between independent groups. We used the Chi-square test or Fisher exact test to compare categorical variables between independent groups, when appropriate. There was no missing data in categorical variables. Missing data was little in continuous variables and we did not imputation data due to data was not random. All analyses were performed using SAS statistical software (version 9.4, SAS Institute, Cary, NC, USA). Statistical significance was set at $p < 0.05$.

3. Results

A total of 211 patients fulfilled the inclusion criteria and were included in the study. After a detailed review of medical records, 140 cases were excluded due to the following: no obvious infection signs and symptoms at presentation, sepsis occurred after admission, or percutaneous coronary artery intervention was not performed at the emergency department. Ultimately, 71 patients were included, with 41 men and 30 women. Coronary angiography results were available for all 71 patients. Among these patients, 31 patients with non-significant coronary artery stenosis, a patent coronary artery, or coronary artery spasm were categorized as having pure T2MI. The other 40 patients who had significant coronary artery stenosis or intraluminal thrombus, according to angiography, were categorized as having mixed MI (Fig. 1).

Comparing the mixed MI and pure T2MI groups, there were no significant differences in age and sex. Regarding their underlying disease, there was no significant difference in the proportion of patients who presented with previous diabetes mellitus, hypertension, end-stage renal disease, cardiovascular disease history, and cancer (Table 1).

All 71 patients underwent coronary artery angiography during emergency department admission. Among them, 31 patients were found to have a patent coronary artery, insignificant stenosis, or coronary artery spasm, and were categorized under the pure T2MI group. In the T2MI group, seven (22.6%) patients underwent intra-aortic balloon pump (IABP) insertion during angiography due to severe shock, and one patient underwent extracorporeal membrane oxygenation (ECMO) during angiography (Table 2). The other 40 patients whose coronary artery angiography showed occlusive myocardial infarction were categorized as having mixed MI with T1MI and T2MI. There were 20 (50%) patients with one-vessel disease, 11 patients with LAD occlusion, seven patients with RCA occlusion, and two patients with LCX occlusion. Seven of the mixed MI groups (17.5%) had a two-vessel disease, and 13 (32.5%) had triple-vessel disease. In the mixed MI group, 36 (90%) patients underwent plain old balloon angioplasty (POBA), and 31 (77.5%) patients underwent POBA and coronary artery stent implantation. Four patients failed to receive POBA or stent due to the severity of thrombus, for whom only underwent staging percutaneous coronary artery intervention (PCI) with heparin flush was performed. In the mixed MI group, six (15%) patients had IABP, and one (2.5%) had ECMO during coronary artery angiography.

Upon comparing vital signs and laboratory data, a higher proportion of the T2MI group patients were found to have fever and a higher qSOFA score ($\geq$2) than the mixed MI group patients. However, this difference was not statistically significant. A majority of ECGs were presented with ischemic changes at both groups, and STEMI (S-T segment elevation MI) or STEMI equivalent was noted in 70% of the mixed MI group and 67.74% in the pure T2MI group. The median conventional troponin-I level was high in both groups. Hemoglobin levels were within the normal range in both groups. Elevated white blood cell count and CRP levels were found in both groups without statistical significance (Table 3). As for prognosis and severity, the proportion of patients with shock and mortality was equivalent in both groups. The patients in the mixed MI group were found to have longer durations of stay in the intensive unit and ward admission but this did not significantly differ from the other group (Table 2). The most common cause of infection was pulmonary infection, followed by intra-abdominal infections and sepsis with an undetermined focus (Table 4).

Missing data was only in CRP variables and there were 7/40 (17.5%) in T1MI group and 6/31 (19.6%) in T2MI group data missed, due to similar percentage, and missing data was not in random, we calculated continuous variables without imputation of missing data.

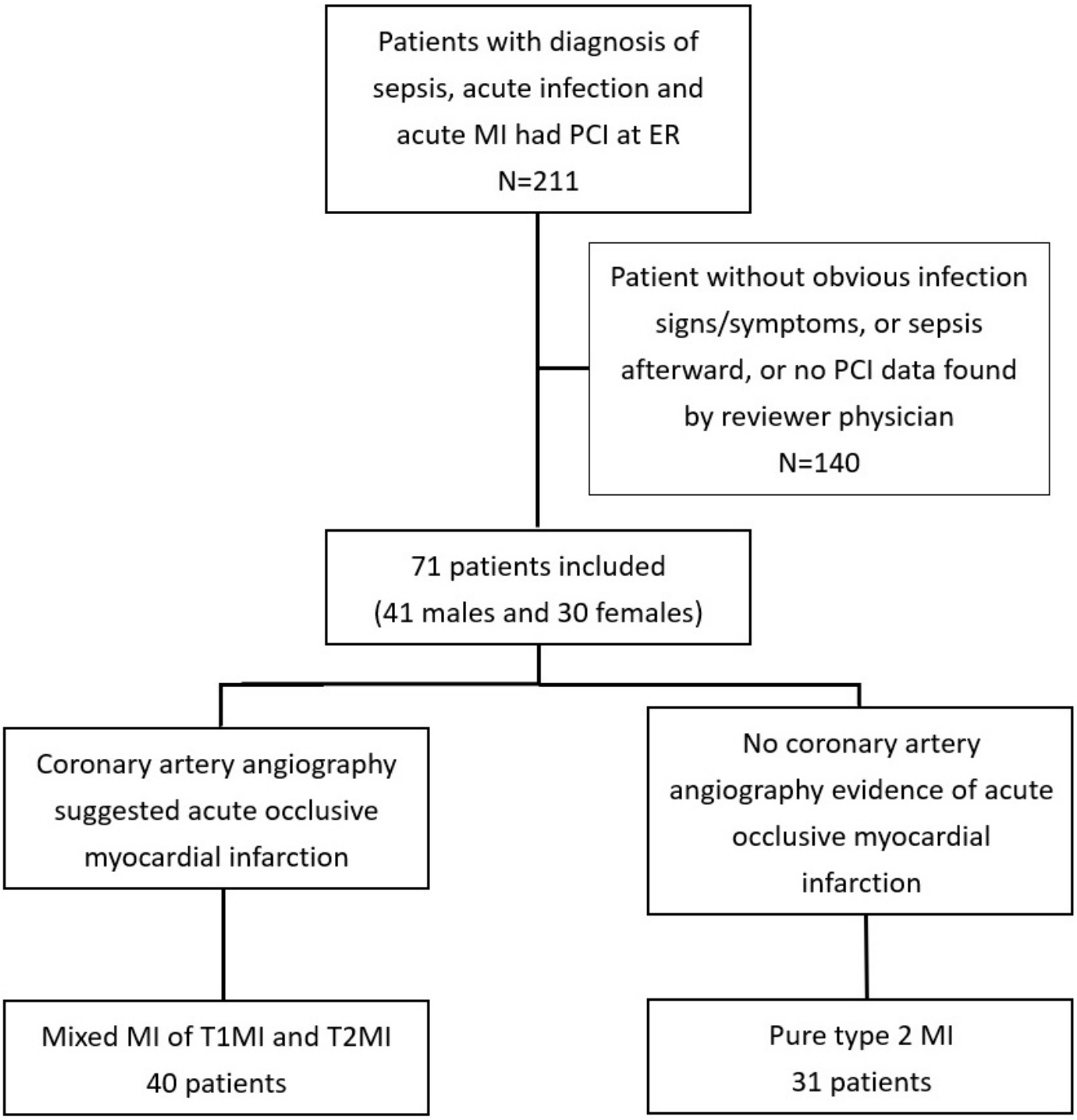

FIGURE 1. Data collection algorithm.

4. Discussion

Myocardial infarction remains the leading cause of death around the globe. This challenging task to distinguish occlusive coronary artery disease from T2MI is especially important in the emergency department that has to make decisions within a limited period of time. Some evidence revealed that the clinical presentation may help distinguish between T1MI and T2MI, but signs and symptoms do not allow a definitive diagnosis [13, 14]. Thus, a definitive diagnosis of T1MI is now made by coronary angiography, and patients with T2MI do not present with plaque rupture or culprit lesions with thrombosis [15].

Previous studies have discussed distinguishing T1MI from T2MI through clinical presentation, CRP, or troponin-I levels. Some studies showed that troponin levels were higher, ranging from 30% to 94%, in patients withT1MI [4, 8, 16–20]. However, in most of these studies, the diagnostic criteria for T2MI and, T1MI were not made according to angiography results but through the universal definition of MI or local protocol. Other studies included a more heterogeneous cohort, including heart failure, anemia, sepsis, or sustained tachycardia, and found that the median troponin values were higher in patients with T1MI than those with T2MI [14, 16, 21, 22]. To date, no study has compared cardiac troponin levels between mixed MI

TABLE 2. Results of the coronary angiography.

	Mixed MI (40)	Type II (31)	*p*-value
1V-D %	20 (50%)	3 (9.68%)	
LAD	11		
RCA	7		
LCX	2		
2 V-D %	7 (17.5%)	1 (3.22%)	
3 V-D %	13 (32.5%)	2 (6.44%)	
Patent	0	14 (45.2%)	
Insignificant stenosis	0	14 (45.2%)	
Coronary artery spasm	0	3 (9.68%)	
POBA	36 (90%)	0	
Stent	31 (77.5%)	0	
IABP	6 (15.0%)	7 (22.6%)	0.413
ECMO	1 (2.50%)	1 (3.22%)	0.855

1 V-D, one vessel disease; LAD, left anterior descending artery; RCA, Right coronary artery; LCX, Left circumflex artery; 2 V-D, two vessel disease; 3 V-D, 3 vessel disease; POBA, Plain Old Balloon Angioplasty; IABP, Intra-Aortic Balloon Pump; ECMO, Extracorporeal Membrane Oxygenation.

TABLE 3. Comparison of mixed MI and type 2 MI.

	Mixed MI (40)	Type II (31)	*p*-value
Fever (>38 °C)	6 (15%)	8 (25.8%)	0.256
qSOFA			
Not high risk (0, 1)	29 (72.5%)	20 (64.5 %)	0.471
High risk (2, 3)	11 (27.5%)	11 (35.5%)	
Initial EKG			0.838
STEMI (or equivalent)	28 (70%)	21 (67.7%)	
NSTEMI	12 (30%)	10 (32.3%)	
Initial troponin I	10.31 ± 22.56	7.13 ± 15.77	0.510
CRP	117.13 ± 103.66	95.51 ± 105.96	0.464
Hb	12.18 ± 2.27	12.35 ± 2.83	0.785
WBC count	15,012 ± 6416	13,409.68 ± 8698.37	0.374
>12000 or <4000	27 (76.5%)	17 (54.8%)	0.276
Seg >75%	78.98 ± 13.15	75.89 ± 19.02	0.414
	28 (70%)	22 (70.9%)	0.929
Band >3%	9 (22.5%)	8 (25.8%)	0.746
Shock (with inotropic)	18 (45%)	16 (51.6%)	0.580
ICU days	11.95 ± 18.37	8.03 ± 9.48	0.284
Admission days	21.25 ± 23.82	14.10 ± 12.24	0.132
Mortality	11 (27.5%)	10 (32.3%)	0.598

qSOFA, quick sepsis-related organ dysfunction assessment; EKG, Electrocardiography; STEMI, ST segment elevation myocardial infarction; NSTEMI, Non-ST segment elevation myocardial infarction; CRP, C-reactive protein; Hb, hemoglobin; WBC, white blood cell; Seg, segment count; ICU, intensive care unit.

and T2MI. Our study included 71 patients, all of whom had angiographic reports. In the current study, the mean troponin-I level in the mixed MI group was higher than in the T2MI group, but the difference was not statistically significant. A majority (56%) of our patients did not undergo a second test for troponin or peak troponin levels. The troponin-I level depends on blood

TABLE 4. Infection focus.

	Mixed MI (40)	Type II (31)	*p*-value
Pulmonary	21 (52.5%)	16 (51.6%)	0.941
Abdominal	6 (15%)	6 (19.4%)	0.627
Sepsis, unknown focus	7 (17.5%)	4 (12.9%)	0.635
Urinary	1 (2.5%)	2 (6.5%)	0.412
Peri-myocarditis	1 (2.5%)	2 (6.5%)	0.412
Bacteremia	3 (7.5%)	1 (3.2%)	0.439
Deep neck infection	1 (2.5%)	0	

Pulmonary: pneumonia, bronchitis, bronchopneumonia. Abdominal: biliary tract infection, peritonitis, colitis, enteritis, cholecystitis. Bacteremia: septicemia, central catheter infection.

flow circulation and the time it was collected after the onset of symptoms [23]. The large standard deviation of troponin values may result from a wide variation in the blood sampling time since onset, which may explain why the troponin-I levels did not differ significantly between the two groups.

Many pathophysiological conditions can cause an imbalance between myocardial oxygen supply and demand, with sepsis being one condition that has been widely reported (19%–38.1%) [5, 24]. Sepsis can cause myocardial cell injury through inducing ischemia and releasing endotoxins, causing cardiac troponin elevation [3, 25]. Our data showed that it remained difficult to differentiate between T2MI and mixed MI using band percentage, white blood cell count, and CRP level. Our study's most common infection focus was pulmonary, which is similar to that of a previous study (63%–65.6%) [11]. Overlapping symptoms from pulmonary infection and myocardial infarction, dyspnea, and chest pain can cause difficulties during the differentiation process. Although there were higher rates of and higher qSOFA scores in the T2MI group in our data, these did not significantly differ from the other group. Therefore, there is currently no evidence to support the use of vital signs, qSOFA, or septic biomarkers in differentiating mixed MI from T2MI.

Large variability was observed in the prevalence of T2MI among previous studies, ranging from 5%–35% [6, 26, 27]. In a single-center retrospective cohort study, patients hospitalized for severe sepsis underwent coronary angiography to identify concomitant AMI. Among these patients, 41% had obstructive coronary artery disease [11]. If these patients were treated for pure T2MI, it would lead to disastrous outcomes. Because patients with sepsis are often under critical conditions, and the fact that the results of a coronary artery angiography among those suspected of having concomitant ACS may largely deviate from the original treatment planning, we propose that ED physicians should lower the threshold for coronary artery angiography in patients with sepsis.

Previous studies have shown that, among pure ACS patients, the mortality and morbidity rates were worse in T2MI than in T1MI [28]. The short and intermediate-term mortality rates were also three times higher in patients with T2MI. These patients tended to be older, female, and had a higher prevalence of cardiac and non-cardiac comorbidities [24]. Very few studies have compared mixed MI and T2MI in terms of prognosis. In our study, despite the longer intensive care unit and ward admission days observed in the mixed MI group, there was no difference in mortality and shock rate. The results indicated a critical role of percutaneous coronary artery intervention in the mixed MI group, resulting in a mortality rate similar to that of T2MI after PCI therapy for OCAD. In other words, lowering the threshold of coronary angiography in patients with suspected myocardial infarction and sepsis can lead to a game-changing diagnosis of OCAD.

5. Limitations

Our study has several limitations. First, the study's retrospective nature prevented some of the important characteristics from being analyzed, such as the degree and characteristics of pain. Second, we analyzed the data only for patients who underwent coronary angiography; thus, patients who refused to undergo the procedure were not included in the current study. Thus, a selection bias may be present. However, the authors regard this bias as non-differential in our case. Third, this was a single-country study. The race distribution is relatively simple in Taiwan, and the majority race is Han Chinese. We look forward to future studies in different countries. Fourth, patients with diagnostic codes of certain focus (pneumonia, UTI, etc.) may not have been included in our study. This may have caused a selection bias.

6. Conclusions

It remains difficult to differentiate mixed MI from pure T2MI through clinical presentation or laboratory results among sepsis patients with possible myocardial infarctions. Lowering the threshold of coronary artery angiography may play a critical role in differentiating OCAD from T2MI.

AUTHOR CONTRIBUTIONS

YHC, SYC, HYL, CJN and CHC has made substantial contributions to conception and design. YHC and SYG, and SYC contributed acquisition of data, or analysis and interpretation of data. HYL, CJN and CHC drafted the article or revised it critically for important intellectual content. All authors listed approved the final version to be published. All individuals who qualify for authorship are listed as authors.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Chang Gung Medical Foundation Institutional Review Board (IRB No. 202100420B0) and was qualified for a waiver of informed consent. This study was prepared with adherence to the STROBE guidelines.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Shou-Yen Chen is a Guest Editor of this journal.

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