Impact of diabetes on outcomes of cardiogenic shock: A systematic review and meta-analysis

Diabetes & Vascular Disease Research XXX-XXX 2022: 1–12 © The Author(s) 2022 Article reuse guidelines: sagepub.com/journals-permissions DOI: 10.1177/14791641221132242 journals.sagepub.com/home/dvr SAGE

Chao Luo¹, Feng Chen², Lingpei Liu¹, Zuanmin Ge¹, Chengzhen Feng¹ and Yuehua Chen¹

Abstract

To provide synthesized evidence on the association of diabetes with clinical outcomes of patients with acute myocardial infarction (AMI) and associated cardiogenic shock (CS). We analyzed observational studies on patients with AMI and CS, identified through a systematic search using PubMed and Scopus databases. The main outcome was mortality and other outcomes of interest were risk of major bleeding, re-infarction, cerebrovascular adverse events, and need for revascularization. We conducted the meta-analysis with data from 15 studies. Compared to patients without diabetes, those with diabetes had an increased risk of in-hospital mortality (OR, 1.34; 95% CI, 1.17–1.54) and cerebrovascular complications (OR, 1.28; 95% CI, 1.11–1.48). We found similar risk of major bleeding (OR, 0.68; 95% CI, 0.43–1.09), re-infarction (OR, 0.98; 95% CI, 0.48–1.98) and need for re-vascularization (OR, 0.96; 95% CI, 0.75–1.22) as well as hospital stay lengths (in days) (WMD 0.00; 95% CI, -0.27-0.28; n = 4; $l^2 = 99.7\%$) in the two groups of patients. Patients with diabetes, acute MI and associated cardiogenic shock have increased risks of mortality and adverse cerebrovascular events than those without diabetes.

Keywords

Acute myocardial infarction, cardiogenic shock, diabetes mellitus, mortality, clinical outcomes, meta-analysis

Introduction

Cardiogenic shock (CS) is responsible for high rates of inhospital mortality among patients with acute myocardial infarction (MI).^{1,2} Approximately 5–10% of patients with acute myocardial infarction develop CS.^{1–3} Acute MI is present in more than 4/5 of the patients with CS.⁴ Cardiogenic shock is characterized by severely abnormal cardiac activity resulting in reduced cardiac output with hypotension, end-organ hypoperfusion, and critical hypoxia.^{1,2,5} An important feature of CS that differentiates it from other types of shock is that it is usually unresponsive to fluids or volume resuscitation.^{1,2}

The underlying mechanisms of cardiogenic shock among patients with MI are not fully understood. The decreased myocardial activity during cardiogenic shock substantially reduces the cardiac output and results in hypotension, peripheral vasoconstriction, end-organ damage, and cardiac ischemia.^{1,6} Peripheral vasoconstriction initially improves the coronary perfusion, but later on, it leads to increased cardiac afterload, thereby damaging the myocardium even more .⁶ In addition,

Corresponding author:

Yuehua Chen, Department of General Practice, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua Municipal Central Hospital, 365 Renming East Road, Jinhua, Zhejiang 321000, China. Email: lcyiyi@163.com



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the

SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

¹Department of General Practice, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua Municipal Central Hospital, Jinhua, China

²Department of Neurosurgery, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua Municipal Central Hospital, Jinhua, China

accompanying systemic inflammation with release of NO (nitric oxide), interleukins, and TNF (tumor necrosis factor)-alpha exerts a cardiotoxic effect.^{6,7}

Several CS risk factors have been documented. These include older age, presence of diabetes, previous infarction, anterior and large infarct, and peripheral vascular disease.^{2,8–10} Out of these factors, diabetes increases the risk of developing CS by approximately 2–3 times that of patients without diabetes.¹¹ Studies have suggested a strong link between diabetes and cardiovascular diseases.¹² Patients with diabetes frequently have obesity, abnormal lipid levels, and high blood pressure, all conditions that increase their risk for adverse cardiac events.^{13–15} However, whether the presence of diabetes alters the prognosis in patients with cardiogenic shock remains unclear. The current meta-analysis is probably the first attempt to synthesize the evidence on the effects of diabetes on clinical outcomes among patients with cardiogenic shock.

Materials and methods

Search strategy

We ensured our study processes complied with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.¹⁶ The protocol was registered in the International Prospective Registry of Systematic Reviews (PROSPERO; registration number CRD42021286109). We carried out a systematic search of PubMed and Scopus databases for English language papers published until 10th November 2021. The search strategy used included the following terms: (cardiogenic shock OR, myocardial infarction) AND (diabetes mellitus OR diabetes OR high blood glucose) AND (mortality OR death OR survival OR clinical outcomes OR all-cause mortality OR need for revascularization OR need for thrombolysis). We aimed at identifying studies that examined the association of diabetes with outcomes of interest in patients with acute myocardial infarction (MI) and associated cardiogenic shock (CS). Mortality was the main outcome of interest, whereas risk of major bleeding, re-infarction, cerebrovascular adverse events, and the need for revascularization were other outcomes of potential interest.

Selection criteria and methods

The first step was to remove the duplicates and arrive at the unique citations identified through the systematic search of the databases. This was followed by two study authors independently screening the title and abstract of the studies. As a subsequent step, the full text of suitable studies was reviewed in detail. In case of any disagreements pertaining to the inclusion of studies, the two authors arrived at a mutual consensus upon discussion. The reference/ bibliographic list of the included studies was also reviewed in an attempt to identify additional studies for inclusion.

We considered observational studies, including those based on analysis of registry data or clinical records for inclusion. All the studies considered were done in patients with MI and associated cardiogenic shock that mentioned the association of diabetes with the outcomes of interest.

We excluded case-reports, review articles, and studies that did not provide findings based on diabetes status.

Statistical analysis including data extraction and quality assessment

We used a pretest data extraction sheet to fill in relevant data from the included studies. This process of data extraction was carried out by two study authors independently. The quality assessment of the studies was done using the Newcastle-Ottawa Quality Assessment Scale for observational studies.¹⁷

We used STATA version 16.0 for all the statistical analyses. For the primary outcome i.e. mortality, we included only those studies that reported adjusted risk of mortality. We considered some set of variables (such as age, sex, treatment modality adopted, presence of comorbidities, previous history of myocardial infarction, prior coronary artery bypass, any fluid or electrolyte disorder, presence of obesity/body mass index) that should preferably be adjusted for. Studies that adjusted for some or most of these variables were included for analysis.

The pooled effect sizes, along with 95% confidence intervals (CI), were reported as odds ratios (ORs) for categorical outcomes and weighted mean differences (WMDs) for continuous outcomes. Selection of the final analytic model was based on the observed value of I² (used to denote the degree of heterogeneity) For outcomes where I² value exceeded 40%, we applied a random effects model and where it was \leq 40%, we used fixed effects model.¹⁸ We considered *p*-values lower than 0.05 as representing statistical significance. Presence or absence of publication bias was assessed using Egger's test.¹⁹

Results

We identified 1077 citations after our initial search and elimination of duplicates. We analyzed the data from 15 studies.^{20–34} Specific steps in the process of selection of articles have been detailed in Figure 1. Included studies had an observational study design (Table 1). All, except one, presented data either from registry or clinical records. The study by Hashmi et al. was prospective in design (30). Three studies were multicentric, 4 were done in the USA and 2 in Denmark. The others were each conducted in

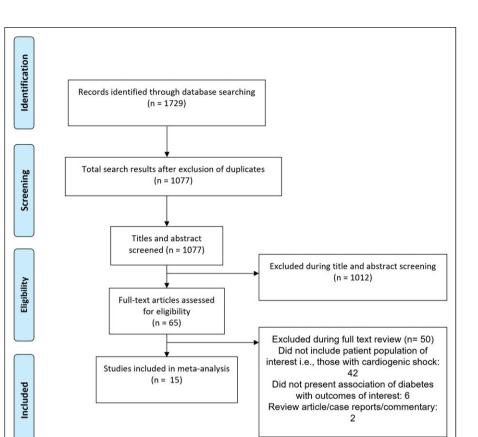


Figure 1. Selection process of the studies included in the review.

Poland, Spain, Italy, South Korea, Afghanistan, and the Netherlands (Table 1). In almost all the studies, the study participants presented ST-segment elevation MI (STEMI). The included studies were judged to have good quality (Supplementary tables 1 and 2).

Association of diabetes with mortality in patients with cardiogenic shock

Compared to the patients without diabetes, those with diabetes had an increased risk of in-hospital mortality (OR, 1.34; 95% CI, 1.17, 1.54; n = 9; $I^2 = 90.2\%$). The increased risk of mortality was also noted at 30-days post discharge (OR, 1.24; 95% CI, 0.95, 1.62; n=3; $I^2 = 0.0\%$) and at 1-year post-discharge (OR, 1.20; 95% CI, 1.01, 1.41; n = 2; $I^2 = 16.7\%$) (Figure 2). The increased risk of mortality persisted beyond 12 months of the post-operative period (OR, 1.19; 95% CI, 0.98, 1.45; n = 3; $I^2 = 38.1\%$) (Figure 2). For these outcomes, we did not find any statistical evidence of publication bias (p > 0.05)

Association of diabetes with adverse outcomes and length of hospital stay in patients with cardiogenic shock Compared to the patients without diabetes, those with diabetes had an increased risk of cerebrovascular complications (OR, 1.28; 95% CI, 1.11, 1.48; n = 3; $I^2 = 0.0\%$) (Figure 3). We found similar risks of major bleeding (OR, 0.68; 95% CI, 0.43, 1.09; n = 2; $I^2 = 0.0\%$) and re-infarction (OR, 0.98; 95% CI, 0.48, 1.98; n = 2; $I^2 = 66.6\%$) as well as similar re-vascularization needs (OR, 0.96; 95% CI, 0.75, 1.22; n = 5; $I^2 = 70.2\%$) in both groups of patients (Figure 3). We found no evidence of publication bias for the above outcomes (p > 0.05). Moreover, we found similar hospital stay lengths (in days) (WMD 0.00; 95% CI, -0.27, 0.28; n = 4; $I^2 = 99.7\%$) regardless of the presence of diabetes (Figure 4).

Discussion

There has been a global upsurge in the incidence of diabetes mellitus. According to the Global Burden of Disease estimates, the worldwide incidence of diabetes was close to 23 million in the year 2017.³⁵ The incidence of acute myocardial infarction complicated with cardiogenic shock is 3–10% and has remained stable over the years.^{9,36,37} Patients with diabetes mellitus have a 2-3 times higher risk of cardiogenic shock than individuals without diabetes.¹¹

Author (year of publication)	Study design	Country	Participant characteristics	Sample size	Key outcomes (DM vs. no DM)
Gasior et al. (2012) ²⁰	Secondary data analysis of polish registry of acute coronary syndromes	Poland	 Patients with ST elevation myocardial infarction (STEMI) and associated cardiogenic shock (CS); those with DM were older, more frequently female (52.6% vs. 36%) and a higher proportion with hypertension (65.6% vs. 47.1%), hypercholesterolaemia (40.3% vs. 29.0%), obesity (34.7% vs. 13.4%), history of coronary artery bypass grafting (6% vs. 4.1%) and MI (28.2% vs. 22.5%) compared to patients without DM. Those with diabetes were on treatment with insulin (54.3%) and oral antidiabetics (8.7%) 	1159-DM; 2985- no DM	Adjusted mortality (in- hospital): OR 1.16 (95% Cl: 1.00, 1.35) Adjusted mortality (3- yr): OR 1.11 (95% Cl: 1.02, 1.20) Unadjusted major bleeding (in-hospital): OR 0.74 (95% Cl: 0.44, 1.23) Unadjusted need for revascularization: OR 1.53 (95% Cl: 0.82, 2.86 Unadjusted cerebrovascula complication (in- hospital): OR 1.23 (95% Cl: 0.72, 2.10) Mean hospitalization [mear (SD)] (days): 2 (1.67) vs. 2 (1.33) Unadjusted Re-infarction (in-hospital): OR 0.74 (95% Cl: 0.55, 0.99)
Tedesco et al. (2003) ²¹	Retrospective cohort	USA	 Patients with anterior MI and cardiogenic shock; majority with ST elevation myocardial infarction (STEMI); no significant differences in the baseline characteristics between those with and without DM; mean age of around 70 years; female (~40%); hyperlipidaemia (~45%); hypertension (~38%) and previous MI (~28%) Patients with type I and type 2 diabetes were included, irrespective of mode of therapy (insulin, oral hypoglycemic agents, or diet alone) 	16-DM; 57- no DM	Adjusted mortality (in- hospital): OR 2.71 (95% Cl: 0.76, 9.73) Adjusted mortality (5- yr): OR 1.93 (95% Cl: 1.04, 3.58)
Lindholm et al. (2005) ²²	Secondary data analysis of the trandolapril cardiac evaluation (TRACE) register	Denmark	 Patients with MI and associated CS; majority with ST elevation myocardial infarction (STEMI); no significant differences in the baseline characteristics between those with and without DM except for history of hypertension (36% vs. 24%) and history of heart failure (47% vs. 29%); mean age of 72 years; 60% male subjects Patients with diabetes were either treated with insulin or with oral hypoglycaemic agents or treated with diet alone. However, the proportions treatment in each type was not provided 	76-DM; 367- no DM	Adjusted mortality (30- days): OR 1.04 (95% CI: 0.63, 1.74) Adjusted mortality (5- yr): OR 1.21 (95% CI: 0.88, 1.67) Unadjusted Re-infarction (in-hospital): OR 1.56 (95% CI: 0.71, 3.46)

Table I. Characteristics of the studies included in the meta-analysis.

(continued)

Author (year of publication)	Study design	Country	Participant characteristics	Sample size	Key outcomes (DM vs. no DM)
Gual et al. (2020) ²³	Retrospective study	Spain	Patients with STEMI and associated CS; those with diabetes were older and had a higher proportion of females (44.9% vs. 35.4%); DM group had higher proportion of subjects with hypertension (53.8% vs. 35.8%), chronic obstructive pulmonary disease (11.3% vs. 7.7%) or renal failure (31.3% vs. 28.6%) Data on mode of diabetes management not provided	7724-DM; I5866- no DM	Adjusted mortality (in- hospital): OR 1.17 (95% Cl: 1.10, 1.25) Cerebrovascular complication (unadjusted): OR 1.26 (95% Cl: 1.08, 1.47) Mean hospitalization [mean (SD)] (days): 8.7 (12.3) vs. 11.4 (19.4)
Echouffo (2018) ²⁴	Secondary data analysis of NIS (national inpatient sample) database	USA	Patients with MI (majority with STEMI) and associated CS; mean age of 68.9 years; 37% were aged more than 75 years; 37% were females; those with diabetes were younger and had higher prevalence of cardiovascular risk factors, peripheral vascular disease, and chronic kidney disease, compared with those without diabetes Data on mode of diabetes management not provided	31,135- DM; 41,630- no DM	Adjusted mortality (in- hospital): OR 1.18 (95% Cl: 1.09, 1.28) Mean hospitalization [mean (SD)] (days): 11.6 (0.16) vs. 10.9 (0.16) Need for revascularization (PCI or CABG) (adjusted): OR 0.88 (95% Cl: 0.80, 0.96) Discharge to skilled nursing care (adjusted): OR 1.19 (95% Cl: 1.07, 1.33)
Thoegersen (2020) ²⁵	Secondary data analysis of patient databased	Denmark	 Patients with MI (majority with STEMI) and associated CS; mean age of around 65 years; >70% males; mean BMI of around 26 kg/m2; DM group had higher proportion of subjects with hypertension (77% vs. 45.5%), hyperlipidaemia (61% vs. 28%) and previous ischemic heart disease (42% vs. 25%) 97.7% of those with type I diabetes were on insulin and 35.2% with type 2 diabetes were on insulin 	319-DM; 1307- no DM	Adjusted mortality (30- days): OR 1.46 (95% CI: 1.01, 2.11) Need for revascularization (unadjusted): OR 1.42 (95% CI: 0.81, 1.63)
Farkouh (2006) ²⁶	Secondary analysis of trial data (SHOCK trial)	Multicentric	Patients with STEMI and associated CS; mean age of around 66 years; ~70% males; DM group had higher proportion of subjects with hypertension (56.2% vs. 42.5%), peripheral vascular disease (24.1% vs. 11.4%) and previous ischemic heart disease (44.4% vs. 27.8%) Of the patients with treatment status known, 77% were treated with oral hypoglycemics and/ or insulin	90-DM; 198- no DM	Adjusted mortality (30- days): OR 1.04 (95% CI: 0.58, 1.88) Need for revascularization (unadjusted): OR 0.83 (95% CI: 0.51, 1.35) Adjusted mortality (1- year): OR 1.02 (95% CI: 0.73, 1.42)

Table I. (continued)

(continued)

Author (year of publication)	Study design	Country	Participant characteristics	Sample size	Key outcomes (DM vs. no DM)
Dauriz (2020) 27	Secondary analysis of registry-based data	Italy	 Patients with MI (with similar proportion of patients with STEMI and non-ST segment elevation) associated CS; mean age of around 68 years; 69.8% males; DM group had higher proportion of subjects with hypertension (70.4% vs. 52.3%), peripheral vascular disease (16.6% vs. 8.0%) and lipid lowering medication (31.7% vs. 18.8%) Of the patients with treatment status known, oral hypoglycemic agents was used in 55.7%, insulin in 22.6%, both oral hypoglycemics and insulin in 19.4% and through diet management only in 2.3% 	8521-DM; 19704- no DM	Adjusted mortality (in- hospital): OR 1.95 (95% Cl: 1.69, 2.26) Mean hospitalization [mean (SD)] (days): 8 (1.0) vs. 7 (0.67)
Shindler (2000) ²⁸	Secondary analysis of registry-based data	Multicentric	Patients with MI (majority with STEMI) and associated CS; mean age of around 69 years; patients with diabetes were more likely to be females (49% vs. 36%); DM group had higher proportion of subjects with hypertension (66% vs. 47%), peripheral vascular disease (28% vs. 13%) and previous MI (43% vs. 34%) and congestive cardiac failure (30% vs. 15%). Data on mode of diabetes management not provided	379-DM; 784- no DM	Adjusted mortality (in- hospital): OR 1.47 (95% Cl: 1.10, 1.96) Unadjusted need for revascularization: OR 0.70 (95% Cl: 0.54, 0.89) Unadjusted major bleeding: OR 0.48 (95% Cl: 0.16, 1.44) Unadjusted cerebrovascular complication: OR 1.67 (95% Cl: 0.90, 3.09)
Yang (2013) ²⁹	Analysis of registry data	South Korea	Patients with STEMI and associated CS; mean age of around 67 years; >50% males; >50% with associated hypertension; 25% with dyslipidaemia Majority of the patients with diabetes were managed using oral hypoglycaemics (88%) followed by insulin (10%)	239-DM; 577- no DM	Unadjusted mortality (30- days): OR 1.29 (95% CI: 0.94, 1.78)
Hashmi (2018) ³⁰	Prospective study	Afghanistan	Patients with acute MI and associated CS; mean age of 65.4 years; 70% males; 66% with associated hypertension; 39% obese; mean BMI of 26.4 kg/m2. Data on mode of diabetes management not provided	208- no DM	Adjusted mortality (in- hospital): OR 2.93 (95% Cl: 1.89, 4.54)
Shaefi (2015) 31	Analysis of registry data	USA	Patients with acute MI (with similar proportion of patients with STEMI and non-ST segment elevation) and associated CS; majority with age >45 years (70%); ~60% males; 45% with previous coronary artery disease; 42% with associated hypertension; 39% with associated peripheral vascular disease. Data on mode of diabetes management not provided	I24340- DM; 408839- no DM	Adjusted mortality (in- hospital): OR 1.09 (95% Cl: 1.05, 1.14)

Table I. (continued)

(continued)

Table I. (continued)

Author (year of publication)	Study design	Country	Participant characteristics	Sample size	Key outcomes (DM vs. no DM)
Kataja (2017) 32	Retrospective analysis of data	Multicentric	Patients with acute MI and associated CS; mean age of 67 years; ~26% females; 34% with previous coronary artery disease; 61% with associated hypertension; 46% with hyperlipidaemia; mean BMI of 26.7 kg/m2. Data on mode of diabetes management not provided	58-DM; 153- no DM	Adjusted mortality (in- hospital): OR 0.59 (95% Cl: 0.25, 1.40)
Edep (2000) ³³	Retrospective analysis of clinical records	USA	Patients with acute MI and associated CS; mean age of 70.4 years; ~45% females; 6% with previous acute MI; 32% with associated hypertension. Data on mode of diabetes management not provided	314-DM; 808- no DM	Unadjusted mortality (in- hospital): OR 1.58 (95% Cl: 1.21, 2.07)
Karami (2021) ³⁴	Analysis of registry- based data	Netherlands	Patients with acute MI (majority with STEMI) and associated CS; mean age of 66 years; 71% males; 17% with previous acute MI; 59% with multivessel disease. Data on mode of diabetes management not provided	522-DM; 2506- no DM	Adjusted mortality (1-year): OR 1.25 (95% CI: 1.08, 1.45)

Author	OR (95% CI)	% Weight
Mortality (In-hospital)		
Gasior (2012)	1.16 (1.00, 1.35)	14.60
Tedesco (2003)	→ 2.71 (0.76, 9.73)	1.08
Gual (2020)	1.17 (1.10, 1.25)	17.07
Echouffo (2018)	1.18 (1.09, 1.28)	16.70
Dauriz (2020)	1.95 (1.69, 2.26)	14.76
Shindler (2000)	1.47 (1.10, 1.96)	9.88
Hashmi (2018)	2.93 (1.89, 4.54)	6.27
Shaefi (2015)	1.09 (1.05, 1.14)	17.45
Kataja (2017)	0.59 (0.25, 1.40)	2.20
Subtotal (I-squared = 90.2%, p = 0.000)	1.34 (1.17, 1.54)	100.00
Mortality (30-day)		
Farkouh (2006)	1.04 (0.58, 1.88)	20.46
Lindholm (2005)	1.04 (0.63, 1.74)	27.41
Thoegersen (2020)	1.46 (1.01, 2.11)	52.13
Subtotal (I-squared = 0.0%, p = 0.459)	1.24 (0.95, 1.62)	100.00
Mortality (at 1 year)		
Farkouh (2006)	1.02 (0.73, 1.42)	21.99
Karami (2021) 🔶	1.25 (1.08, 1.45)	78.01
Subtotal (I-squared = 16.7%, p = 0.273)	1.20 (1.01, 1.41)	100.00
Mortality (>1 year)		
Gasior (2012) •	1.11 (1.02, 1.20)	65.74
Tedesco (2003)	1.93 (1.04, 3.58)	9.03
Lindholm (2005)	1.21 (0.88, 1.67)	25.23
Subtotal (I-squared = 38.1%, p = 0.199) 🔯	1.19 (0.98, 1.45)	100.00
NOTE: Weights are from random effects analysis		
.103 1 9	1.73	

Figure 2. Pooled risk of mortality among individuals with cardiogenic shock with or without diabetes.

Author	OR (95% CI)	% Weight
Major bleeding		
Gasior (2012)	0.74 (0.44, 1.23)	82.04
Shindler (2000)	0.48 (0.16, 1.44)	17.96
Subtotal (I-squared = 0.0%, p = 0.484)	0.68 (0.43, 1.09)	100.00
Need for revascularization		
Gasior (2012)	1.53 (0.82, 2.86)	10.31
Thoegersen (2020)	1.42 (0.81, 1.63)	19.55
Echouffo (2018)	0.88 (0.80, 0.96)	31.57
Shindler (2000)	0.70 (0.54, 0.89)	24.44
Farkouh (2006)	0.83 (0.51, 1.35)	
Subtotal (I-squared = 70.2%, p = 0.009)	0.96 (0.75, 1.22)	100.00
Cerebrovascular complications		
Gasior (2012)	1.23 (0.72, 2.10)	7.24
Gual (2020) +	1.26 (1.08, 1.47)	87.30
Shindler (2000)	1.67 (0.90, 3.09)	5.45
Subtotal (I-squared = 0.0%, p = 0.679)	1.28 (1.11, 1.48)	100.00
Reinfarction		
Gasior (2012)	0.74 (0.55, 0.99)	62.65
Lindholm (2005)	1.56 (0.71, 3.46)	
Subtotal (I-squared = 66.6%, p = 0.084)	0.98 (0.48, 1.98)	
NOTE: Weights are from random effects analysis		
	1	

Figure 3. Pooled risk of adverse outcomes among patients with cardiogenic shock with or without diabetes.

		%
Author	WMD (95% CI)	Weight
Gasior (2012)	0.00 (-0.11, 0.11)	26.80
Gual (2020) (+-	-2.70 (-3.11, -2.29)	17.41
Echouffo (2018)	0.70 (0.70, 0.70)	27.92
Dauriz (2020)	• 1.00 (0.98, 1.02)	27.87
Overall (I-squared = 99.7%, p = 0.000)	0.00 (-0.27, 0.28)	100.00
NOTE: Weights are from random effects analysis	3	
-3.11 0	3.11	

Figure 4. Length of hospital stay (in days) among patients with cardiogenic shock with or without diabetes.

We conducted this meta-analysis to provide updated evidence on the influence of diabetes on outcomes of patients with acute MI and cardiogenic shock. Our findings suggest that the presence of diabetes in patients with acute MI and cardiogenic shock raises their risk for in-hospital mortality as well as mortality in the follow-up period (during at least 12 months post-operatively). Further, the presence of diabetes increases the risk of adverse cerebrovascular events. These findings underscore the need for better care and follow-up in patients with diabetes.

While we noted a poor survival among patients with diabetes, the underlying mechanisms through which diabetes may underlie other diseases is still under investigation. One possibility is that diabetes leads to extensive preexisting coronary artery disease (CAD) and multivessel involvement due to its ability to induce micro- and macrovascular changes.³⁸ Studies have also suggested that individuals with diabetes may have a comparatively larger infarct size, substantially reduced reperfusion, and a heightened susceptibility to arrhythmias of the ventricle than individuals without diabetes.³⁹⁻⁴¹ In addition, hyperglycemia triggers the stress response, increasing levels of circulating cytokines and the leucocyte count.42 Moreover, leukocytosis has been associated with increased risk of mortality in patients with STEMI.⁴² Another factor that could partially explain the poor outcomes in individuals with diabetes is the low left ventricular function reserve in diabetic cardiomyopathy.43 The underlying inflammation and micro- and macro vessel changes due to diabetes and associated hyperglycemia possibly explain the increased risk of adverse cerebrovascular events we found in this review.

Adequate glycemic control is of utmost importance as the evidence suggests that normoglycemic patients tend to have only mild abnormalities in arterial PH and lactate levels indicating less severe hypoperfusion than patients with hyperglycemia.⁴⁴ Stress-related hyperglycemia has been associated with increased risk of developing cardiac failure, cardiogenic shock, and death.^{32,44} Hyperglycemia may be considered a reliable sign of deranged homeostasis. Management of hyperglycemia is important and insulin therapy provides adequate glycemic control and may offer additional benefits through its positive ionotropic effect on the heart.⁴⁵ Moreover, studies in animal models have suggested that insulin has an anti-apoptotic effect on myocytes in the presence of ischemia.⁴⁶ An important practical challenge is to identify "persons-at-risk" with STEMI complicated by cardiogenic shock. One of the most commonly used tools is the GRACE risk score applicable during all forms of acute coronary syndrome.⁴⁷ The TIMI risk score for STEMI is another alternative, derived from its application to patients treated with fibrinolytics.⁴⁸ However, a robust risk model that is thoroughly applicable to the whole of the population is still needed.

We are aware of the limitations of this meta-analysis. As included studies had an observational design and many of them used data collected as part of registry or used data from clinical records, the possibility of important variables or potential confounder(s) being not accounted for in the final analytic model cannot be ruled out. Because almost all the studies had patients with STEMI, subgroup analyses based on the nature of MI (non-ST elevation MI and STEMI) could not be done. Also, the included studies had a heterogenous diabetes population (type 1 or type 2) and their results were not stratified based on these. This prevented us from performing subgroup analyses based on type of diabetes. It is clinically well known that patients with acute myocardial infarction and associated cardiogenic shock have a poor prognosis. Further, if there is associated diabetes, then the prognosis is even poorer. Based on these considerations, an analysis based on the mode of management of diabetes would have helped to understand this issue better. However, most of the studies did not provide required information on the mode of diabetes management. While some studies provided this information, majority of them did not furnish data on the management of diabetes in patients with diabetes. This is an important limitation as in general practice, clinical management of diabetes is quite heterogenous and this might have influenced the outcomes. It would also have been desirable to conduct an analysis based on blood glucose level at admission and HbA1c (%) but the studies lacked the relevant variables. Another limitation stems from the differences in the baseline socio-demographic and clinical characteristics among the patients with diabetes and those without diabetes. It was not completely clear whether the researchers of the studies in our analyses had adjusted for these differences or how these differences impacted the final effect sizes reported. For the analysis related to the primary outcome (mortality), we included studies that had presented adjusted risk estimates. However, we could not follow the similar principle for the secondary outcomes as almost all the included studies had presented unadjusted measures of risk. Therefore, especially for the secondary outcomes, the interpretation must be made cautiously as unadjusted estimates are likely to be biased.

Conclusions

Our current meta-analysis, after synthesizing the findings from 15 observational studies, suggests an increased risk of mortality for patients with acute MI with associated cardiogenic shock if they also present diabetes. The findings stress the need for close and careful monitoring of patients with AMI and associated CS. More research is needed to identify optimal management strategies for improving survival of such patients.

Author contributions

CL, FC conceived and designed the study; LL, ZG, CF and YC were involved in literature search and data collection; FC, LL, ZG and CF analyzed the data; CL and YC wrote the paper; and YC

reviewed and edited the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Jinhua City Science and Technology Plan Project Social Development Key Project (2019-3–007).

Inclusion Criteria

We considered observational studies, including those based on analysis of registry data or clinical records for inclusion. All the studies considered were done in patients with MI and associated cardiogenic shock that mentioned the association of diabetes with the outcomes of interest.

Exclusion Criteria

We excluded case-reports, review articles, and studies that did not provide findings based on diabetes status that failed to provide findings on the outcomes of interest.

ORCID iD

Yuehua Chen D https://orcid.org/0000-0003-1917-2243

Supplemental Material

Supplemental material for this article is available online.

References

- van Diepen S, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation* 2017; 136: e232–e268.
- Khalid L and Dhakam SH. A review of cardiogenic shock in acute myocardial infarction. *Curr Cardiol Rev* 2008; 4: 34–40.
- Kolte D, Khera S, Aronow WS, et al. Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. J Am Heart Assoc 2014; 3: e000590.
- Harjola V-P, Lassus J, Sionis A, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. *Eur J Heart Fail* 2015; 17: 501–509.
- Vahdatpour C, Collins D and Goldberg S. Cardiogenic Shock. J Am Heart Assoc 2019; 8: e011991.
- Hochman JS. Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm. *Circulation* 2003; 107: 2998–3002.

- Prondzinsky R, Unverzagt S, Lemm H, et al. Interleukin-6, -7, -8 and -10 predict outcome in acute myocardial infarction complicated by cardiogenic shock. *Clin Res Cardiol* 2012; 101: 375–384.
- Hochman JS, Buller CE, Sleeper LA, et al. Cardiogenic shock complicating acute myocardial infarction--etiologies, management and outcome: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries for cardiogenic shock? *J Am Coll Cardiol* 2000; 36: 1063–1070.
- Obling L, Frydland M, Hansen R, et al. Risk factors of late cardiogenic shock and mortality in ST-segment elevation myocardial infarction patients. *Eur Heart J Acute Cardio*vasc Care 2018; 7: 7–15.
- Liu Y, Zhao Y, Liu G, et al. [Analysis of risk factors of cardiogenic shock secondary to acute myocardial infarction]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2013; 25: 399–402.
- Franklin K, Goldberg RJ, Spencer F, et al. Implications of diabetes in patients with acute coronary syndromes. The Global Registry of Acute Coronary Events. *Arch Intern Med* 2004; 164: 1457–1463.
- Cui J, Liu Y, Li Y, et al. Type 2 diabetes and myocardial infarction: recent clinical evidence and perspective. *Front Cardiovasc Med* 2021; 8: 644189.
- Leon BM and Maddox TM. Diabetes and cardiovascular disease: epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes* 2015; 6: 1246–1258.
- King RJ and Grant PJ. Diabetes and cardiovascular disease: pathophysiology of a life-threatening epidemic. *Herz* 2016; 41: 184–192.
- Petrie JR, Guzik TJ and Touyz RM. Diabetes, hypertension, and cardiovascular disease: clinical insights and vascular mechanisms. *Can J Cardiol* 2018; 34: 575–584.
- PRISMA. Transparent reporting of systematic reviews and meta-analyses. PRISMA. Transparent reporting of systematic reviews and meta-analyses. http://www.prismastatement.org/
- 17. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta- analysis. 21.
- Higgins Julian PT, Higgins JPT and Green S (eds) Cochrane handbook for systematic reviews of interventions. *IDoStatistics*. https://idostatistics.com/higgins-green-2008cochrane-handbook-systematic-reviews-interventions/ (2016, accessed December 13, 2019).
- Egger M, Smith GD, Schneider M, et al. Bias in metaanalysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
- Gąsior M, Pres D, Gierlotka M, et al. The influence of diabetes on in-hospital and long-term mortality in patients with myocardial infarction complicated by cardiogenic shock: results from the PL-ACS registry. *Kardiol Pol* 2012; 70: 1215–1224.

- Tedesco JV, Wright RS, Williams BA, et al. Effect of diabetes on the mortality risk of cardiogenic shock in a communitybased population. *Mayo Clin Proc* 2003; 78: 561–566.
- Lindholm MG, Boesgaard S, Torp-Pedersen C, et al. Diabetes mellitus and cardiogenic shock in acute myocardial infarction. *Eur J Heart Fail* 2005; 7: 834–839.
- Gual M, Albert-Solé A, Maárquez MG, et al. Diabetes mellitus, revascularization and outcomes in elderly patients with myocardial infarction-related cardiogenic shock. *J Geriatr Cardiol* 2020; 17: 604–611.
- 24. Echouffo-Tcheugui JB, Kolte D, Khera S, et al. Diabetes mellitus and cardiogenic shock complicating acute myocardial infarction. *Am J Med* 2018; 131: 778–786.e1.
- 25. Thoegersen M, Josiassen J, Helgestad OK, et al. The association of diabetes and admission blood glucose with 30-day mortality in patients with acute myocardial infarction complicated by cardiogenic shock. *Eur Heart J Acute Cardiovasc Care* 2020; 9: 626–635.
- Farkouh ME, Ramanathan K, Aymong ED, et al. An early revascularization strategy is associated with a survival benefit for diabetic patients in cardiogenic shock after acute myocardial infarction. *Clin Cardiol* 2006; 29: 204–210.
- Dauriz M, Morici N, Gonzini L, et al. Fifteen-year trends of cardiogenic shock and mortality in patients with diabetes and acute coronary syndromes. *Am J Med* 2020; 133: 331–339.e2.
- Shindler DM, Palmeri ST, Antonelli TA, et al. Diabetes mellitus in cardiogenic shock complicating acute myocardial infarction: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries for cardiogenic shock? J Am Coll Cardiol 2000; 36: 1097–1103.
- Yang JH, Song PS, Song YB, et al. Prognostic value of admission blood glucose level in patients with and without diabetes mellitus who sustain ST segment elevation myocardial infarction complicated by cardiogenic shock. *Crit Care* 2013; 17: R218.
- Hashmi KA, Abbas K, Hashmi AA, et al. In-hospital mortality of patients with cardiogenic shock after acute myocardial infarction; impact of early revascularization. *BMC Res Notes* 2018; 11: 721.
- Shaefi S, O'Gara B, Kociol RD, et al. Effect of cardiogenic shock hospital volume on mortality in patients with cardiogenic shock. *J Am Heart Assoc* 2015; 4: e001462.
- Kataja A, Tarvasmäki T, Lassus J, et al. The association of admission blood glucose level with the clinical picture and prognosis in cardiogenic shock - Results from the CardShock Study. *Int J Cardiol* 2017; 226: 48–52.
- Edep ME and Brown DL. Effect of early revascularization on mortality from cardiogenic shock complicating acute myocardial infarction in California. *Am J Cardiol* 2000; 85: 1185–1188.
- Karami M, Peters EJ, Lagrand WK, et al. Outcome and predictors for mortality in patients with cardiogenic shock: a dutch nationwide registry-based study of 75, 407 patients

with acute coronary syndrome treated by PCI. *J Clin Med* 2021; 10: 2047.

- 35. Lin X, Xu Y, Pan X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Sci Rep* 2020; 10: 14790.
- Chioncel O, Parissis J, Mebazaa A, et al. Epidemiology, pathophysiology and contemporary management of cardiogenic shock - a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020; 22: 1315–1341.
- Lindholm MG, Køber L, Boesgaard S, et al. Cardiogenic shock complicating acute myocardial infarction; prognostic impact of early and late shock development. *Eur Heart J* 2003; 24: 258–265.
- Gregg EW, Sattar N and Ali MK. The changing face of diabetes complications. *Lancet Diabetes Endocrinol* 2016; 4: 537–547.
- Alegria JR, Miller TD, Gibbons RJ, et al. Infarct size, ejection fraction, and mortality in diabetic patients with acute myocardial infarction treated with thrombolytic therapy. *Am Heart J* 2007; 154: 743–750.
- Movahed M-R, Hashemzadeh M and Jamal M. Increased prevalence of ventricular fibrillation in patients with type 2 diabetes mellitus. *Heart Vessels* 2007; 22: 251–253.
- Iwakura K, Ito H, Ikushima M, et al. Association between hyperglycemia and the no-reflow phenomenon in patients with acute myocardial infarction. *J Am Coll Cardiol* 2003; 41: 1–7.
- Seropian IM, Sonnino C, Van Tassell BW, et al. Inflammatory markers in ST-elevation acute myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2016; 5: 382–395.
- Ha J-W, Lee H-C, Kang E-S, et al. Abnormal left ventricular longitudinal functional reserve in patients with diabetes mellitus: implication for detecting subclinical myocardial dysfunction using exercise tissue Doppler echocardiography. *Heart* 2007; 93: 1571–1576.
- 44. Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000; 355: 773–778.
- 45. Hsu C-H, Wei J, Chen Y-C, et al. Cellular mechanisms responsible for the inotropic action of insulin on failing human myocardium. *J Heart Lung Transpl* 2006; 25: 1126–1134.
- Xing W, Yan W, Fu F, et al. Insulin inhibits myocardial ischemia-induced apoptosis and alleviates chronic adverse changes in post-ischemic cardiac structure and function. *Apoptosis* 2009; 14: 1050–1060.
- Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003; 163: 2345–2353.
- Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: an

intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation* 2000; 102: 2031–2037. WARNING: Set minimum 6 Lines per Column in Last Page