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Comparison of long-term mortality in patients with acute myocardial infarction associated with or without sepsis

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ABSTRACT

Objectives: Although the association between systemic infection and cardiovascular events has been identified, uncertainty remains regarding the incidence and prognosis of sepsis in acute myocardial infarction (AMI). The purpose of this research was to assess the impact of sepsis on survival after first AMI.
Methods: This was a nationwide cohort study involving the analysis of data from the Taiwan National Health Insurance Research Database for the period 2000–2012, for patients with a primary diagnosis of first AMI. Among the 186 112 prospective patients, sepsis was diagnosed in 13 065 (7.0%). The propensity score matching technique was used to match 13 065 controls to the patients with sepsis and AMI with similar baseline characteristics. Cox proportional hazards regression models, including sepsis, percutaneous coronary intervention (PCI), and comorbidities, were performed to further evaluate the different influences on the mortality risk in patients hospitalized for first AMI.
Results: Overall, the 12-year survival rate was lower in AMI patients with sepsis than in those without sepsis (log rank p-value <0.001); this was also shown in the different age and sex groups. The AMI patients with sepsis had a longer length of hospital stay than those without sepsis (32.5 days vs. 11.74 days, $p < 0.001$). In the Cox proportional hazards regression analysis, sepsis was an independent risk factor for mortality in patients after AMI (hazard ratio 1.78; 95% confidence interval 1.72–1.83). Interventional management with PCI or coronary artery bypass grafting improved survival in both the sepsis and non-sepsis patients after first AMI.
Conclusions: In conclusion, sepsis significantly increased the mortality risk of patients after first AMI. PCI may improve the long-term survival of patients in comparison to those managed conservatively.
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Introduction

Cardiovascular disease, especially ischemic heart disease, is one of the leading causes of mortality and morbidity worldwide. More than lipid accumulation within the artery wall, inflammation plays an important role in atherosclerosis, both in vulnerable and stable plaques (Ross, 1999; Mauriello et al., 2005). Systemic infection may cause exaggerated inflammation in atherosclerotic coronary arteries, triggering rupture of plaques and acute myocardial infarction (AMI) (Madjid et al., 2007). Several studies have demonstrated an association between infection and AMI (Madjid et al., 2007; Ramirez et al., 2008; Dalager-Pedersen et al., 2014; Kwong et al., 2018).

Sepsis is a clinical syndrome caused by a dysregulated inflammatory response to an infectious process (Rhodes et al., 2017; Singer et al., 2016). The aberrant production of proinflammatory mediators during sepsis can lead to tissue injury and organ damage (Remick, 2007). For patients with coronary artery disease (CAD), sepsis may exert a negative influence on vascular walls through a hyper-inflammation response, activated

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coagulation, or direct bacterial invasion of atherosclerotic plaques. These pathophysiological changes contribute to subsequent atheroma instability and plaque rupture (Madjid et al., 2007; Ramirez et al., 2008; Remick, 2007). Other than acute thrombosis, the link between AMI and systemic infection can also be explained by an oxygen supply-and-demand mismatch (Ramirez et al., 2008; Dalager-Pedersen et al., 2014; Thygesen et al., 2012). However, inflammation has been suggested to play the central role. In an autopsy study, increased infiltration of inflammatory cells (e.g., the macrophage density) in the atherosclerotic coronary arteries was noted in patients with AMI and systemic infection, in comparison to the non-infected group (Madjid et al., 2007). Another study found that patients with an infection associated with a stronger inflammatory response (e.g., lower respiratory tract infection) were at greater risk of developing AMI than those whose infections were associated with a mild inflammatory response (e.g., urinary tract infection) (Smeeth et al., 2004). These findings in systemic infection and sepsis might further affect the prognosis of AMI.

Globally, both ischemic heart disease and sepsis are the leading contributors to the burden of disease (Murray et al., 2015; Jawad et al., 2012). Although the association and possible mechanism of the association between AMI and sepsis have been reported, the impact of infection on clinical outcomes in patients with AMI remains unclear (Madjid et al., 2007; Ramirez et al., 2008; Dalager-Pedersen et al., 2014; Kwong et al., 2018; Smeeth et al., 2004). Therefore, this nationwide cohort study was performed to evaluate the influence of sepsis on survival after first AMI through an analysis of the data from the Taiwan National Health Insurance Research Database (NHIRD).

Methods

Data source

Unweighted data from the NHIRD for the period 2000–2012 were analyzed. National Health Insurance (NHI) in Taiwan is a mandatory health insurance program established in 1995, and covers nearly 100% of the population of Taiwan. The NHIRD contains comprehensive patient medical records, offering researchers detailed data. The Human Research Committee of Kaohsiung Veterans General Hospital approved this study.

Definition of the AMI population

The 186 326 prospective participants hospitalized with a primary diagnosis of first AMI were identified using ICD-9 diagnosis codes 410–410.92 for patients admitted to hospital between January 2000 and December 2012 in Taiwan. Patients whose insurance record was unclear and those who were younger than 18 years of age or older than 120 years of age were excluded from this group, leaving 186 112 cases for study (Figure 1).

Study population

Among patients who qualified as cases of first hospitalization for AMI, those with sepsis were identified using ICD-9 diagnosis codes 038–038.9 (Supplementary material, Table S1). Of the remaining 173 047 patients, those with an infection but who did not fulfill the criteria for sepsis were excluded by identifying the cases with ICD-9 diagnosis codes for an infectious process (Supplementary material, Table S2). Propensity score matching was used to identify cohorts of patients with similar baseline characteristics for the sepsis group and the control group. For the comparison study, the 13 065 matched controls were selected by one-to-one matching protocol according to sex, age group, and comorbidities (Figure 1). The type of AMI and comorbidities were identified by ICD-9 codes (Supplementary material, Table S3). The influence of drugs was also analyzed by recognition of ATC codes (Supplementary material, Table S4).

Outcome analysis

All enrolled patients were followed until death or December 31, 2012, whichever occurred first. To measure the outcome, mortality was defined as the end date of NHI coverage. As NHI in Taiwan is mandatory and the premium is paid monthly, the difference between the date of admission and the end date of NHI coverage offers a valid measure of survival, limiting the maximum error to within 1 month (Cheng et al., 2015; Wang et al., 2017a; Kuo et al., 2016; Kuo et al., 2018).

Statistical analyses

Categorical data were recorded as percentages and were evaluated by Chi-square test. Continuous variables were recorded as the mean and standard deviation (SD) and compared by paired *t*-test. The Cox proportional hazards regression model was applied to calculate the hazard ratio (HR) and associated 95% confidence interval (95% CI). The Kaplan–Meier method was used to estimate cumulative survival and the differences between the patients with sepsis and the control group, as well as to compare subgroups including sex, age, and management with invasive interventions. The differences between the curves were tested by log-rank test. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). A two-sided statistical test with a *p*-value of <0.05 was considered statistically significant.

Results

Descriptive characteristics of the study group

A total of 186 112 patients with AMI were enrolled in this study. Among these patients, sepsis developed in 13 065 (7.0%). The clinical characteristics of the patients forming the sepsis group and those forming the matched control group are displayed in Table 1. The two groups were comparable for baseline variables including sex, age, and medical comorbidities. Patients with sepsis displayed a higher proportion of non-ST-elevation myocardial infarction (NSTEMI) (77.18% vs. 64.15%, $p<0.001$) (Table 1). The proportions of medications prescribed for cardiovascular diseases were higher in the non-sepsis control cohort. The results also revealed that higher proportions of patients in the control group received a percutaneous coronary intervention (PCI) (42.09% vs. 21.08%, $p<0.001$) and coronary artery bypass grafting (CABG) (8.2% vs. 4.62%, $p<0.001$) (Table 1). Moreover, patients with AMI and sepsis had a longer length of hospital stay in comparison to the patients with AMI without sepsis (32.5 days vs. 11.74 days, $p<0.001$) (Table 1).

Survival analysis

Overall, the 12-year survival rate was lower for AMI patients with sepsis (log rank $p<0.001$; Figure 2A). The sex-specific analysis of the cohorts also revealed lower survival rates in both sexes for those with AMI and sepsis (log rank $p<0.0001$; Figure 2B, C). In order to evaluate the interactive effects of sepsis and age on the survival of AMI patients, the patients were divided into four age categories: <60 years, 60–69 years, 70–79 years, and ≥80 years. The Kaplan–Meier cumulative survival curves for the four groups according to age all revealed a lower survival rate in the sepsis group (log rank $p<0.0001$; Figure 3). The difference in survival rates between patients with sepsis and those without sepsis (control group) decreased steadily as age increased.

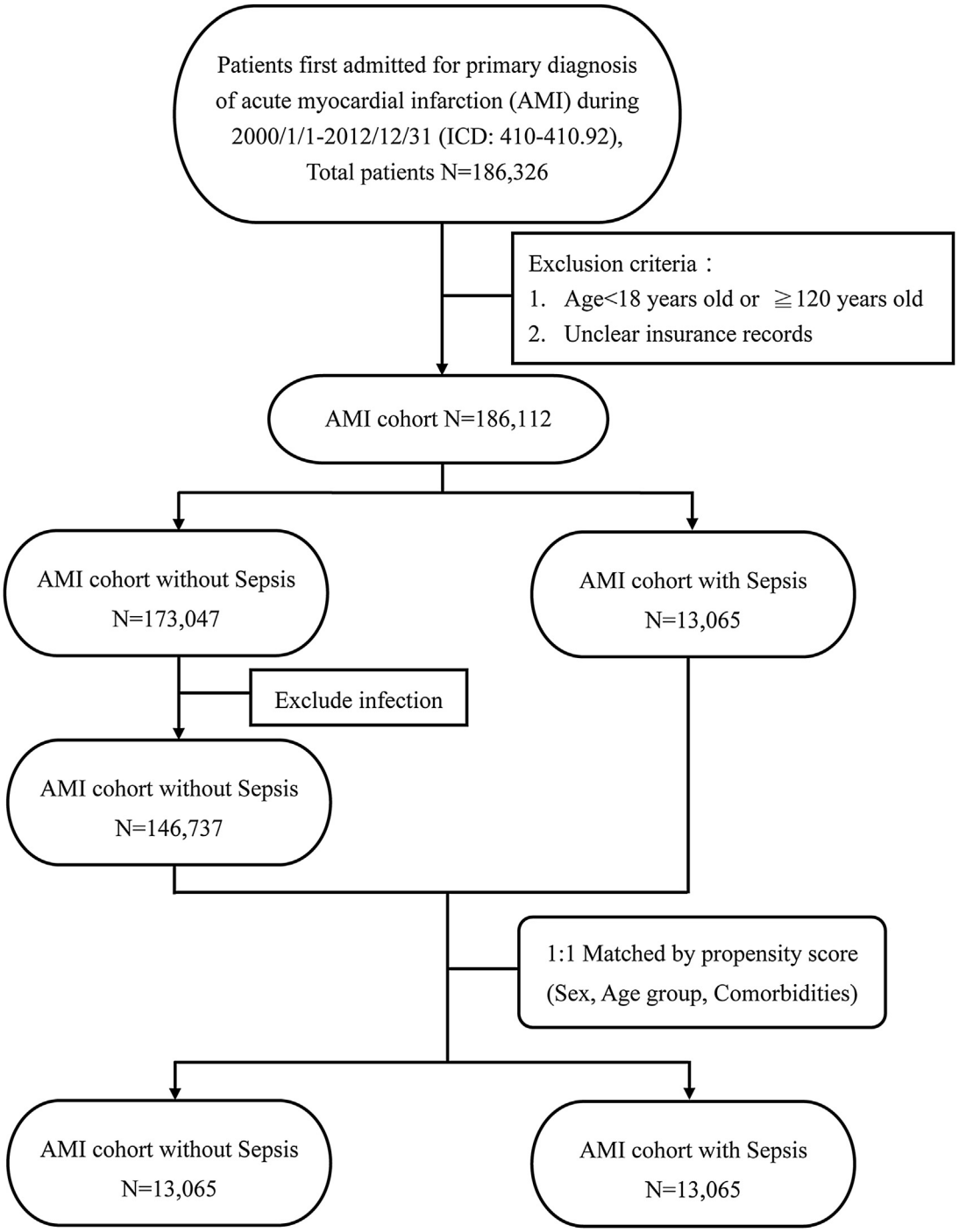

Figure 1. Flow chart of case selection from the Taiwan National Health Insurance Research Database. AMI = acute myocardial infarction.

The effect of invasive management on the 12-year survival rate was also investigated. The survival rate of patients who received conservative treatment for AMI was lower if sepsis developed (log rank $p < 0.0001$; Figure 4A). In the other three categories of patients who received invasive management (PCI only, CABG only, and PCI or CABG), the survival rate was still lower for patients with AMI and sepsis (log rank $p < 0.0001$; Figure 4B–D). Interventional management with PCI or CABG improved survival in both sepsis and non-sepsis patients after first AMI (log rank $p < 0.0001$; Figure 4E, F).

Cox proportional hazards regression analysis showed increased mortality for each of the following characteristics in patients hospitalized for first AMI (Table 2): male sex (HR 1.08, 95% CI 1.05–1.12), older age (60–69 years vs. <60 years: HR 1.59, 95% CI 1.50–1.69; 70–79 years vs. <60 years: HR 2.14, 95% CI 2.02–2.26; ≥80 years vs. <60 years: HR 2.91, 95% CI 2.75–3.08), sepsis (HR 1.79, 95% CI 1.74–1.85), diabetes mellitus (HR 1.14, 95% CI 1.10–1.17), peripheral vascular disease (HR 1.25, 95% CI 1.18–1.31), heart failure (HR 1.18, 95% CI 1.14–1.21), end-stage renal disease (HR 1.52, 95% CI 1.44–1.60), cerebrovascular accident (HR 1.17, 95% CI 1.13–1.20), ST-elevation myocardial infarction (STEMI) (HR 1.50, 95% CI 1.12–2.01), and NSTEMI (HR 1.55, 95% CI 1.16–2.08). HRs for mortality were lower for patients who received management with PCI (HR 0.62, 95% CI 0.60–0.65), antiplatelet medication (HR 0.70,

Table 1
Characteristics of hospitalized patients with first AMI, with and without sepsis.

Characteristics	Sepsis		*p*-Value
	No (n = 13 065)	Yes (n = 13 065)	
Male (%)	7366 (56.38%)	7359 (56.33%)	0.9304
Age group (%)			0.9982
<60	1672 (12.8%)	1682 (12.87%)	
60–69	2091 (16%)	2090 (16%)	
70–79	4407 (33.73%)	4405 (33.72%)	
≥80	4895 (37.47%)	4888 (37.41%)	
Type (%)			<0.0001
STEMI	4647 (35.57%)	2962 (22.67%)	
NSTEMI	8381 (64.15%)	10 083 (77.18%)	
Comorbidities (%)			
Hypertension	7914 (60.57%)	7889 (60.38%)	0.7517
Dyslipidemia	3725 (28.51%)	3732 (28.56%)	0.9236
Diabetes mellitus	6075 (46.5%)	6070 (46.46%)	0.9505
PVD	876 (6.7%)	871 (6.67%)	0.9014
Heart failure	4101 (31.39%)	4090 (31.31%)	0.8834
ESRD	963 (7.37%)	974 (7.46%)	0.7951
CVA	4900 (37.5%)	4899 (37.5%)	0.9898
COPD	2649 (20.28%)	2651 (20.29%)	0.9755
Medication (%)			
Any antiplatelet	10 647 (81.49%)	9814 (75.12%)	<0.0001
ACEI	6050 (46.31%)	4680 (35.82%)	<0.0001
ARB	2228 (17.05%)	1958 (14.99%)	<0.0001
Statin	2667 (20.41%)	2317 (17.73%)	<0.0001
Beta blocker	5872 (44.94%)	4787 (36.64%)	<0.0001
Calcium channel blocker	4434 (33.94%)	4854 (37.15%)	<0.0001
Heparin + LMWH	8834 (67.62%)	7734 (59.2%)	<0.0001
Nitrate	9993 (76.49%)	8197 (62.74%)	<0.0001
Intervention (%)			
PCI	5499 (42.09%)	2754 (21.08%)	<0.0001
CABG	1071 (8.2%)	604 (4.62%)	<0.0001
Hospital days, mean (SD)	11.74 (39.14%)	32.5 (112%)	<0.0001

STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PVD, peripheral vascular disease; ESRD, end-stage renal disease; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; SD, standard deviation.

95% CI 0.67–0.72), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (HR 0.73, 95% CI 0.71–0.75), statins (HR 0.90, 95% CI 0.85–0.96), or beta blockers (HR 0.82, 95% CI 0.79–0.84). Multivariable Cox proportional hazards regression analysis and forest plots were also performed for the subgroup analysis of AMI patients with or without sepsis. Overall, sepsis resulted in a higher HR for mortality in the classifications according to sex, age, comorbidities, intervention, and medications (Figure 5).

Discussion

This study is novel in presenting the first nationwide population-based investigation evaluating outcomes of sepsis in patients with first AMI. The results showed that sepsis occurred in nearly 7% of patients with AMI and was associated with a longer length of hospital stay and higher mortality. This impact was present in patients with AMI, regardless of invasive intervention or conservative treatment, and persisted in analyses stratified by age and sex. Furthermore, among the risk factors for mortality in patients with AMI, sepsis was second only to increasing age.

Sepsis is a condition with organ dysfunction, resulting from infection-induced dysregulation of the inflammatory host response (Singer et al., 2016). Since inflammation also plays a major role in atherosclerosis (Ross, 1999), the correlation between systemic infection and cardiovascular diseases has been discussed. Ramirez et al. found that the development of AMI was common among patients admitted for severe community-acquired pneumonia, especially those who had experienced clinical failure during hospitalization (Ramirez et al., 2008).

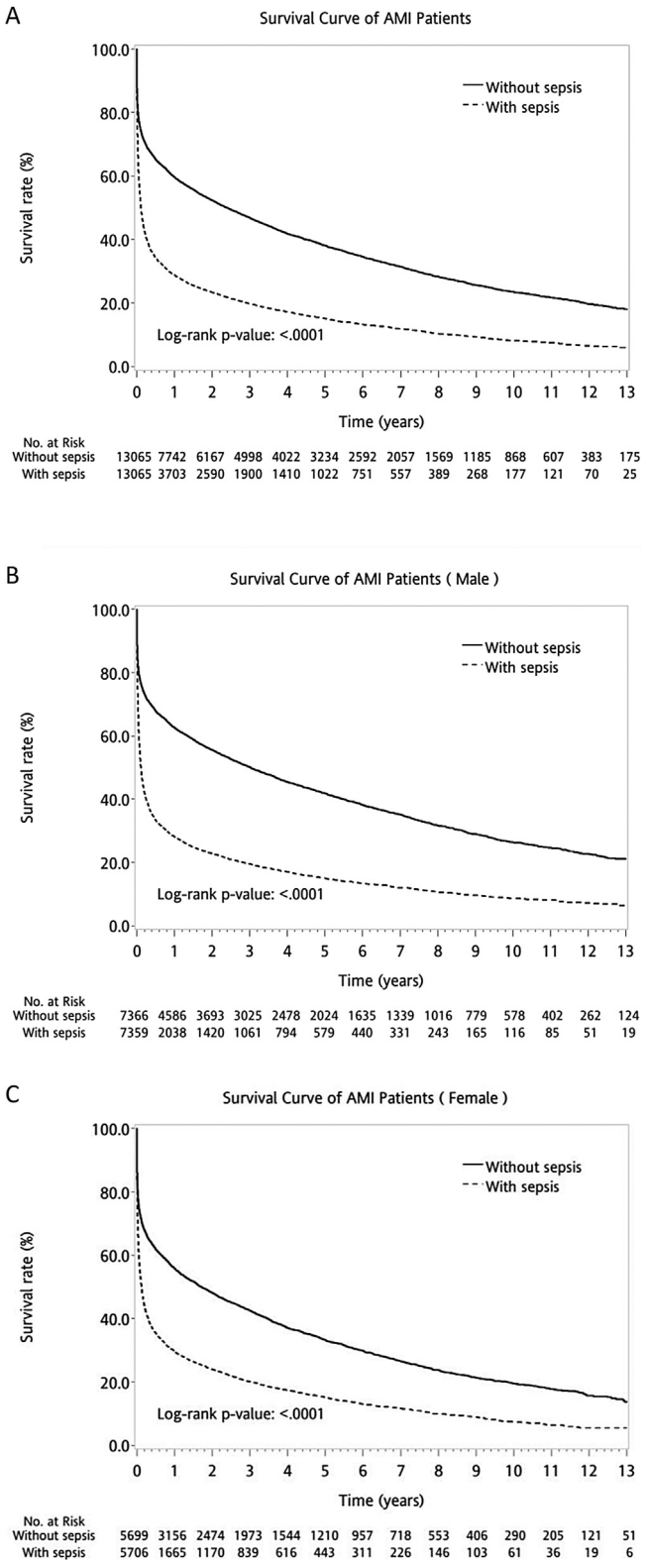

Figure 2. Kaplan–Meier survival curves for survival after first acute myocardial infarction (AMI) according to patient sex: (A) comparison of survival between patients with and without sepsis; (B) comparison of survival between male patients with and without sepsis; (C) comparison of survival between female patients with and without sepsis.

In another large cohort study, Dalager-Pedersen et al. reported that patients with community-acquired bacteremia had a transient increased risk of AMI and stroke compared to other hospitalized patients (Dalager-Pedersen et al., 2014).

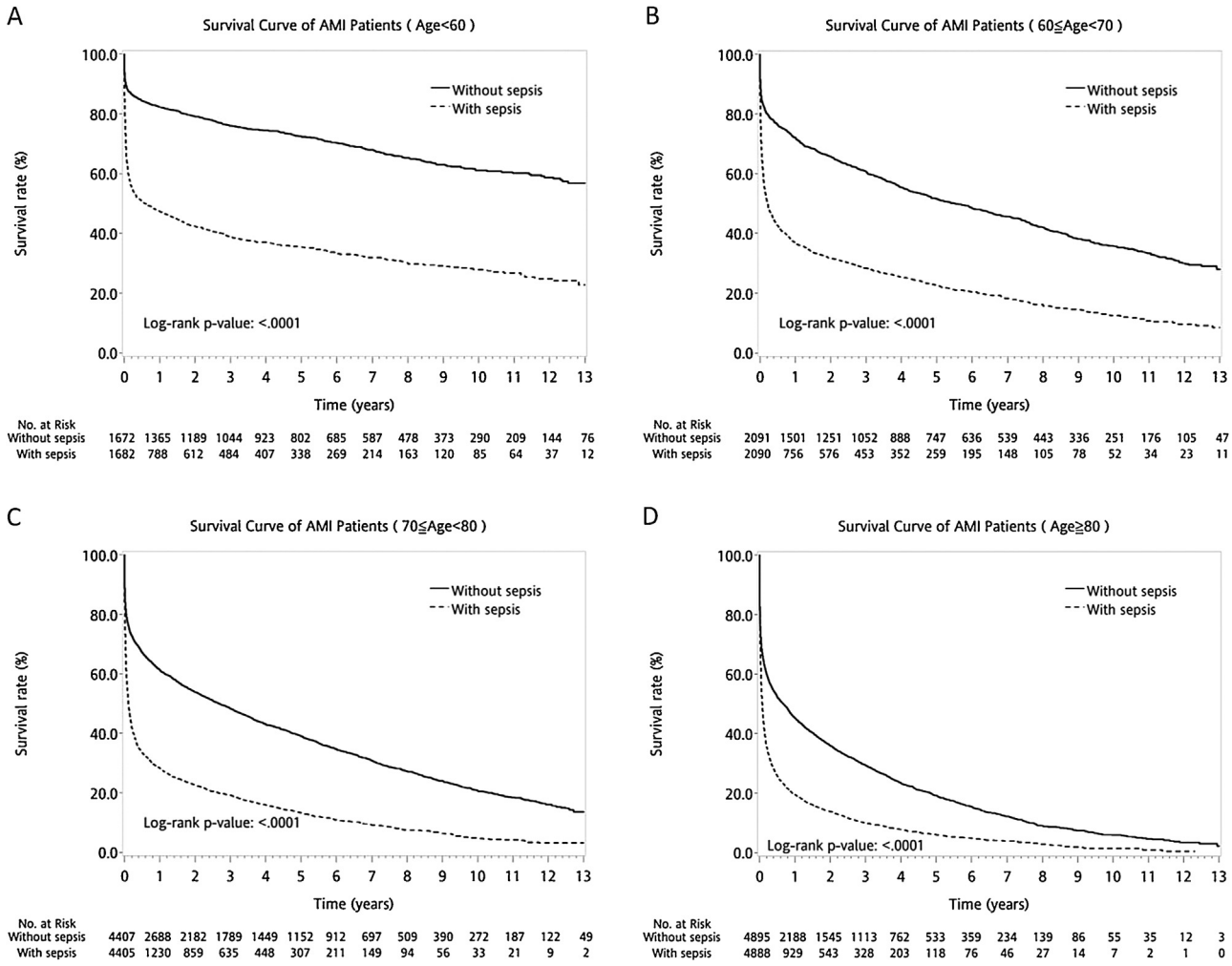

Figure 3. Kaplan–Meier survival curve for survival after first acute myocardial infarction (AMI) according to age group: (A) comparison of survival between patients <60 years of age with and without sepsis; (B) comparison of survival between patients 60–69 years of age with and without sepsis; (C) comparison of survival between patients 70–79 years of age with and without sepsis; (D) comparison of survival between patients ≥80 years of age with and without sepsis.

The possible pathophysiological mechanisms involved in the association between systemic infection and AMI include destabilization of atherosclerotic plaques, endothelial dysfunction, direct platelet activation, increasing oxygen demand, and impaired contractility of myocardial cells (Madjid et al., 2007; Cangemi et al., 2014; Smilowitz et al., 2015; Saaby et al., 2013; Fitzgerald et al., 2006). The exaggerated inflammatory response and hemodynamic instability evoked by systemic infection may affect the stability of atheroma and trigger endothelial dysfunction (Madjid et al., 2007; Cangemi et al., 2014; Fitzgerald et al., 2006). Furthermore, since tachycardia, hypotension, hypoxemia, and anemia commonly occur in severe infection, the imbalances in oxygen supply and demand could lead to myocardial ischemia (type 2 MI) (Smilowitz et al., 2015; Saaby et al., 2013). The reasons given above may explain the association between sepsis and higher long-term mortality in patients after first AMI found in the present study (Figures 2–4).

A worse prognosis for AMI in women has been reported (Anderson and Pepine, 2007; Milcent et al., 2007), and further studies revealed that this condition could largely be attributed to older age, more comorbidities, and less frequent utilization of invasive interventions in women (Milcent et al., 2007; Bairey Merz et al., 2006; Shaw et al., 2006; Bucholz et al., 2014). In contrast, a recent nationwide study in Sweden reported no significant sex differences in survival following AMI after adjustment for comorbidities (Rosengren et al., 2001). The results of the present study also revealed that women were not at higher risk of a worse outcome after AMI. Another study conducted by Tillmanns et al. suggested that being female was not an independent risk factor for increased AMI-associated mortality, and that sex-related differences in survival would be eliminated if PCI was performed (Tillmanns et al., 2005). Mehta et al. reported a dramatic decline in mortality from AMI in women in America over the last decade, which was due to an increase in awareness of the disease risk and diagnosis, as well as the application of evidence-based interventions (Mehta et al., 2016). Since NHI in Taiwan covers nearly all of the population and provides almost free access to health care services with only a small co-payment, rural–urban disparities and income inequalities in access to medical care have been reduced (Huang et al., 2006; Lee et al., 2010; Chen et al., 2007). The present study findings might be explained in part by higher utilization of PCI or CABG and better control of comorbidities when compared to previous studies.

Advancing age is well-documented as a risk factor for mortality from AMI (Mehta et al., 2016; Wang et al., 2017b; Haller et al., 2017). In a Spanish study, hospital mortality almost doubled with each 10-year increase in age, from 2.6% in patients <55 years old to 25.8% in the >84 years group (Hasdai et al., 2000). Another research study also found that hospital mortality rates increased with age (odds ratio 15.7 for the comparison of patients ≥85 years

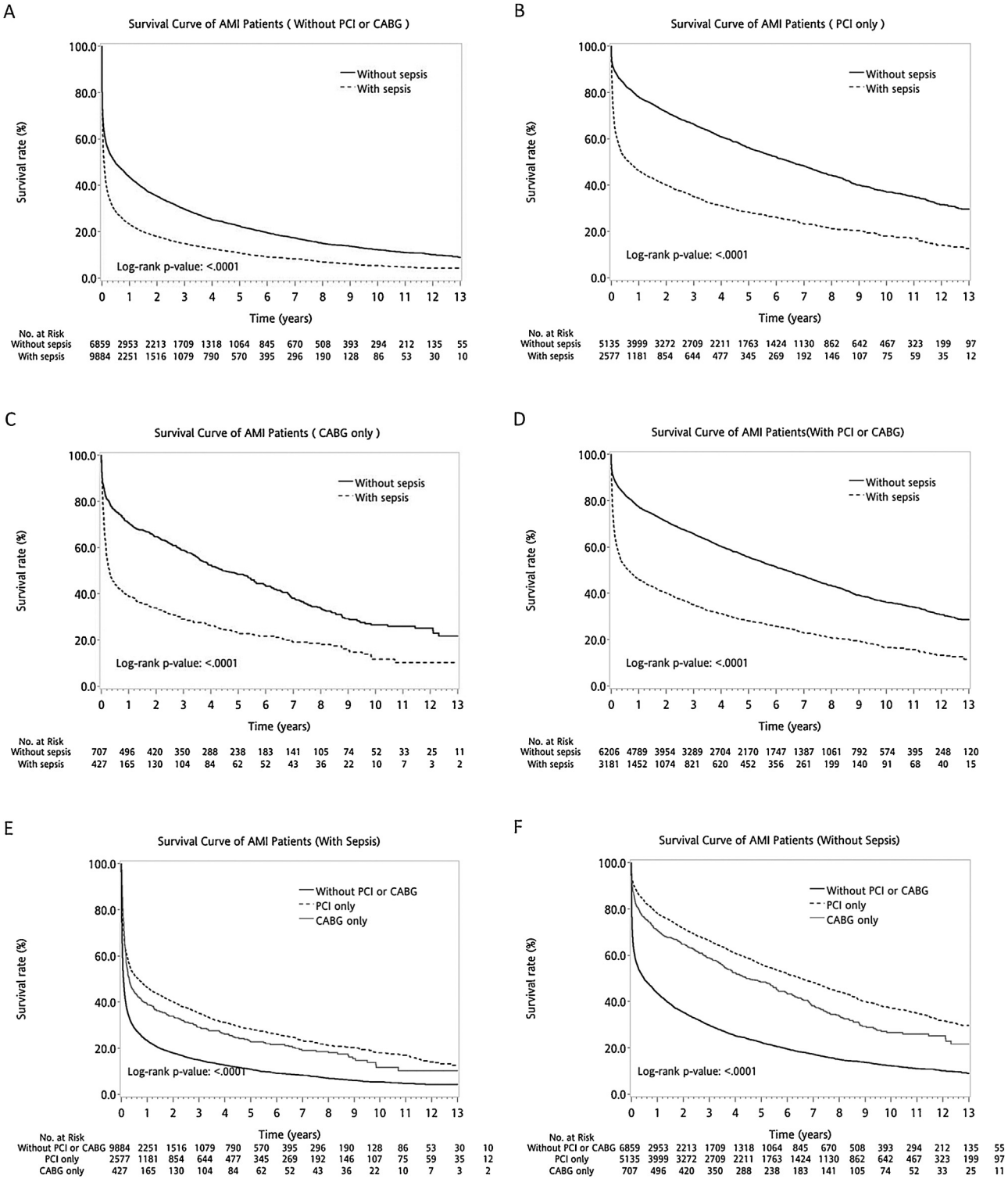

Figure 4. Kaplan–Meier survival curve for survival after first acute myocardial infarction (AMI) according to the interventions used: (A) comparison of survival between septic and non-septic patients managed without PCI or CABG; (B) comparison of survival between septic and non-septic patients managed with PCI only; (C) comparison of survival between septic and non-septic patients managed with CABG only; (D) comparison of survival between septic and non-septic patients managed with PCI or CABG; (E) comparison of survival among septic patients managed without PCI or CABG, with PCI only, and with CABG only; (F) comparison of survival among non-septic patients managed without PCI or CABG, with PCI only, and with CABG only. PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting.

to those <45 years of age), after adjustment for baseline risk differences (Avezum et al., 2005). Due to the increasing frequency of atypical clinical presentations, cognitive impairment, and comorbidities, delays in seeking medical assistance is common among elderly patients (Bayer et al., 1986; Goldberg et al., 2002). As well as suffering higher rates of heart failure, major bleeding events, and stroke, many elderly patients with acute coronary syndrome also do not receive evidence-based management (Avezum et al., 2005). Consistent with the results of previous studies, the present research also indicated that older age was

Table 2
Cox proportional hazards regression analysis for hospitalized patients with first AMI, with and without sepsis.

Variables	HR (95% CI) All (N = 26 130)
Sex (male vs. female)	1.08 (1.05–1.12)
Age (60–69 vs. <60)	1.59 (1.50–1.69)
Age (70–79 vs. <60)	2.14 (2.02–2.26)
Age (≥80 vs. <60)	2.91 (2.75–3.08)
Hypertension (yes vs. no)	1.02 (0.98–1.05)
Dyslipidemia (yes vs. no)	0.99 (0.94–1.03)
Diabetes mellitus (yes vs. no)	1.14 (1.10–1.17)
PVD (yes vs. no)	1.25 (1.18–1.31)
Heart failure (yes vs. no)	1.18 (1.14–1.21)
ESRD (yes vs. no)	1.52 (1.44–1.60)
Previous CVA (yes vs. no)	1.17 (1.13–1.20)
COPD (yes vs. no)	1.00 (0.97–1.04)
STEMI (yes vs. no)	1.50 (1.12–2.01)
NSTEMI (yes vs. no)	1.55 (1.16–2.08)
PCI (yes vs. no)	0.62 (0.60–0.65)
Any antiplatelet (yes vs. no)	0.70 (0.67–0.72)
ACEI or ARB (yes vs. no)	0.73 (0.71–0.75)
Statin (yes vs. no)	0.90 (0.85–0.96)
Beta blocker (yes vs. no)	0.82 (0.79–0.84)
Sepsis (yes vs. no)	1.79 (1.74–1.85)

AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval; PVD, peripheral vascular disease; ESRD, end-stage renal disease; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

independently associated with higher mortality after AMI (60–69 years vs. <60 years, HR 1.59; 70–79 years vs. <60 years, HR 2.14; ≥80 years vs. <60 years, HR 2.91).

In addition, elderly patients also have an increased risk of developing sepsis and higher mortality from sepsis (Martin et al., 2006; Angus et al., 2001; Girard et al., 2005; Nasa et al., 2012). Sepsis after AMI may further worsen heart function. Previous studies have demonstrated both elevated troponin I and heart dysfunction to be associated with the mortality of elderly patients with sepsis (Arlati et al., 2000; Ammanns et al., 2001). In the present analysis, evidence was found that sepsis might be the second most important factor for mortality from AMI after age. However, as a consequence of the substantial impact of age on mortality after AMI, the influence of sepsis on outcomes in the octogenarian group may not be as obvious as in the younger age groups, leading to a narrowing of disparities in mortality with increasing age. The younger age group would benefit most from the prevention of sepsis after AMI.

The results of this study suggest that PCI might be the most significant factor in determining the clinical outcome of patients hospitalized for first AMI. The importance of timely PCI management for patients who qualify for this intervention, according to current evidence-based guidelines, cannot be overemphasized (Wright et al., 2011; O'Gara et al., 2013). The analysis also found that the negative influence of sepsis on AMI still presented in the patients who received invasive interventions. Recently, Smilowitz et al. retrospectively analyzed patients with sepsis, and reported that a concomitant diagnosis of AMI was associated with higher in-hospital mortality in comparison to sepsis alone. In that study, it was also found that invasive interventions, such as PCI or CABG, could improve the outcome of AMI in patients with sepsis (Smilowitz et al., 2016). The present study showed that interventional therapy improved long-term survival in both sepsis and non-sepsis patients (Figure 4 and Table 2). Furthermore, this study also showed a higher frequency of use of invasive management strategies (PCI or CABG) in patients with AMI and sepsis (25.7%) than a previous study (10.1%) (Smilowitz et al., 2016). Further randomized studies are needed to establish the risk stratification and identify the subgroups that would derive the greatest benefit from invasive management in this condition.

In this study, PCI was shown to have a better impact than CABG in the survival curves (Figure 4). It appears that there has been no randomized study to compare PCI with CABG after AMI. For patients with stable CAD, CABG has demonstrated a survival benefit to left main (LM) or three-vessel disease, particularly when the proximal left anterior descending coronary artery is involved (Yusuf et al., 1994; Windecker et al., 2014). Current recommendations for the type of revascularization in patients with stable CAD with LM or three-vessel disease are based on the evaluation of surgical risk and assessment of anatomical complexity of coronary lesions (the SYNTAX score) (Neumann et al., 2018). The available evidence to date indirectly suggests that the criteria applied to patients with stable CAD should also be applied to patients with acute coronary syndromes without ST-segment elevation (Neumann et al., 2018). For patients with AMI, emergent CABG should be considered for the management of patients with an anatomy unsuitable for PCI and either a large myocardial area at jeopardy or with cardiogenic shock (Ibanez et al., 2018). CABG is also recommended for patients with MI-related mechanical complications who require repair and coronary revascularization (Ibanez et al., 2018). Since the characteristics of patients receiving CABG and patients undergoing PCI might differ in terms of age, comorbidities, anesthesia risk, severity of MI-related complications, and complexity of the coronary artery anatomy, caution must be taken when interpreting the data. It cannot be concluded that PCI outweighs CABG in terms of the survival benefit for patients with AMI, and this needs to be investigated in further randomized studies.

The strength of this retrospective study lies in the use of population-based data from NHI, which covers nearly all citizens in Taiwan and provides data for large numbers of patients and long periods of time. NHI also ensures that patients receive appropriate management, regardless of their socioeconomic status. Thus, this would not affect the physician's or patient's decision about invasive interventions. The one-to-one propensity score matching strategy for confounding factors was also applied to confirm the impact of sepsis on the outcome in patients with AMI. In contrast to previous studies that have emphasized the relationship of cardiovascular events after systemic infection (Ramirez et al., 2008; Dalager-Pedersen et al., 2014; Smilowitz et al., 2016; Allou et al., 2016), this study is the first to investigate the impact of sepsis on first myocardial infarction.

The study has a few limitations. First, although a previous study has confirmed the accuracy of NHIRD as a valid resource for the research of cardiovascular disease (Cheng et al., 2014), relevant clinical variables such as cardiac biomarkers, left ventricular ejection fraction, and Killip grade were unavailable. The severity of heart failure complicating AMI, such as cardiogenic shock, was also not available in this database. Similarly, there were no results for PCI. Thus, the individual differences in coronary artery anatomy and reperfusion status were not shown in this study. Second, the diagnostic criteria for sepsis changed in 2016 (Rhodes et al., 2017). A recent study conducted by Seymour et al. supported the validity of the quick Sequential (Sepsis-related) Organ Failure Assessment (qSOFA) score and Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score as clinical criteria for sepsis (Seymour et al., 2016). Since the newer criteria have greater predictive validity for in-hospital mortality in comparison to the systemic inflammatory response syndrome (SIRS) criteria, which were used prior to 2016 (Seymour et al., 2016), the influence of sepsis on patients with AMI might have been underestimated. Third, although a number of clinical covariates were adjusted for in the propensity score matching analysis, potential biases may still exist due to unmeasured confounding factors. Additional research

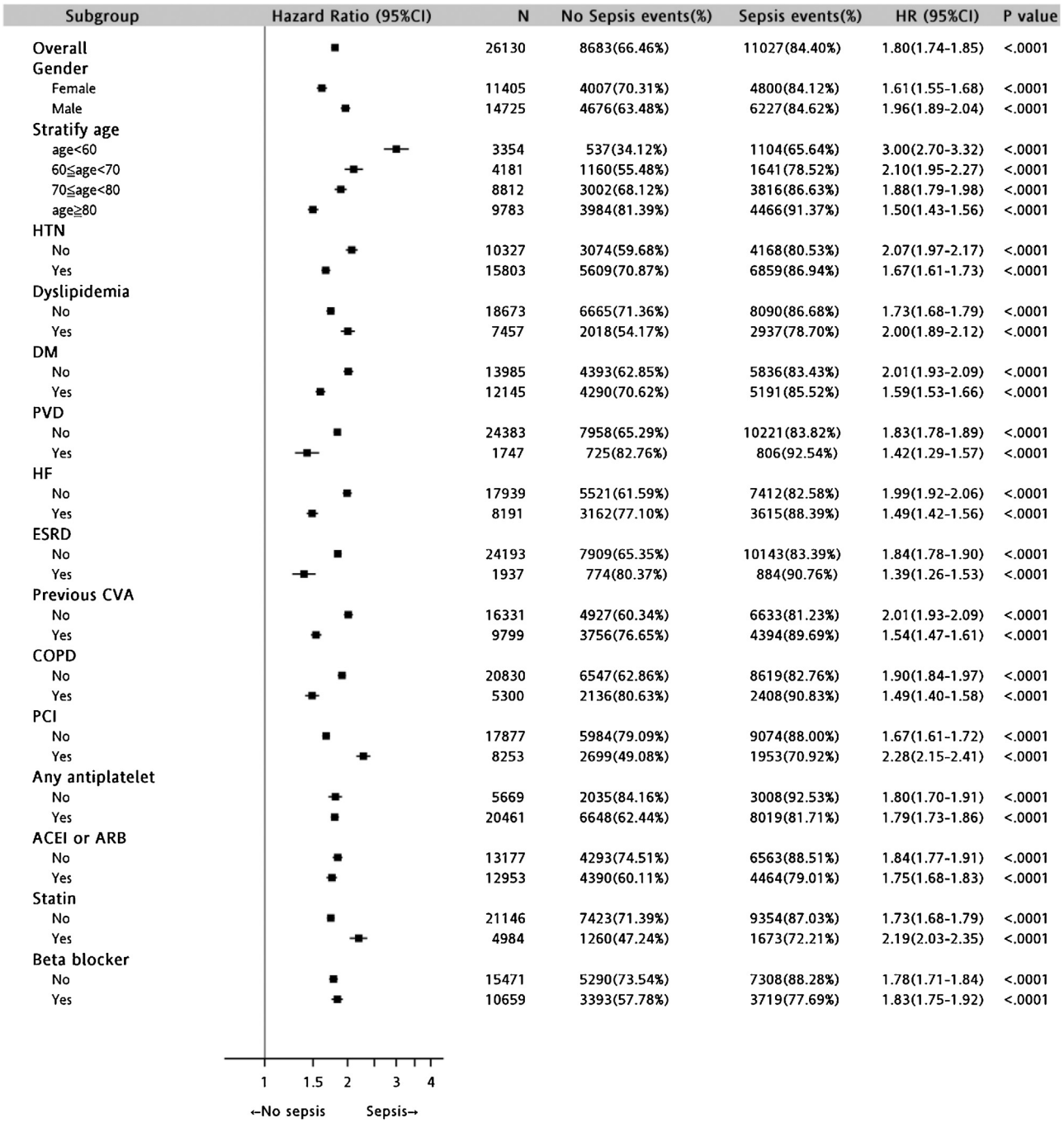

Figure 5. Forest plots for the subgroup analysis of AMI patients with or without sepsis. HTN = hypertension, DM = diabetes mellitus, PVD = peripheral vascular disease, HF = heart failure, ESRD = end-stage renal disease, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease, PCI = percutaneous coronary intervention, ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers.

to support the study findings is necessary. Despite this, the study is the first and largest study evaluating the impact of sepsis on patients with first AMI. The study findings emphasize the worse outcome associated with sepsis, regardless of age, sex, and management of AMI.

In conclusion, this nationwide cohort study demonstrated the substantial impact of sepsis on the survival of patients with AMI, regardless of age, sex, and management of AMI. The findings also highlight PCI management as an independent factor associated with improved long-term outcomes in AMI patients with or without sepsis.

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Ethical approval

The study protocol was reviewed and approved by the Human Research Committee of Kaohsiung Veterans General Hospital.

Conflict of interest

The authors have no conflicts of interest to disclose.

Author contributions

WCH, CPL, YSC, and GYM conceived and designed the study. SHK and CCH conducted the research. PLT and WTH analyzed the data. ESL and CHC wrote the manuscript. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.11.021.

References

Allou N, Brulliard C, Valance D, Esteve JB, Martinet O, Corradi L, et al. Obstructive coronary artery disease in patients hospitalized for severe sepsis or septic shock with concomitant acute myocardial infarction. J Crit Care 2016;32:159–64.

Ammanns P, Fehr T, Minder EI, Günter C, Bertel O. Elevation of troponin I in sepsis and septic shock. Intensive Care Med 2001;27(6):965–9.

Anderson RD, Pepine CJ. Gender differences in the treatment for acute myocardial infarction: bias or biology?. Circulation 2007;115(7):823–6.

Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29(7):1303–10.

Arlati S, Brenna S, Prencipe L, Marocchi A, Casella GP, Lanzani M, et al. Myocardial necrosis in ICU patients with acute non-cardiac disease: a prospective study. Intensive Care Med 2000;26(1):31–7.

Avezum A, Makdisse M, Spencer F, Gore JM, Fox KA, Montalescot G, et al. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). Am Heart J 2005;149(1):67–73.

Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. J Am Coll Cardiol 2006;47(3 Suppl):S21–9.

Bayer AJ, Chadha JS, Farag RR, Pathy MSJ. Changing presentation of myocardial infarction with increasing old age. J Am Geriatr Soc 1986;34(4):263–6.

Bucholz EM, Butala NM, Rathore SS, Dreyer RP, Lansky AJ, Krumholz HM. Sex differences in long-term mortality after myocardial infarction: a systematic review. Circulation 2014;130(9):757–67.

Cangemi R, Casciaro M, Rossi E, Calvieri C, Bucci T, Calabrese CM, et al. Platelet activation is associated with myocardial infarction in patients with pneumonia. J Am Coll Cardiol 2014;64(18):1917–25.

Chen L, Yip W, Chang MC, Lin HS, Lee SD, Chiu YL, et al. The effects of Taiwan's National Health Insurance on access and health status of the elderly. Health Econ 2007;16(3):223–42.

Cheng C-L, Lee C-H, Chen P-S, Li Y-H, Lin S-J, Yang Y-HK. Validation of acute myocardial infarction cases in the national health insurance research database in Taiwan. J Epidemiol 2014;24(6):500–7.

Cheng CL, Chien HC, Lee CH, Lin SJ, Yang YH. Validity of in-hospital mortality data among patients with acute myocardial infarction or stroke in National Health Insurance Research Database in Taiwan. Int J Cardiol 2015;201:96–101.

Dalager-Pedersen M, Sogaard M, Schonheyder HC, Nielsen H, Thomsen RW. Risk for myocardial infarction and stroke after community-acquired bacteremia: a 20-year population-based cohort study. Circulation 2014;129(13):1387–96.

Fitzgerald JR, Foster TJ, Cox D. The interaction of bacterial pathogens with platelets. Nat Rev Microbiol 2006;4(6):445–57.

Girard TD, Opal SM, Ely EW. Insights into severe sepsis in older patients: from epidemiology to evidence-based management. Clin Infect Dis 2005;40(5):719–27.

Goldberg RJ, Steg PG, Sadiq I, Granger CB, Jackson EA, Budaj A, et al. Extent of, and factors associated with, delay to hospital presentation in patients with acute coronary disease (the GRACE registry). Am J Cardiol 2002;89(7):791–6.

Haller PM, Jager B, Farhan S, Christ G, Schreiber W, Weidinger F, et al. Impact of age on short- and long-term mortality of patients with ST-elevation myocardial infarction in the VIENNA STEMI network. Wien Klin Wochenschr; 2017.

Hasdai D, Holmes DR, Criger DA, Topol EJ, Califf RM, Harrington RA. Age and outcome after acute coronary syndromes without persistent ST-segment elevation. Am Heart J 2000;139(5):858–66.

Huang N, Yip W, Chang HJ, Chou YJ. Trends in rural and urban differentials in incidence rates for ruptured appendicitis under the National Health Insurance in Taiwan. Public Health 2006;120(11):1055–63.

Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39(2):119–77.

Jawad I, Luksic I, Rafnsson SB. Assessing available information on the burden of sepsis: global estimates of incidence, prevalence and mortality. J Glob Health 2012;2(1):010404.

Kuo P-L, Lin K-C, Tang P-L, Cheng C-C, Huang W-C, Chiang C-H, et al. Contribution of hepatitis B to long-term outcome among patients with acute myocardial infarction: a nationwide study. Medicine (Baltimore) 2016;95(5):e2678.

Kuo S-H, Hung W-T, Tang P-L, Huang W-C, Yang J-S, Lin H-C, et al. Impact of hepatitis C virus infection on long-term mortality after acute myocardial infarction: a nationwide population-based, propensity-matched cohort study in Taiwan. BMJ Open 2018;8(1)e017412.

Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med 2018;378(4):345–53.

Lee YC, Huang YT, Tsai YW, Huang SM, Kuo KN, McKee M, et al. The impact of universal National Health Insurance on population health: the experience of Taiwan. BMC Health Serv Res 2010;10:225.

Madjid M, Vela D, Khalili-Tabrizi H, Casscells SW, Litovsky S. Systemic infections cause exaggerated local inflammation in atherosclerotic coronary arteries: clues to the triggering effect of acute infections on acute coronary syndromes. Tex Heart Inst J 2007;34(1):11–8.

Martin G, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. Crit Care Med 2006;34:15–21.

Mauriello A, Sangiorgi G, Fratoni S, Palmieri G, Bonanno E, Anemona L, et al. Diffuse and active inflammation occurs in both vulnerable and stable plaques of the entire coronary tree: a histopathologic study of patients dying of acute myocardial infarction. J Am Coll Cardiol 2005;45(10):1585–93.

Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. Circulation 2016;133(9):916–47.

Milcent C, Dormont B, Durand-Zaleski I, Steg PG. Gender differences in hospital mortality and use of percutaneous coronary intervention in acute myocardial infarction: microsimulation analysis of the 1999 nationwide French hospitals database. Circulation 2007;115(7):833–9.

Murray CJL, Barber RM, Foreman KJ, Ozgoren AA, Abd-Allah F, Abera SF, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. Lancet 2015;386(10009):2145–91.

Nasa P, Juneja D, Singh O. Severe sepsis and septic shock in the elderly: an overview. World J Crit Care Med 2012;1(1):23–30.

Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2018;00(1–96):16–25.

O'Gara PT, Kushner FG, Ascheim DD, CaseyJr DE, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127(4):529–55.

Ramirez J, Aliberti S, Mirsaeidi M, Peyrani P, Filardo G, Amir A, et al. Acute myocardial infarction in hospitalized patients with community-acquired pneumonia. Clin Infect Dis 2008;47(2):182–7.

Remick DG. Pathophysiology of sepsis. Am J Pathol 2007;170(5):1435–44.

Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43(3):304–77.

Rosengren A, Spetz CL, Koster M, Hammar N, Alfredsson L, Rosen M. Sex differences in survival after myocardial infarction in Sweden; data from the Swedish National Acute Myocardial Infarction Register. Eur Heart J 2001;22(4):314–22.

Ross R. Atherosclerosis — an inflammatory disease. N Engl J Med 1999;340(2):115–26.

Saaby L, Poulsen TS, Hosbond S, Larsen TB, Pyndt Diederichsen AC, Hallas J, et al. Classification of myocardial infarction: frequency and features of type 2 myocardial infarction. Am J Med 2013;126(9):789–97.

Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315(8):762–74.

Shaw LJ, Bairey Merz CN, Pepine CJ, Reis SE, Bittner V, Kelsey SF, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. J Am Coll Cardiol 2006;47(3 Suppl):S4–S20.

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315(8):801–10.
Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P, et al. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med 2004;351(25):2611–8.
Smilowitz NR, Naoulou B, Sedlis SP. Diagnosis and management of type II myocardial infarction: increased demand for a limited supply of evidence. Curr Atheroscler Rep 2015;17(2):478.
Smilowitz NR, Gupta N, Guo Y, Bangalore S. Comparison of outcomes of patients with sepsis with versus without acute myocardial infarction and comparison of invasive versus noninvasive management of the patients with infarction. Am J Cardiol 2016;117(7):1065–71.
Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60 (16):1581–98.
Tillmanns H, Waas W, Voss R, Grempels E, Holschermann H, Haberbosch W, et al. Gender differences in the outcome of cardiac interventions. Herz 2005;30 (5):375–89.
Wang M-T, Lin S-C, Tang P-L, Hung W-T, Cheng C-C, Yang J-S, et al. The impact of DPP-4 inhibitors on long-term survival among diabetic patients after first acute myocardial infarction. Cardiovasc Diabetol 2017a;16:89.
Wang J, Yu W, Zhao D, Liu N, Yu Y. In-hospital and long-term mortality in 35,173 Chinese patients undergoing coronary artery bypass grafting in Beijing: impact of sex, age, myocardial infarction, and cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2017b;31(1):26–31.
Windecker S, Stortecky S, Stefanini GG, da Costa BR, Rutjes AW, Di Nisio M, et al. Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. BMJ 2014;348: g3859–g3859.
Wright RS, Anderson JL, Adams CD, Bridges CR, CaseyJr DE, Ettinger SM, et al. 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;123(18):2022–60.
Yusuf S, Zucker D, Passamani E, Peduzzi P, Takaro T, Fisher LD, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. Lancet 1994;344(8922):563–70.