

Prognostic factors of Takotsubo cardiomyopathy: a systematic review

Xiaojia Lu¹, Pengyang Li², Catherine Teng³, Peng Cai⁴, Ling Jin⁵, Chenlin Li¹, Qi Liu⁶, Su Pan⁶, Richard A.F. Dixon⁶ and Bin Wang^{1,7*}

¹Department of Cardiology, the First Affiliated Hospital of Shantou University Medical College, 57 Changping Road, Shantou, 515041, China; ²Division of Cardiology, Pauley Heart Center, Virginia Commonwealth University, Richmond, VA, USA; ³Department of Medicine, Yale New Haven Health Greenwich Hospital, Greenwich, CT, USA; ⁴Department of Mathematical Sciences, Worcester Polytechnic Institute, Worcester, MA, USA; ⁵Department of Medicine, Metrowest Medical Center, Framingham, MA, USA; ⁶Wafic Said Molecular Cardiology Research Laboratory, Texas Heart Institute, Houston, TX, USA; and ⁷Clinical Research Center, the First Affiliated Hospital of Shantou University Medical College, Shantou, China

Abstract

Takotsubo cardiomyopathy (TCM), characterized by reversible ventricular dysfunction, has similar mortality to acute coronary syndrome. With the growing interest in the diagnosis of and interventions for TCM, many risk factors had been found to affect the prognosis of TCM patients, such as age, sex, and pre-existing diseases. Because of the incomplete understanding of the pathophysiologic mechanism in TCM, evidence-based medical therapy for this condition is lacking. Early intervention on risk factors may improve the outcomes of TCM. In this review, we sought to provide up-to-date evidence on risk factors and medical therapies that affect TCM outcome. We found that male sex, physical triggers, and certain comorbidities such as chronic kidney disease, malignant disease, higher body mass index, sepsis, chronic obstructive pulmonary disease, and anaemia were associated with poor TCM prognosis. In contrast, race, hyperlipidaemia, diabetes mellitus, and mood disorders were not clearly associated with TCM prognosis. We also reviewed the effect of medical therapies on TCM outcome, including angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β -blockers, calcium channel blockers, and statins. The evidence that these medications confer a survival benefit on TCM patients is limited. Understanding these prognostic factors could help develop risk-stratification tools for TCM and establish effective prevention and interventions for this not-so-benign condition. Further multicentre clinical studies with large samples and meta-analyses of findings from previous studies are needed to address the inconsistent findings among the many potential risk factors for TCM.

Keywords Risk factors; Treatment; Prognosis; Takotsubo cardiomyopathy

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*Correspondence to: Bin Wang, Department of Cardiology, the First Affiliated Hospital of Shantou University Medical College, 57 Changping Road, Shantou 515041, China. Tel: +86 075488905399; Fax: +07 5488259850. Email: wangbin_pku@126.com

Xiaojia Lu and Pengyang Li contributed equally to the writing of this article and share primary authorship.

Introduction

Having been first introduced in Japan, Takotsubo cardiomyopathy (TCM) is characterized by temporary, reversible regional wall motion abnormalities that extend beyond a single coronary artery distribution without any evidence of acute coronary artery occlusion.¹ Takotsubo, which means ‘octopus trap’ in Japanese, is used to describe the classic morphology of the left ventricle in systole as seen on echocardiograms.² The true prevalence of the TCM remains unknown. Over the past few years, the number of reported cases has increased. Previous reports indicated that between 0.7% and

2.2% of acute coronary syndrome (ACS) cases were eventually discovered to be TCM.^{3–6}

Based on the initial presentation, TCM is classified into two clinical subtypes: primary and secondary. In primary TCM, TCM is the chief reason for the patient’s acute presentation; this includes cases with clear triggers or any coexisting medical conditions that are risk factors for TCM. Secondary TCM is considered a complication of the patient’s primary medical condition, such as medical, surgical, and psychiatric conditions.⁷

Moreover, whereas TCM was once thought to be a reversible and benign condition, it is now recognized to have a

mortality rate similar to that of ACS.⁸ Major adverse cardiovascular events, such as cardiac arrhythmias,⁹ cardiogenic shock,⁸ and ventricular thrombus,¹⁰ are also not uncommon in TCM patients. Rare conditions such as ventricular rupture¹¹ and ventricular septal defect¹² can occur, as well. The overall rarity of TCM had limited the study of TCM outcomes in the past. Recent advances in using administrative and registry databases have enabled us to uncover several prognostic factors in both short-term and long-term outcomes of TCM. A recent study has also identified distinct TCM clinical phenotypes according to their risk factors and found different in-hospital outcomes among these phenotypes.¹³ Understanding these risk factors could facilitate the development of risk-stratification tools for TCM and effective interventions to improve TCM prognosis. In this review, we summarize the available evidence regarding risk factors and medical therapies and their effect on TCM prognosis.

Methods

We performed a systematic review of observational studies on the association between risk factors with TCM.

Search strategy

We searched the key words ‘apical ballooning syndrome,’ ‘broken heart syndrome,’ ‘stress cardiomyopathy,’ ‘takotsubo syndrome,’ ‘takotsubo cardiomyopathy,’ ‘takotsubo cardiomyopath*,’ ‘takotsubo,’ ‘ampulla cardiomyopathy,’ ‘neurogenic pulmonary edema,’ and ‘stress induced cardiomyopathy’ to identify articles from PubMed, Embase, and Cochrane databases from January 1, 2010 to February 28, 2020.

Inclusion and exclusion criteria

Studies were selected according to the following pre-specified inclusion criteria (all of which had to be met for inclusion): (i) diagnosis of TCM on the basis of pre-defined specific TCM diagnostic criteria or International Classification of Diseases (ICD) code; (ii) the end point of study was mortality, including short-term and long-term mortality; and (iii) the study sample comprised more than 100 patients. Exclusion criteria included duplicate reporting: if multiple articles reported the same number of patients and follow-up time, the most recent article was selected. Single case reports and previous systematic reviews on TCM were also excluded.

Study selection

Two unblinded investigators (Lu and Li) independently screened the retrieved citations. Studies whose title or abstract indicated potential relevance to our study were fully reviewed, and their appropriateness for the study was judged independently by the two reviewers according to the previously described inclusion and exclusion criteria. Disagreements were resolved by consensus, with adjudication by a third party when needed.

Outcome measures

Two clinical outcomes were analysed: short-term mortality and long-term mortality (i.e. including both cardiac and non-cardiac deaths). Data were extracted into standard spreadsheets and included date of study publication, sample size, diagnostic criteria, duration of follow-up, analysis strategy, and clinical outcomes, as previously defined. Methodological study quality was assessed with the Quality in Prognostic Factor Studies tool.¹⁴ The domains of patient selection, study attrition, measurement of prognostic factors, outcome measurement, study confounding, and statistical analysis and reporting were rated as having a low, moderate, or high risk of bias. Studies with five or six domains with a low risk of bias were classified as having a low overall risk of bias, and studies with two or more domains with a high risk of bias were classified as having a high overall risk of bias. All other studies were considered to have a moderate overall risk of bias.¹⁵

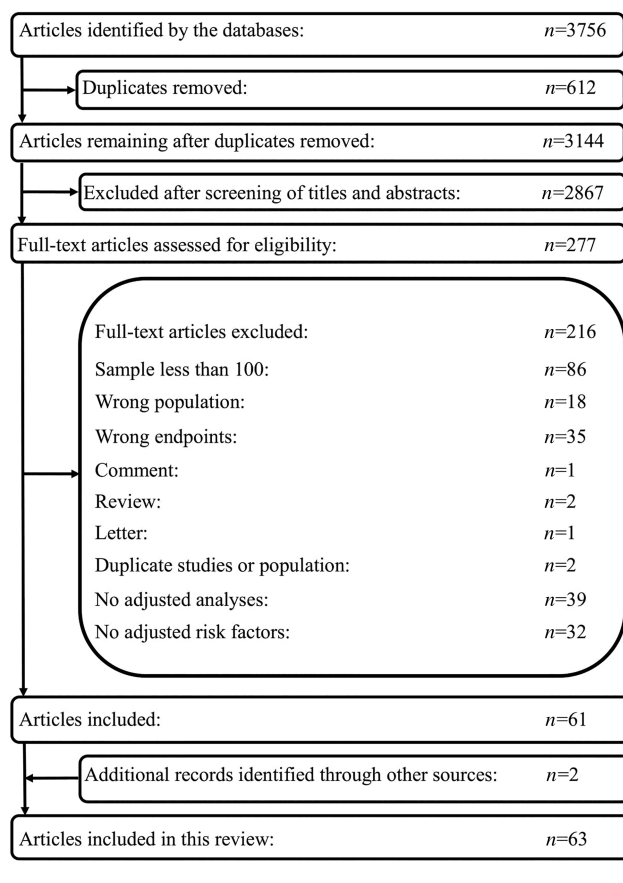
Results

The process of study selection (*Figure 1*) identified 61 studies for review. Another two articles, which were published after we performed our search, were added at the suggestion of peer reviewers. Finally, we identified 63 observational studies. Quality assessment by the Quality in Prognostic Factor Studies checklist disclosed moderate bias in 42 studies, high bias in 20 studies, and low bias in 1 study.

Factors affecting prognosis of Takotsubo cardiomyopathy

Sex

Female sex has been identified as a strong risk factor for TCM.¹⁶ Previous studies have found that women comprise about 82.0% to 92.7% of the overall TCM patient population.^{17–23} In a study of postmenopausal women who

Figure 1 Flow chart of article selection process.

presented with ACS, approximately 5.9% of them were noted to have TCM.¹⁶

Despite female sex being a strong risk factor for TCM, most of the studies we identified suggest that it is associated with favourable short-term outcomes in TCM (*Table 1*). Some studies have found that male patients have poorer short-term outcomes, such as higher rates of in-hospital mortality^{19,23–31} and complications.^{18,20,32} One retrospective study of 14 639 patients found that female patients had a lower rate of in-hospital mortality [odds ratio (OR) 0.521, 95% confidence interval (CI) 0.389–0.699].³⁰ In another study that included 24 701 TCM patients, Brinjikji *et al.* found that male sex was associated with higher in-hospital mortality (OR 2.07, 95% CI 1.71–2.49).¹⁹ Similarly, a study of 39 662 TCM patients found that male patients had higher rates of in-hospital mortality (OR 3.89, 95% CI 2.41–6.24) and in-hospital complications, such as cardiogenic shock (OR 1.51, 95% CI 1.03–2.06), ventricular fibrillation (VF) or tachycardia (VT) (OR 1.52, 95% CI 1.07–2.16), and acute kidney injury (OR 1.93, 95% CI 1.44–2.59).²⁰ On the other hand, some studies have found no association between sex and TCM in-hospital outcome.^{8,23,33–39} A study of 1750 TCM patients found that female sex was not associated with

in-hospital outcomes, including catecholamine use, cardiogenic shock, ventilation use, cardiopulmonary resuscitation, and all-cause mortality ($P = 0.14$).⁸ Similarly, another study with relatively large sample size (705 male patients and 6805 female patients) did not find a sex difference in in-hospital mortality in patients with TCM.³⁶

No consensus has been reached in terms of the long-term effects of sex on TCM outcomes (*Table 1*). Some studies indicate that being male is associated with poorer outcomes.^{21,22,40–51} Ghadri *et al.* found that the risk of all-cause mortality of male patients was 1.75 times higher than that of female patients in a 5 year follow-up study [hazard ratio (HR) 1.75, 95% CI 1.13–2.70] in a prospective study with a large sample (1450 female and 163 male).⁴² Another retrospective study, which included 19 966 TCM patients, by Murugiah *et al.* noted that among patients with primary TCM, male patients had a higher 1 year mortality rate (12.0% vs. 6.6%, $P < 0.05$). Similarly, in the secondary TCM group, male patients also had a higher 1 year mortality rate than female patients (18.2% vs. 10.7%, $P < 0.05$).²² Other studies found no association between sex and the long-term outcomes of TCM.^{52–60} One study by Uribarri *et al.* found that male sex was not associated with 5 year mortality in TCM patients ($P = 0.076$).⁵⁵ Another study that included 1604 TCM patients found that sex was not associated with 10 year mortality ($P = 0.17$).⁵⁶

Age

Although TCM occurs predominantly in postmenopausal women, younger individuals, even children, can also be affected by this condition. The mean age of study population ranges from 53 to 76 years.^{22,27,61–63} However, whether the age gap translates into outcome differences is unclear.

The association between age and the short-term outcomes in TCM is controversial (*Table 2*). Some studies have associated older age with a higher short-term mortality rate.^{22,24,28,30,33–37,44,64–68} For example, in one prospective study with 19 966 TCM patients (8068 patients with a primary diagnosis of TCM and 11 898 with a secondary diagnosis), patients were grouped by age into three categories: 65–74, 75–84, and ≥ 85 years. The patients 85 years or older had the highest overall in-hospital mortality rate (primary TCM: 2.6% in patients aged more than 85 years vs. 1.5% in patients aged 75 to 84 vs. 0.74% in patients aged 65 to 74, $P < 0.05$; secondary TCM: 4.5% vs. 3.3% vs. 2.2%, $P < 0.05$) and the highest 30 day mortality rate (primary TCM, 4.9% vs. 2.7% vs. 1.7%, $P < 0.05$; secondary TCM 7.7% vs. 5.1% vs. 3.6%, $P < 0.05$).²² Another study of 10 861 TCM patients found that greater age was independently associated with higher in-hospital mortality (OR 1.05, 95% CI 1.04–1.07). In a subanalysis of sex in the same study, age predicted in-hospital mortality in female patients (OR 1.06, 95% CI

Table 1 Clinical studies on the effect of sex in TCM patients

Sex	Author (year)	Diagnostic criteria	Sample size	Type of study	Follow-up	Mortality	Analysis strategy	Risk of bias
Male vs. Female	Brinjikji et al. (2012)	ICD-9	24 701	Retrospective	In-hospital	OR 2.07 (95% CI 1.71–2.49), P < 0.0001	Multivariable logistic regression	High
	Isogai et al. (2014)	ICD-10	3719	Retrospective	In-hospital	No difference	Multivariable logistic regression	High
	Lee et al. (2016)	Mayo criteria	128	Retrospective	In-hospital	No difference	Multivariable logistic regression	Moderate
	Khera et al. (2016)	ICD-9	11 193	Retrospective	In-hospital	Primary diagnosis of TCM: OR 3.85 (95% CI 1.74–8.51), P = 0.0009	Multivariable logistic regression	High
						Secondary diagnosis of TCM: No difference		
						No difference		
	Siermaier et al. (2016)	Mayo criteria	285	Prospective	6 months	No difference	Multivariate Cox regression	Moderate
	Siermaier et al. (2016)	Mayo criteria	286	Prospective	Mean = 3.8 ± 2.5 years	HR 1.97 (95% CI 1.03–3.78), P = 0.04	Multivariate Cox regression	Moderate
	Siermaier et al. (2017)	Mayo criteria and ESC criteria (2016)	387	Prospective	Median = 2.9 years	HR 2.97 (95% CI 1.68–5.24), P < 0.001	Multivariate Cox regression	Moderate
	El-Battrawy et al. (2017)	Mayo criteria	114	Prospective	Mean = 1529 ± 1121 days	No difference	Multivariate Cox regression	Moderate
Huseynov et al. (2017)	Mayo criteria	114	Prospective	Mean = 1591 ± 1079 days	HR 2.8 (95% CI 1.1–7.2), P = 0.02	Multivariate Cox regression	Moderate	
Weidner et al. (2017)	Mayo criteria	114	Prospective	5 years	HR 2.8 (95% CI 1.1–7.2), P = 0.02	Multivariate Cox regression	Moderate	
Bill et al. (2017)	Mayo criteria	114	Prospective	2 years	No difference	Multivariate Cox regression	Moderate	
Almendo-Delia et al. (2018)	Modified Mayo criteria	711	Prospective	Median = 284 days	HR 1.93 (95% CI 1.46–2.55), P < 0.0001	Multivariate Cox regression	Moderate	
Ansari et al. (2018)	Modified Mayo criteria	114	Prospective	5 years	No difference	Multivariate Cox regression	Moderate	
Ghadri et al. (2018)	Modified Mayo criteria	1613	Prospective	5 years	HR 1.75 (95% CI 1.13–2.70), P = 0.012	Multivariate Cox regression	Moderate	
Siermaier et al. (2018)	Mayo criteria and ESC criteria (2016)	826	Prospective	Median = 2.5 years	HR 1.65 (95% CI 1.09–2.51), P = 0.018	Multivariate Cox regression	Moderate	
Siermaier et al. (2018)	Mayo criteria and ESC criteria (2016)	177	Prospective	Median = 2.3 years	HR 5.52 (95% CI 1.74–17.47), P = 0.004	Multivariate Cox regression	Moderate	
Giannakopoulos et al. (2019)	Mayo criteria	138	Prospective	5 years	HR 2.7 (95% CI 1.1–6.5), P = 0.02	Multivariate Cox regression	Moderate	
Hohneck et al. (2019)	Mayo criteria	105	Prospective	Mean = 1494 days	No difference	Multivariate Cox regression	Moderate	
Gietzen et al. (2019)	Mayo criteria	138	Prospective	5 years	HR 2.7 (95% CI 1.1–6.5), P = 0.02	Multivariate Cox regression	Moderate	
Lemor et al. (2019)	ICD-9	39 662	Retrospective	In-hospital	OR 3.89 (95% CI 2.41–6.24), P < 0.001	Multivariate logistic regression	High	
Misumida et al. (2019)	ICD-9	22 818	Retrospective	In-hospital	OR 3.80 (95% CI 1.94–7.46), P < 0.001	Multivariate logistic regression	High	

(Continues)

Table 1 (continued)

Sex	Author (year)	Diagnostic criteria	Sample size	Type of study	Follow-up	Mortality	Analysis strategy	Risk of bias
	Uribarri et al. (2019)	Modified Mayo criteria	939	Prospective	5 years	No difference	Multivariate Cox regression	Moderate
	Alashi et al. (2020)	Modified Mayo criteria	650	Prospective	Median = 2.2 years	HR 1.75 (95% CI 1.06–2.89), P = 0.032	Multivariate Cox regression	Moderate
	Arcari et al. (2020)	Mayo criteria and ESC criteria (2016)	1071	Prospective	Median = 576 days	OR 1.89 (95% CI 1.13–3.18), P = 0.015	Multivariate logistic regression	Moderate
	Cammann et al. (2020)	Modified Mayo criteria	2098	Prospective	In-hospital	OR 2.18 (95% CI 1.26–3.77), P = 0.005	Multivariate logistic regression	Moderate
	Kimura et al. (2020)	Modified Mayo criteria	421	Retrospective	In-hospital	No difference	Multivariate logistic regression	Moderate
	Malanchini et al. (2020)	Mayo criteria ICD-9	10 861	Retrospective	In-hospital	OR 2.32 (95% CI 1.65–3.27), P < 0.001	Multivariate logistic regression	High
	Syed et al. (2020)	ICD-9 and ICD-10	260 144	Retrospective	In-hospital	OR 1.78 (95% CI 1.70–1.85), P < 0.01	Stepwise logistic regression	High
Female vs. Male	Kwon et al. (2013)	Modified Mayo criteria	208	Retrospective	In-hospital	No difference	Multivariate logistic regression	Moderate
	Krishnamoorthy et al. (2015)	Mayo criteria ICD-9	7510	Retrospective	In-hospital	No difference	Multivariate logistic regression	High
	Núñez-Gil et al. (2016)	Modified Mayo criteria	328	Prospective	18.1 ± 24.2 months	HR 0.258 (95% CI 0.080–0.832), P = 0.023	Multivariate Backwards Wald	Moderate
	Vallabhajosyula et al. (2018)	ICD-9	2214	Retrospective	In-hospital	No difference	stepwise regression Multivariate logistic regression	High
	Cammann et al. (2019)	Modified Mayo criteria	1604	Prospective	10 years	No difference	Multivariate logistic regression	Low
	Yerasi et al. (2019)	Mayo criteria ICD-9	12 255	Retrospective	In-hospital	OR 0.68 (95% CI 0.55–0.84), P < 0.001	Cox regression Multivariate regression	High
	Napierkowski et al. (2021)	ICD-9	14 639	Retrospective	In-hospital	OR 0.521 (95% CI 0.389–0.699), P < 0.001	Multivariate logistic regression	High
	Kato et al. (2021)	Modified Mayo criteria	1670	Prospective	5 years	HR 0.56 (95% CI 0.37–0.85), P = 0.007	Multivariate Cox regression	Moderate

CI, confidence interval; ESC, European Society of Cardiology; HR, hazard ratio; ICD, International Classification of Diseases; NA, not applicable; OR, odds ratio; TCM, Takotsubo cardiomyopathy.

Table 2 Clinical studies on the effects of age (years) in TCM patients

Age	Author (year)	Diagnostic criteria	Sample size	Type of study	Follow-up	Mortality	Analysis strategy	Risk of bias
Older vs. Younger	Brinjikji et al. (2012)	ICD-9	24 701	Retrospective	In-hospital	50–64 vs. <50: No difference; >64 vs. <50: No difference OR 1.063 (95% CI 1.007–1.123), $P = 0.028$	Multivariable logistic regression	High
	Kwon et al. (2013)	Modified Mayo criteria ICD-10	208	Retrospective	In-hospital	Per 10 year increase: OR 1.33 (95% CI 1.15–1.53), $P < 0.001$	Multivariable logistic regression	Moderate
	Isogai et al. (2014)	ICD-9	3719	Retrospective	In-hospital	OR 1.05 (95% CI 1.01–1.09), $P = 0.02$	Multivariable logistic regression	High
	Krishnamoorthy et al. (2015)	ICD-9	7510	Retrospective	In-hospital	HR 1.09 (95% CI 1.02–1.17), $P < 0.01$	Multivariable Cox regression	High
	Nishida et al. (2015)	Mayo criteria	251	Prospective	Mean = 2.6 ± 2.8 years	>70 vs. ≤70: No difference	Multivariable Cox regression	Moderate
	Ghadri et al. (2016)	Modified Mayo criteria	1750	Prospective	1 year	Cardiac mortality: HR 1.11 (95% CI 1.03–1.2), $P = 0.006$	Multivariable Cox regression	Moderate
	Girardey et al. (2016)	Madias criteria	154	Prospective	Median = 364 days	All-cause mortality: No difference	Multivariable Cox regression	Moderate
	Lee et al. (2016)	Mayo criteria	128	Retrospective	In-hospital	No difference	Multivariable logistic regression	Moderate
	Khera et al. (2016)	ICD-9	11 193	Retrospective	In-hospital	OR 1.04 (95% CI 1.01–1.08), $P = 0.0081$	Multivariable logistic regression	High
	Núñez-Gil et al. (2016)	Modified Mayo criteria	328	Prospective	Mean = 18.1 ± 24.2 months	Per 1 year increasing: No difference	Backwards Wald stepwise regression	Moderate
	Stiermaier et al. (2016)	Mayo criteria	285	Prospective	6 months	No difference	Multivariable Cox regression	Moderate
	Stiermaier et al. (2016)	Mayo criteria	286	Prospective	Mean = 3.8 ± 2.5 years	>70 vs. ≤70: No difference	Multivariable Cox regression	Moderate
	Nayeri et al. (2017)	Mayo criteria	306	Prospective	30 days	No difference	Multivariable Cox regression	High
	Parodi et al. (2017)	In-TAK criteria	371	Prospective	Mean = 15 years	No difference	Multivariable Cox regression	Moderate
	Stiermaier et al. (2017)	Mayo criteria and ESC criteria (2016)	387	Prospective	Median = 26 ± 20 months	HR 1.11 (95% CI 1.06–1.16), $P < 0.001$	Multivariable Cox regression	Moderate
	Almendo-Delia et al. (2018)	Modified Mayo criteria	711	Prospective	Median = 2.9 years	HR 1.04 (95% CI 1.01–1.07), $P = 0.006$	Multivariable Cox regression	Moderate
	Ghadri et al. (2018)	Modified Mayo criteria	1613	Prospective	Median = 284 days	Per 10 year increase: HR 2.61 (95% CI 1.18–3.42), $P = 0.02$	Multivariable Cox regression	Moderate
	Kim et al. (2018)	Modified Mayo criteria	257	Prospective	5 years	>70 vs. ≤70: HR 1.50 (95% CI 1.08–2.09), $P = 0.016$	Multivariable Cox regression	Moderate
	Stiermaier et al. (2018)	Mayo criteria and ESC criteria (2016)	826	Prospective	Median = 5.8 ± 3.6 years	HR 1.057 (95% CI 1.035–1.080), $P < 0.05$	Multivariable Cox regression	Moderate
	Stiermaier et al. (2018)	Mayo criteria and ESC criteria (2016)	177	Prospective	Median = 2.5 years	HR 1.05 (95% CI 1.03–1.07), $P < 0.001$	Multivariable Cox regression	Moderate
	Stiermaier et al. (2018)	Mayo criteria and ESC criteria (2016)	177	Prospective	Median = 2.3 years	HR 1.10 (95% CI 1.04–1.18), $P = 0.002$	Multivariable Cox regression	Moderate

(Continues)

Table 2 (continued)

Age	Author (year)	Diagnostic criteria	Sample size	Type of study	Follow-up	Mortality	Analysis strategy	Risk of bias
	Vallabhajosyula et al. (2018)	ICD-9	2214	Retrospective	In-hospital	45–64 vs. 22–24: No difference 65–79 vs. 22–24: OR 1.8 (95% CI 1.1–3.3), <i>P</i> = 0.04; ≥80 vs. 22–24: OR 2.9 (95% CI 1.6–5.6), <i>P</i> = 0.001 >70 vs. ≤70: HR 1.6 (95% CI 1.16–2.20), <i>P</i> = 0.004	Multivariable logistic regression	High
	Cammann et al. (2019)	Modified Mayo criteria	1604	Prospective	10 years	Cardiovascular mortality: OR 1.072 (95% CI 1.023–1.123), <i>P</i> = 0.004 Per 10 year increase: OR 1.46 (95% CI 1.10–1.95), <i>P</i> = 0.01 >70 vs. ≤70: HR 2.894 (95% CI 1.657–5.054), <i>P</i> < 0.001	Multivariate Cox regression	Low
	Jesel et al. (2019)	Modified Mayo criteria	214	Prospective	In-hospital	50–64 vs. 18–49: OR 0.75 (95% CI 0.55–1.00), <i>P</i> = 0.05	Multivariate Cox regression	Moderate
	Misumida et al. (2019)	ICD-9	22 818	Retrospective	In-hospital	65–79 vs. 18–49: No difference ≥80 vs. 18–49: No difference	Multivariate Cox regression	Moderate
	Uribarri et al. (2019)	Modified Mayo criteria	939	Prospective	5 years	Per each 10 years of age: HR 1.35 (95% CI 1.17–1.55), <i>P</i> < 0.001	Multivariable logistic regression	High
	Yerasi et al. (2019)	ICD-9	12 255	Retrospective	In-hospital	HR 1.05 (95% CI 1.03–1.07), <i>P</i> < 0.01	Multivariate Cox regression	Moderate
	Alashi et al. (2020)	Modified Mayo criteria	650	Prospective	Median = 2.2 years	Cardiac mortality: OR 1.09, (95% CI 1.02–1.16), <i>P</i> = 0.01	Multivariate Cox regression	Moderate
	El-Batrawy et al. (2020)	ESC criteria (2016)	906	Prospective	Mean = 1038 ± 838 days	Per 1 year increasing: OR 1.05 (95% CI 1.04–1.07), <i>P</i> < 0.001	Multivariate Cox regression	Moderate
	Lachmet-Thébaud et al. (2020)	Madias criteria/In-TAK criteria	215	Prospective	1 year	No difference	Multivariate Cox regression	Moderate
	Malanchini et al. (2020)	ICD-9	10 861	Retrospective	In-hospital		Multivariate Cox regression	High
	Nayeri et al. (2020)	Mayo criteria	538	Prospective	30 days		Multivariate Cox regression	Moderate
	Núñez-Gil et al. (2020)	Modified Mayo criteria	1097	Prospective	Median = 27.5 months	HR 1.088 (95% CI 1.06–1.11), <i>P</i> < 0.001	Multivariate Cox regression	Moderate
	Napierkowski et al. (2021)	ICD-9	14 639	Retrospective	In-hospital	OR 1.023 (95% CI 1.013–1.035), <i>P</i> < 0.001	Multivariable logistic regression	High
	Scudiero et al. (2020)	In-TAK criteria	561	Prospective	Median = 29 months	HR 1.97 (95% CI 1.02–3.78), <i>P</i> = 0.042	Multivariate Cox regression	Moderate
Younger vs. Older	Cammann et al. (2020)	Modified Mayo criteria	2098	Prospective	In-hospital	≤50 vs. 51–74: No difference; ≥75 vs. 51–74: No difference	Multivariable logistic regression	Moderate

CI, confidence interval; ESC, European Society of Cardiology; HR, hazard ratio; ICD, International Classification of Diseases; In-TAK, International Takotsubo; NA, not applicable; OR, odds ratio; TCM, Takotsubo cardiomyopathy.

1.04–1.08) but did not have the same predictive value among male patients ($P = 0.08$).²⁸

Other studies suggest that age is not associated with short-term mortality in TCM patients (Table 2).^{18,19,23,27,38,63,69,70} After a multivariable logistic regression analysis, Cammann *et al.* found no significant difference among different age groups in in-hospital mortality (age 51–74 years old as reference, ≤ 50 years old, $P = 0.14$; ≥ 75 years old, $P = 0.75$) or 60 day mortality ($P = 0.16$).²⁷ In a univariate meta-regression analysis of 54 studies with 4679 TCM patients, in-hospital mortality in each study was not associated with age ($P = 0.67$, coefficient: 0.002, 95% CI 0.000–0.004), although the in-hospital mortality rate had wide heterogeneity ($I^2 = 78\%$).⁶³

Counterintuitively, some literature has shown that younger age is associated with more inpatient complications.^{8,27,61} Compared with older groups of TCM patients (1194 patients 51–74 years old, 662 patients ≥ 75 years old), a younger group (242 patients ≤ 50 years old) more often had complications that required in-hospital acute cardiac care interventions, such as invasive or non-invasive ventilation ($P < 0.001$), catecholamine use ($P < 0.001$), cardiopulmonary resuscitation ($P < 0.001$), and cardiogenic shock ($P = 0.004$).²⁷ Another study that included 90 TCM patients found that being less than 55 years old was independently associated with ventricular arrhythmia (adjusted OR 9.5, 95% CI 1.7–52.6).⁶¹ In addition, Templin *et al.* found that among TCM patients, older age (>70 years) was associated with fewer in-hospital complications (OR 0.44, 95% CI 0.30–0.66)—including all-cause mortality, cardiogenic shock, and the need for catecholamine administration, ventilation, and cardiopulmonary resuscitation—than younger age (≤ 70 years).⁸

Results differ among outcome studies of the effect of age on the long-term outcomes of TCM (Table 2). The majority of current studies suggest that older TCM patients have worse long-term outcomes than younger patients.^{22,26,27,41,42,44,47–49,55,56,62,71–78} Cammann *et al.* found that elderly patients with TCM (≥ 75 years old) had a higher long-term (>60 days) mortality rate ($P < 0.001$) than younger (≤ 50 years old) and middle-age patients (51 to 74 years old).²⁷ Similarly, another study found that older TCM patients had a higher 1 year mortality rate in both primary (12.5% in ≥ 85 years old vs. 7.0% in 75–84 vs. 5.3% in 65–74, $P < 0.05$) and secondary TCM patients (16.0% vs. 11.6% vs. 9.6%, $P < 0.05$), in a large sample of 19 966 TCM patients.²² A prospective study of 1604 TCM patients found that being more than 70 years old is a predictor of worse long-term outcomes (HR 1.6, 95% CI 1.16–2.20) during a 10 year follow-up period.⁵⁶ However, some other studies suggest that age is not associated with long-term outcomes.^{40,46,52,53,69,79–81} One study that included 1750 TCM patients indicated that age > 70 years was not associated with 1 year mortality ($P = 0.49$).⁶⁹ Another study, by Núñez-Gil *et al.*, found that age was not associated with

long-term mortality ($P = 0.085$) or with complications such as all-cause death, TCM recurrence, and readmission due to cardiovascular causes ($P = 0.072$) after a mean follow-up time of 18.1 ± 24.2 months.⁴⁶

Race

When TCM was originally found in Japan, it was thought to occur predominantly in Asia. However, cases of TCM have been increasingly reported worldwide. Studies of the effect of race on TCM outcome have not yet produced definitive results. Some studies have found that race is associated with short-term prognosis in TCM patients (Table 3).^{22,82,83} One retrospective study that included 97 650 TCM patients showed that compared with White patients (89 624 patients), African American (AA) patients (8026 patients) had a lower incidence of inpatient complications, including cardiogenic shock (OR 0.58, 95% CI 0.46–0.75), the use of mechanical ventilation (OR 0.78, 95% CI 0.68–0.9), and the use of intra-aortic balloon pump (OR 0.6, 95% CI 0.39–0.94), after adjustment for baseline characteristics. In the same study, mortality did not differ significantly between the White and AA patients ($P = 0.21$).⁸² In a smaller study (205 TCM patients), Dias *et al.* had found that compared with White patients, AA patients had a longer hospital stay (15 days vs. 7 days, $P < 0.05$) and a higher incidence of acute respiratory failure requiring mechanical ventilation (44% vs. 20%, $P < 0.05$) during hospitalization, although inpatient mortality did not differ significantly between the two groups.⁸³ Murugiah *et al.* found a race-based mortality difference in patients with secondary TCM (4.6% in the non-White group vs. 2.8% in the White group, $P < 0.05$) but not in those with primary TCM.²² A study of 24 701 TCM patients indicated that race was not associated with in-hospital mortality after adjustment for age, Charlson comorbidity index (CCI), sex, and underlying critical illness.¹⁹ The discrepancies among these studies may be due to the retrospective design of most of the studies. In addition, the variables adjusted to control bias were not the same in each study. Lastly, race was categorized differently in each study, which may have contributed to the different outcomes.

The long-term outcome of TCM patients of different races also remains unclear (Table 3). One study that included 19 966 TCM patients found that the non-White group had a higher 1 year mortality rate in both primary and secondary TCM (primary TCM: 8.9% in non-Whites vs. 6.7% in Whites, $P < 0.05$; secondary TCM: 14.1% vs. 11.1%, $P < 0.05$).²² In contrast, one study that included 205 TCM patients (152 White and 53 AA) found that the long-term all-cause mortality was not significantly different between the two groups ($P = 0.40$).⁸³ It is worth noting that the aforementioned studies compared the outcomes between races without adjusting for other variables.

Table 3 Clinical studies on the effects of race in TCM patients

Race	Author (year)	Diagnostic criteria	Sample size	Type of study	Follow-up	Mortality	Analysis strategy	Risk of bias
Black vs. White	Brinjikji et al. (2012)	ICD-9	24 701	Retrospective	In-hospital	No difference	Multivariable logistic regression	High
	Vallabhajosyula et al. (2018)	ICD-9	2214	Retrospective	In-hospital	OR 1.6 (95% CI 1.1–2.4), $P = 0.03$	Multivariable logistic regression	High
Black vs. Hispanic	Zaghlol et al. (2020)	ICD-9	97 650	Retrospective	In-hospital	No difference	Multivariate regression	High
	Brinjikji et al. (2012)	ICD-9	24 701	Retrospective	In-hospital	No difference	Multivariable logistic regression	High
Hispanic vs. White	Vallabhajosyula et al. (2018)	ICD-9	2214	Retrospective	In-hospital	No difference	Multivariable logistic regression	High
Asian vs. White	Brinjikji et al. (2012)	ICD-9	24 701	Retrospective	In-hospital	No difference	Multivariable logistic regression	High
	Vallabhajosyula et al. (2018)	ICD-9	2214	Retrospective	In-hospital	No difference	Multivariable logistic regression	High
Non-White vs. White	Napierkowski et al. (2021)	ICD-9	14 639	Retrospective	In-hospital	OR 1.412 (95% CI 1.071–1.861), $P = 0.015$	Multivariable logistic regression	High

AAs, African Americans; CI, confidence interval; HR, hazard ratio; ICD, International Classification of Diseases; NA, not applicable; OR, odds ratio; TCM, Takotsubo cardiomyopathy.

Trigger events

A prospective study of 1750 TCM patients in the International Takotsubo Registry noted that about 36% of TCM cases were triggered by specific physical activities, 27.7% was triggered by emotion, 2.8% were triggered by both physical and emotional activities, and 28.5% of cases had no identifiable trigger.⁸

Many studies show that physical triggers are associated with poor short-term^{8,70,80,84,85} and long-term^{41,42,49,55,62,75,86,87} outcomes in TCM (Table 4). One study divided TCM patients into three classes according to their triggers: emotional triggers as Class I (485 patients), physical triggers as Class II (532 patients with physical activities, medical conditions, or procedures as Class IIa, 98 patients with neurologic disorders as Class IIb), and no identifiable trigger as Class III (498 patients). The study showed that TCM patients in Classes II and III had higher rates of 30 day mortality (Class IIa, HR 5.3, 95% CI 2.05–13.7; Class IIb, HR 8.58, 95% CI 2.96–24.9; Class III, HR 2.81, 95% CI 1.01–7.81) and 5 year mortality (Class IIa, HR 3.78, 95% CI 2.21–6.44; Class IIb, HR 5.76, 95% CI 2.96–11.2; Class III: HR 2.14, 95% CI 1.20–3.82) than those with Class I triggers.⁴² A study of 939 TCM patients from the Spanish National Registry on Takotsubo Syndrome used multiple Cox regression to show that patients with physical triggers (HR 3.073, 95% CI 1.758–4.302) and those with no identifiable trigger (HR 1.913, 95% CI 1.003–3.649) had a higher 5 year mortality rate than patients with emotional triggers group.⁵⁵

Emotional triggers, on the other hand, predict better short-term^{8,27} and long-term^{44,47,56} TCM outcomes (Table 4). Studies also associated emotional triggers with a lower in-hospital complication rate. For example, one retrospective study that included 2098 TCM patients concluded that emotional triggers are associated with a lower in-hospital mortality rate (OR 0.31, 95% CI 0.14–0.65).²⁷ Another study found that emotional triggers predicted a lower long-term mortality rate during a median follow-up of 2.5 years (HR 0.41, 95% CI 0.25–0.67).⁴⁴

Some retrospective studies found that different triggers do not affect short-term^{39,68,88} or long-term^{40,71,89} outcomes in TCM. One study that included 421 TCM patients found that different triggers were not associated with in-hospital mortality in TCM patients (physical triggers vs. emotional triggers, $P = 0.342$; no triggers vs. emotional triggers, $P = 0.937$).³⁹ Another small retrospective study with 154 TCM patients found that physical and emotional triggers were not associated with in-hospital complications (pulmonary oedema, cardiogenic shock, sustained VF or VT, complete atrioventricular block, thromboembolism, cardiac rupture, and cardiac death; $P = 0.22$ for physical triggers, $P = 0.30$ for emotional triggers, compared with no identifiable trigger).⁸⁸ In addition, one study that included 286 TCM patients found that different triggers were not associated with long-term mortality during

Table 4 Clinical studies on the effects of triggers in TCM patients

Triggers	Author (year)	Diagnostic criteria	Sample size	Type of study	Follow-up	Mortality	Analysis strategy	Risk of bias
Physical triggers vs. Other triggers	Girardey et al. (2016)	Madias criteria	154	Prospective	Median = 364 days	No difference	Multivariate Cox regression	Moderate
	Stiermaier et al. (2016)	Mayo criteria	286	Prospective	Mean = 3.8 ± 2.5 years	No difference	Multivariate Cox regression	Moderate
	Kato et al. (2017)	Modified Mayo criteria	144	Retrospective	In-hospital	OR 5.03 (95% CI 1.01–39.8), $P = 0.049$	logistic regression	Moderate
	Kim et al. (2017)	Mayo criteria	103	Prospective	Median = 25.6 months	HR 3.77, (95% CI 1.02–13.9), $P < 0.05$	Multivariate Cox regression	Moderate
	Nayeri et al. (2017)	Mayo criteria	306	Prospective	30 days	OR 7.55 (95% CI 2.21–25.71), $P < 0.001$	Multivariate Cox regression	High
	Almendro-Delia et al. (2018)	Modified Mayo criteria	711	Prospective	15 years	No difference	Multivariate Cox regression	Moderate
	Ghadri et al. (2018)	Modified Mayo criteria	1613	Prospective	Median = 284 days	HR 1.43 (95% CI 1.20–3.80), $P = 0.013$	Multivariate Cox regression	Moderate
	Kim et al. (2018)	Modified Mayo criteria	257	Prospective	5 years	Physical triggers vs. Emotional triggers: HR 3.78 (95% CI 2.21–6.44), $P < 0.001$	Multivariate Cox regression	Moderate
	Cammann et al. (2019)	Modified Mayo criteria	1604	Prospective	Median = 5.8 ± 3.6 years	HR 1.723 (95% CI 1.126–2.638), $P = 0.012$	Multivariate Cox regression	Moderate
	Jesel et al. (2019)	Madias criteria	214	Prospective	10 years	No difference	Multivariate Cox regression	Low
	Uribarri et al. (2019)	Modified Mayo criteria	939	Prospective	In-hospital	No difference	Multivariate Cox regression	Moderate
	Alashi et al. (2020)	Modified Mayo criteria	650	Prospective	5 years	Physical triggers vs. Emotional triggers: HR 3.073 (95% CI 1.758–4.302), $P < 0.001$	Multivariate Cox regression	Moderate
	El-Battrawy et al. (2020)	ESC criteria (2016)	906	Prospective	Median = 2.2 years	Physical triggers vs. No trigger: HR 2.64 (95% CI 1.63–4.20), $P < 0.001$	Multivariate Cox regression	Moderate
	Kimura et al. (2020)	Modified Mayo criteria	421	Retrospective	Mean = 1038 ± 838 days	HR 1.64 (95% CI 1.0–2.6), $P = 0.04$	Multivariate Cox regression	Moderate
	Nayeri et al. (2020)	Mayo criteria	538	Prospective	In-hospital	Physical triggers vs. Emotional triggers: No difference	logistic regression	Moderate
	Stiermaier et al. (2020)	Mayo criteria	147	Prospective	30 days	OR 3.93 (95% CI 1.71–9.05), $P < 0.001$	Multivariate logistic regression	Moderate
	Stiermaier et al. (2020)	Mayo criteria and ESC criteria (2016)	387	Prospective	3 years	HR 4.77 (95% CI 1.58–14.39), $P = 0.006$	Multivariate Cox regression	Moderate
	Stiermaier et al. (2020)	ESC criteria (2016)	826	Prospective	Median = 2.9 years	HR 0.37 (95% CI 0.16–0.85), $P = 0.020$	Multivariate Cox regression	Moderate
	Stiermaier et al. (2020)	ESC criteria (2016)	1604	Prospective	Median = 2.5 years	HR 0.41 (95% CI 0.25–0.67), $P < 0.001$	Multivariate Cox regression	Moderate
	Alashi et al. (2020)	Modified Mayo criteria	650	Prospective	10 years	HR 0.56 (95% CI 0.33–0.96), $P = 0.034$	Multivariate Cox regression	Low
Cammann et al. (2020)	Modified Mayo criteria	2098	Retrospective	Median = 2.2 years	Emotional triggers vs. No trigger: No difference	Multivariate Cox regression	Moderate	
Cammann et al. (2020)	Modified Mayo criteria	2098	Retrospective	In-hospital	OR 0.31 (95% CI 0.14–0.65), $P = 0.002$	Multivariate logistic regression	Moderate	

(Continues)

Table 4 (continued)

Triggers	Author (year)	Diagnostic criteria	Sample size	Type of study	Follow-up	Mortality	Analysis strategy	Risk of bias
Other triggers vs. Emotional triggers	Kimura <i>et al.</i> (2020) Ghadri <i>et al.</i> (2018)	Modified Mayo criteria Modified Mayo criteria	421 1613	Retrospective Prospective	In-hospital 5 years	No trigger vs. Emotional triggers: No difference Neurologic disorder triggers vs. Emotional triggers: HR 5.76 (95% CI 2.96–11.2), $P < 0.001$; No trigger vs. Emotional triggers: HR 2.14 (95% CI 1.20–3.82), $P = 0.010$ No trigger vs. Emotional triggers: HR 1.913 (95% CI 1.003–3.649), $P = 0.049$	Multivariable logistic regression Multivariable Cox regression	Moderate Moderate
	Uribarri <i>et al.</i> (2019)	Modified Mayo criteria	939	Prospective	5 years		Multivariable Cox regression	Moderate

CI, confidence interval; ESC, European Society of Cardiology; HR, hazard ratio; ICD, International Classification of Diseases; In-TAK, International Takotsubo; OR, odds ratio; TCM, Takotsubo cardiomyopathy.

a mean follow-up time of 3.8 ± 2.5 years.⁴⁰ In a study of 114 TCM patients, emotional triggers were not associated with complications (thromboembolic events, life-threatening arrhythmias, all-cause mortality, and rehospitalization) after a mean follow-up of 1529 ± 1121 days ($P = 0.15$).⁸⁹

In a study of emotional triggers of TCM, compared with TCM triggered by negative emotions, TCM triggered by preceding pleasant emotional events did not show a more favourable outcome in terms of mortality, cardiogenic shock, ventricular or septal rupture, VT, ventricular thrombus, and new atrial fibrillation.⁹⁰

Effects of comorbidities

Takotsubo cardiomyopathy patients carry certain risk factors such as chronic kidney disease (CKD), mood disorders, and common cardiovascular comorbidities.⁹¹ The effect of comorbidities on TCM outcome is discussed below. Studies are shown in *Table 5*.

Diabetes mellitus

The reported percentage of TCM patients with comorbid diabetes mellitus (DM) varies widely among studies (1.6–25.5%).^{35,44,92} Although DM is a known risk factor in patients with cardiovascular disease, the association between DM and the outcomes of TCM is uncertain (*Table 5*). Many studies have found DM not to be associated with TCM outcome.^{29,36,42,66} One study with 12 255 patients, for example, in-hospital mortality did not differ between TCM patients with and without DM ($P = 0.44$), although patients with DM had a higher 90 day readmission rate (OR 1.36, 95% CI 1.27–1.47).²⁹ Some other studies found DM to be a predictor of mortality, especially long-term mortality, in TCM patients.^{40,41,44,55,74,77,78,88} For example, one retrospective study by Kato *et al.* found that TCM patients with a history of DM had more in-hospital complications (pulmonary oedema, cardiogenic shock, sustained VT or VF, complete atrio-ventricular block, thromboembolism, cardiac rupture, and cardiac death) (OR 2.92, 95% CI 1.01–8.41).⁸⁸ Another study by Núñez-Gil *et al.* of 1097 TCM patients found that DM was associated with long-term mortality (median follow-up = 27.5 months) (HR 2.17, 95% CI 1.41–3.34).⁷⁷

In contrast, Madias proposed the interesting hypothesis that DM has a protective effect on TCM patients. Because of diabetic autonomic neuropathy, TCM patients with DM may have a relatively lower level of catecholamine release than patients without DM, thus protecting individuals with DM from adverse events associated with TCM.⁹³ One single-centre retrospective observational study of 114 TCM patients (88 without DM and 26 with DM) found that adverse events, including all-cause mortality, TCM recurrence,

Table 5 Clinical studies on the effects of comorbidities in TCM patients

Comorbidities	Author (year)	Diagnostic criteria	Sample size	Type of study	Follow-up	Mortality	Analysis strategy	Risk of bias	
DM	Krishnamoorthy et al. (2015)	ICD-9	7510	Retrospective	In-hospital	DM vs. Non-DM No difference	Multivariable logistic regression	High	
	Khera et al. (2016)	ICD-9	11 193	Retrospective	In-hospital	No difference	Multivariable logistic regression	High	
	Stiermaier et al. (2016)	Mayo criteria	286	Prospective	Mean = 3.8 ± 2.5 years	HR 2.11 (95% CI 1.23–3.65), P < 0.01	Multivariable Cox regression	Moderate	
	Parodi et al. (2017)	In-TAK criteria	371	Prospective	Mean = 26 ± 20 months	HR 2.86 (95% CI 1.29–6.35), P = 0.01	Multivariable Cox regression	Moderate	
	Almendo-Delia et al. (2018)	Modified Mayo criteria	711	Prospective	Median = 284 days	HR 2.68 (95% CI 1.55–4.60), P < 0.0001	Multivariable Cox regression	Moderate	
	Ghadri et al. (2018)	Modified Mayo criteria	1613	Prospective	5 years	No difference	Multivariable Cox regression	Moderate	
	Stiermaier et al. (2018)	Mayo criteria and ESC	826	Prospective	Median = 2.5 years	HR 1.66 (95% CI 1.16–2.39), P = 0.006	Multivariable Cox regression	Moderate	
	Uribarri et al. (2019)	Modified Mayo criteria	939	Prospective	5 years	HR 2.750 (95% CI 1.758–4.302), P < 0.001	Multivariable Cox regression	Moderate	
	Yerasi et al. (2019)	ICD-9	12 255	Retrospective	In-hospital	No difference	Multivariable regression	High	
	Núñez-Gil et al. (2020)	Modified Mayo criteria	1097	Prospective	Median = 27.5 months	HR 2.17 (95% CI 1.41–3.34), P < 0.001	Multivariable Cox regression	Moderate	
	Scudiero et al. (2020)	In-TAK criteria	561	Prospective	Median = 29 months	HR 2.90 (95% CI 1.53–5.40), P = 0.001	Multivariable Cox regression	Moderate	
	Stiermaier et al. (2020)	Mayo criteria and ESC	147	Prospective	3 years	HR 6.15 (95% CI 2.18–17.32), P = 0.001	Multivariable Cox regression	Moderate	
	CKD	Isogai et al. (2014)	ICD-10	3719	Retrospective	In-hospital	CKD vs. Non-CKD No difference	Multivariable logistic regression	High
		Khera et al. (2016)	ICD-9	11 193	Retrospective	In-hospital	No difference	Multivariable logistic regression	High
		Weidner et al. (2017)	Mayo criteria	114	Prospective	5 years	HR 3.1 (95% CI 1.4–7.0), P < 0.01	Multivariable Cox regression	Moderate
		El-Battrawy et al. (2017)	Mayo criteria	114	Prospective	Mean = 1529 ± 1121 days	HR 3.5 (95% CI 1.0–11.0), P = 0.03	Multivariable Cox regression	Moderate
		Huseynov et al. (2017)	Mayo criteria	114	Prospective	Mean = 1591 ± 1079 days	HR 3.1 (95% CI 1.4–7.0), P < 0.01	Multivariable Cox regression	Moderate
		El-Battrawy et al. (2018)	Mayo criteria	114	Prospective	Mean = 3 years	HR 3.84 (95% CI 1.3–11.2), P = 0.01	Multivariable Cox regression	Moderate
		Giannakopoulos et al. (2019)	Mayo criteria	138	Prospective	5 years	HR 2.8 (95% CI 1.2–6.0), P = 0.01	Multivariable Cox regression	Moderate
		Gietzen et al. (2019)	Mayo criteria	138	Prospective	5 years	HR 2.8 (95% CI 1.2–6.0), P = 0.01	Multivariable Cox regression	Moderate
Yassin et al. (2019)		ICD-9	2959	Retrospective	In-hospital	No difference	Multivariable logistic regression	High	

(Continues)

Table 5 (continued)

Comorbidities	Author (year)	Diagnostic criteria	Sample size	Type of study	Follow-up	Mortality	Analysis strategy	Risk of bias
Cancer	Syed et al. (2020)	ICD-9 and ICD-10	260 144	Retrospective	In-hospital	OR 1.2 (95% CI 1.16–1.30), $P < 0.01$	Stepwise logistic regression	High
	Zalewska-Adamiec et al. (2020)	Mayo criteria	101	Prospective	Mean = 7.2 years	OR 0.954 (95% CI 0.920–0.989), $P = 0.01$	Multivariable logistic regression	Moderate
	Napierkowski et al. (2021)	ICD-9	14 639	Retrospective	In-hospital	OR 1.756 (95% CI 1.266–2.436), $P = 0.001$	Multivariable logistic regression	High
	Isogai et al. (2014)	ICD-10	3719	Retrospective	In-hospital	Cancer vs. Non-cancer OR 3.23 (95% CI 2.21–4.72), $P < 0.001$	Multivariable logistic regression	High
	Krishnamoorthy et al. (2015)	ICD-9	7510	Retrospective	In-hospital	OR 3.38 (95% CI 1.35–8.41), $P < 0.01$	Multivariable logistic regression	High
	Lee et al. (2016)	Mayo criteria	128	Retrospective	In-hospital	No difference	Multivariable logistic regression	Moderate
	Girardey et al. (2016)	Madias criteria	154	Prospective	Median = 364 days	Cardiac mortality: HR 4.77 (95% CI 1.02–22.17), $P = 0.046$ All-cause mortality: HR 2.62 (95% CI 1.26–5.44), $P = 0.01$	Multivariable logistic regression Cox regression	Moderate
	Khera et al. (2016)	ICD-9	11 193	Retrospective	In-hospital	No difference	Multivariable logistic regression	High
	Bill et al. (2017)	Mayo criteria	114	Prospective	2 years	HR 2.76 (95% CI 0.8–9.0), $P = 0.09$	Multivariate Cox regression	Moderate
	Almendro-Delia et al. (2018)	Modified Mayo criteria	711	Prospective	Median = 284 days	HR 2.38 (95% CI 1.18–4.81), $P = 0.016$	Multivariate Cox regression	Moderate
El-Battrawy et al. (2018)	Mayo criteria	114	Prospective	Mean = 3 years	No difference	Multivariate Cox regression	Moderate	
Ghadri et al. (2018)	Modified Mayo criteria	1613	Prospective	5 years	HR 1.65 (95% CI 1.14–2.40), $P = 0.009$	Multivariate Cox regression	Moderate	
Joy et al. (2018)	ICD-9	122 855	Retrospective	In-hospital	Primary TCM: Solid cancer: OR 3.43 (95% CI 1.38–8.52), $P = 0.008$ Secondary TCM: Haematological cancer: OR 3.21 (95% CI 2.31–4.48), $P < 0.001$; Metastatic cancer: OR 1.99 (95% CI 1.46–2.71), $P < 0.001$ HR 1.857 (95% CI 1.214–2.841), $P = 0.004$	Multivariable Cox regression Multivariate Cox regression Cox regression	Moderate	
Kim et al. (2018)	Modified Mayo criteria	257	Prospective	Mean = 5.8 ± 3.6 years	HR 2.12 (95% CI 1.44–3.12), $P < 0.001$	Multivariable Cox regression	High	
Stiermaier et al. (2018)	Mayo criteria and ESC criteria (2016)	826	Prospective	Median = 2.5 years	HR 3.6 (95% CI 1.4–9.3), $P < 0.01$	Multivariate Cox regression	Moderate	
Giannakopoulos et al. (2019)	Mayo criteria	138	Prospective	5 years	HR 1.84 (95% CI 1.29–2.61), $P = 0.001$	Multivariate Cox regression	Moderate	
Cammann et al. (2019)	Modified Mayo criteria	1604	Prospective	10 years	HR 3.6 (95% CI 1.4–9.3), $P < 0.01$	Multivariate Cox regression	Low	
Gietzen et al. (2019)	Mayo criteria	138	Prospective	5 years	HR 3.6 (95% CI 1.4–9.3), $P < 0.01$	Multivariate Cox regression	Moderate	

(Continues)

Table 5 (continued)

Comorbidities	Author (year)	Diagnostic criteria	Sample size	Type of study	Follow-up	Mortality	Analysis strategy	Risk of bias
	Misumida et al. (2019)	ICD-9	22 818	Retrospective	In-hospital	OR 5.36 (95% CI 1.32–21.80), $P = 0.02$	Multivariable logistic regression	High
	Yerasi et al. (2019)	ICD-9	12 255	Retrospective	In-hospital	OR 2.61 (95% CI 2.04–3.32), $P < 0.001$	Multivariable regression	High
	El-Battrawy et al. (2020)	ESC criteria (2016)	906	Prospective	Mean = 1038 ± 838 days	HR 1.99 (95% CI, 1.3–2.9), $P < 0.01$	Multivariable Cox regression	Moderate
	Núñez-Gil et al. (2020)	Modified Mayo criteria	1097	Prospective	Median = 27.5 months	HR 1.73 (95% CI 1.04–2.87), $P = 0.03$	Multivariable Cox regression	Moderate
	Ding et al. (2020)	In-TAK criteria	1676	Prospective	6 months	HR, 1.96 (95% CI 1.32–2.87) $P = 0.001$	Multivariable Cox regression	Moderate
	Stiermaier et al. (2020)	Mayo criteria and ESC criteria (2016)	147	Prospective	3 years	HR 4.32 (95% CI 1.53–12.19), $P = 0.006$	Multivariable Cox regression	Moderate
	Napierkowski et al. (2021)	ICD-9	14 639	Retrospective	In-hospital	OR 2.16 (95% CI 1.398–3.337), $P = 0.001$	Multivariable logistic regression	High
	Kato et al. (2021)	Modified Mayo criteria	1670	Prospective	5 years	HR 2.24 (95% CI 1.57–3.21), $P < 0.001$	Multivariable Cox regression	Moderate
	Desai et al. (2018)	ICD-9	1140	Retrospective	In-hospital	Lower BMI vs. Higher BMI Non-obesity (BMI < 30) vs. Obesity (BMI > 30): No difference	Propensity score matching	High
	Zalewska-Adamiec et al. (2020)	Mayo criteria	101	Prospective	Mean = 7.2 years	BMI < 20 vs. ≥20: OR 0.857 (95% CI 0.738–0.995), $P = 0.042$	Multivariable logistic regression	Moderate
Mood diseases	Isogai et al. (2014)	ICD-10	3719	Retrospective	In-hospital	Mood diseases vs. Non-mood diseases OR 0.43 (95% CI 0.19–0.96), $P = 0.039$	Multivariable logistic regression	High
	Krishnamoorthy et al. (2015)	ICD-9	7510	Retrospective	In-hospital	Anxiety or depression: No difference	Multivariable logistic regression	High
	Khera et al. (2016)	ICD-9	11 193	Retrospective	In-hospital	No difference	Multivariable logistic regression	High
	Nayeri et al. (2017)	Mayo criteria	306	Prospective	30 days	No difference	Multivariable logistic regression	High
	Kim et al. (2018)	Modified Mayo criteria	257	Prospective	15 years	No difference	Multivariable logistic regression	High
	Cammann et al. (2019)	Modified Mayo criteria	1604	Prospective	Mean = 5.8 ± 3.6 years	Depression: HR 1.764 (95% CI 1.155–2.694), $P = 0.009$	Multivariable Cox regression	Moderate
	Syed et al. (2020)	ICD-9 and ICD-10	260 144	Prospective	10 years	HR 1.40 (95% CI 1.01–1.94), $P = 0.041$	Multivariable Cox regression	Low
	Napierkowski et al. (2021)	ICD-9	14 639	Retrospective	In-hospital	Depression: OR 0.63 (95% CI 0.60–0.69), $P < 0.01$	Cox regression	High
	Isogai et al. (2014)	ICD-10	3719	Retrospective	In-hospital	Anxiety: OR 0.592 (95% CI 0.399–0.880), $P = 0.01$	Stepwise logistic regression	High
	Krishnamoorthy et al. (2015)	ICD-9	7510	Retrospective	In-hospital	Sepsis vs. Non-sepsis OR 2.02 (95% CI 1.17–3.49), $P = 0.011$	Multivariable logistic regression	High

(Continues)

Table 5 (continued)

Comorbidities	Author (year)	Diagnostic criteria	Sample size	Type of study	Follow-up	Mortality	Analysis strategy	Risk of bias
	Khera <i>et al.</i> (2016)	ICD-9	11 193	Retrospective	In-hospital	OR 6.93 (95% CI 2.54–18.93), P = 0.0002	Multivariable logistic regression	High
	Napierkowski <i>et al.</i> (2021)	ICD-9	14 639	Retrospective	In-hospital	OR 4.278 (95% CI 3.047–6.007), P < 0.001	Multivariable logistic regression	High
	Vallabhajosyula <i>et al.</i> (2018)	ICD-9	10 746	Retrospective	In-hospital	TCM vs. Non-TCM OR 0.58 (95% CI 0.51–0.65), P < 0.001	Multivariable logistic regression	High
COPD	Khera <i>et al.</i> (2016)	ICD-9	11 193	Retrospective	In-hospital	COPD vs. Non-COPD No difference	Multivariable logistic regression	High
	Li <i>et al.</i> (2020)	ICD-10	1748	Retrospective	In-hospital	OR 2.93 (95% CI 1.39–6.15), P = 0.005	Multivariable logistic regression	High
	Napierkowski <i>et al.</i> (2021)	ICD-9	14 639	Retrospective	In-hospital	OR 1.444 (95% CI 1.140–1.829), P = 0.002	Multivariable logistic regression	High
	Khera <i>et al.</i> (2016)	ICD-9	11 193	Retrospective	In-hospital	HLD vs. Non-HLD No difference	Multivariable logistic regression	High
	Kato <i>et al.</i> (2017)	Modified Mayo criteria	144	Retrospective	In-hospital	No difference	Multivariable logistic regression	Moderate
	Li <i>et al.</i> (2021)	ICD-10	2324	Retrospective	In-hospital	OR 0.46 (95% CI 0.24–0.89), P = 0.027	Multivariable logistic regression	High
Anaemia	Gaede <i>et al.</i> (2021)	Mayo criteria	126	Prospective	Median = 4.4 years	Anaemia vs. Non-Anaemia OR 3.93 (95% CI 1.02–2.08), P = 0.015	Multivariable logistic regression	Moderate
	Lu <i>et al.</i> (2021)	ICD-10	1731	Retrospective	In-hospital	No difference	Multivariable logistic regression	High

BMI, body mass index; CI, confidence interval; CKD, chronic kidney diseases; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ESC, European Society of Cardiology; eGFR, estimated glomerular filtration rate; HLD, hyperlipidaemia; HR, hazard ratio; ICD, International Classification of Diseases; In-TAK, International Takotsubo; NA, not applicable; OR, odds ratio; TCM, Takotsubo cardiomyopathy.

thromboembolic events, life-threatening arrhythmias, rehospitalization due to heart failure, and stroke, had a lower 1 year incidence in patients with DM than in patients without DM, although each adverse event rate was not significantly different between the two groups ($P = 0.004$).⁹⁴

Chronic kidney disease

Chronic kidney disease is a known independent risk factor for cardiovascular diseases such as heart failure⁹⁵ and myocardial infarction (MI).⁹⁶ Likewise, our review of the literature showed that CKD has different effects on in-hospital outcomes. Several studies suggest that CKD is a predictor of worse short-term outcomes in TCM patients.^{30–32,97} In one small retrospective study, 61 TCM patients were separated into three groups: estimated glomerular filtration rate (eGFR) > 60 mL/[min 1.73 m²] (31 patients), eGFR 30–60 mL/[min 1.73 m²] (17 patients), and eGFR < 30 mL/[min 1.73 m²] (13 patients). In a multivariable Cox proportional hazard analysis, compared with the highest eGFR group, the lowest eGFR group (< 30 mL/[min 1.73 m²]) had a higher incidence of overall inpatient complications (HR 2.84, 95% CI 1.20–6.69), while the middle eGFR group had no difference with the highest eGFR group ($P = 0.184$).³² A large retrospective study with 2959 TCM patients also found that propensity-matched patients with advanced CKD (1478 patients), defined as eGFR < 60 mL/[min 1.73 m²], were associated with a higher incidence of acute kidney injury and length of inpatient stay than non-advanced CKD (eGFR > 60 mL/[min 1.73 m²]), although inpatient mortality was not different ($P = 0.269$).⁹⁸ In addition, several studies have found that CKD is not associated with inpatient mortality in TCM patients.^{33,66}

Regarding long-term outcomes, CKD seems to have an adverse effect in TCM patients. Some studies with small cohorts have shown that CKD is a predictor of poor long-term outcomes in TCM patients.^{21,43,45,50,51,54,58,99–101} A study of 95 patients compared mortality between patients with an eGFR higher than 60 mL/[min 1.73 m²] (65 patients) with those who had eGFR < 60 mL/[min 1.73 m²] (30 patients). Patients in the lower eGFR group had a higher 3 year mortality rate (33.3% vs. 15.4%, $P = 0.047$) than patients in the higher eGFR group. In that study, elevated serum creatinine level was also an independent predictor of long-term mortality (OR 13.813, 95% CI 1.8–105.9).¹⁰¹ Another study compared TCM outcomes among three groups: eGFR > 60 mL/[min 1.73 m²] (45 patients), 60–30 mL/[min 1.73 m²] (43 patients), and < 30 mL/[min 1.73 m²] (20 patients). Patients with eGFR < 30 mL/[min 1.73 m²] had more adverse events (all-cause mortality, cardiovascular mortality, TCM recurrence, and hospitalization for any cardiovascular cause) than those who had eGFR > 60 mL/[min 1.73 m²] (HR 1.817, 95% CI 1.097–3.009).¹⁰⁰ On the other hand, only one small prospective study of 101 TCM patients found that patients

with lower eGFR (< 60 mL/[min 1.73 m²]) had a lower long-term mortality rate (OR 0.954, 95% CI 0.920–0.989), after a mean follow-up of 7.2 years.¹⁰²

Malignant disease

Malignant disease is found between 6.6% and 28.5% of TCM patients in different studies.^{54,62,71,103} Malignant disease and associated chemotherapy have been reported to be associated with TCM under certain circumstances,^{104,105} especially in cases of pheochromocytoma.¹⁰⁶

Past studies of malignant disease and TCM suggested that malignant disease is a predictor of higher inpatient adverse events.^{24,29,30,33,36,103} In a study of 122 855 TCM patients, Joy *et al.* found that malignant disease was a predictor of inpatient mortality: solid-tumour disease in primary TCM (OR 3.43, 95% CI 1.38–8.52), and haematological cancer (OR 3.21, 95% CI 2.31–4.48) and metastatic cancer (OR 1.99, 95% CI 1.46–2.71) in secondary TCM.¹⁰³ Another study of 14 639 TCM patients also showed comorbid malignant disease was associated with higher in-hospital mortality (OR 2.160, 95% CI 1.398–3.337).³⁰

Malignant disease remains a predictor of poorer long-term outcome in TCM patients.^{26,41–45,51,54,56,60,62,71,75,77,86,107–109} The latest meta-analysis of the association between malignant disease and TCM patients included 10 studies and 126 322 patients and suggested that malignant disease was associated with greater mortality in TCM patients (RR 2.23, 95% CI 1.64–3.03), including both inpatient mortality (RR 2.26, 95% CI 1.34–3.82) and long-term mortality (RR 2.04, 95% CI 1.63–2.55).¹⁰⁷ In one study of 1604 TCM patients, those with malignant disease had a higher 10 year mortality rate (HR 1.84, 95% CI 1.29–2.61).⁵⁶ In addition, compared with patients with MI, patients with TCM had higher incidence of new malignant disease over 4 year follow-up (13 TCM patients had new cancer vs. 3 MI patients, $P = 0.01$), whereas TCM patients with malignant disease have greater mortality over 4 years of follow-up than MI patients with malignant disease ($P = 0.03$).⁴³

In contrast, some studies found that malignant disease was not associated with the outcomes of TCM patients.^{38,66,89,99,110} However, given the available data, we believe that malignant disease is associated with poor outcomes in TCM patients (*Table 5*).

Body mass index

As a common cardiovascular risk factor, the prevalence of body mass index (BMI) > 30 kg/m² in TCM patients ranges from 8.5% to 12.7%.^{36,111,112} However, the true association between BMI and TCM is still uncertain (*Table 5*).

Most current studies have associated higher BMI with a poor short-term prognosis in TCM patients.^{102,113} One 58-patient retrospective study noted that a BMI less than 20 kg/m² was associated with early recovery (less than 10 days) from left ventricular systolic dysfunction in TCM patients after multivariate logistic regression analysis (OR 0.11, 95% CI 0.01–0.55).¹¹³ In addition, using the data from National Inpatient Sample (NIS) database, Desai *et al.* found that TCM patients with obesity (BMI > 30 kg/m²) had higher incidences of inpatient acute MI (9.0% vs. 7.4%, $P = 0.025$), cardiogenic shock (4.3% vs. 3.2%, $P = 0.032$), cardiac arrest (2.3% vs. 0.4%, $P < 0.001$), and respiratory failure (12.9% vs. 11.0%, $P = 0.021$). Overall inpatient mortality was not significantly different between two groups ($P = 0.354$) after propensity-matching analysis in a 1:1 ratio (528 non-obese and 612 obese patients).¹¹¹

However, another study supports a negative association between lower BMI and TCM patients' outcome. It categorized 80 TCM patients into three groups (6 patients with BMI < 18.5 kg/m², 28 patients with 18.5 ≤ BMI < 25 kg/m², and 46 patients with BMI ≥ 25 kg/m²) and found that the lowest-BMI group had the highest 5 year mortality rate. In a multivariate analysis, higher BMI was associated with lower long-term mortality (OR 0.768, 95% CI 0.599–0.985).¹¹⁴

Mood disorders

There is a growing body of literature regarding the association between mental illness and TCM.^{8,80,115,116} Compared with MI patients, TCM patients have a significantly higher prevalence of mood disorders.^{8,115} Multiple case reports have described exacerbations of anxiety, depression, mania, and psychosis as potential triggers of TCM episodes,^{117,118} and undergoing therapies such as serotonin-norepinephrine reuptake inhibitors¹¹⁹ and selective norepinephrine reuptake inhibitor¹²⁰ for mood disorders was also noted to be a risk factor for TCM.

According to the current literature, mood disorders have uncertain effects on the in-hospital outcomes of TCM patients (Table 5). Some studies found that mood disorders predicted better short-term outcomes in TCM patients.^{30,31,33} One prospective study, registering 3719 TCM patients from Japan, found that psychiatric disorders were associated with lower inpatient mortality (OR 0.43, 95% CI 0.19–0.96).³³ Conversely, other studies have found that mood disorders were not associated with short-term outcomes in TCM patients.^{27,36,66,80} For example, one study of 7510 TCM patients found that mood disorders (anxiety or depression) were not associated with in-hospital mortality in TCM patients.³⁶ Likewise, Nayeri *et al.* reported that pre-existing psychiatric illness was not associated with 30 day mortality in TCM patients ($P = 0.32$).⁸⁰

The effect of mood disorders on the long-term outcome of TCM remains unclear (Table 5). Using the data from the Mayo Clinic Takotsubo Syndrome Registry from 2002 to 2016, Kim *et al.* found that a history of depression was a predictor of long-term mortality in TCM patients (HR 1.764, 95% CI 1.155–2.694).⁶² On the other hand, the study from Nayeri *et al.* found that pre-existing psychiatric illness was not associated with long-term mortality ($P = 0.621$), but it was associated with a higher risk of recurrent TCM (OR 7.44, 95% CI 2.30–24.01) after adjustment for age, CCI score, and type of cardiomyopathy trigger.⁸⁰

Differing protocols to identify mood disorders in patients may account for the differing results found in each study. Different studies variously identified mood disorders by ICD codes, medications, or chart review. In addition, studies did not identify the severity of mood disorders, which may affect the outcome in TCM patients.

Sepsis

Sepsis has an incidence ranging from 2.8% to 7.1% for TCM patients^{19,32,33} and is a potential trigger of TCM patients in many cases, as well.^{121,122} TCM is estimated to be present in 0.15% of severe sepsis cases in the United States.³⁷ Our review of the literature revealed a dearth of studies that focus on the association between sepsis and the outcomes of TCM (Table 5).

Most studies we found support the conclusion that sepsis is associated with worse outcomes in TCM.^{30,33,66} Napierkowski *et al.* studied 14 639 TCM patients and concluded that sepsis was a predictor of in-hospital mortality (OR 4.278, 95% CI 3.047–6.007).³⁰ Several other investigators drew a similar conclusion. For example, Khera *et al.*'s multivariable logistic regression analysis showed that sepsis independently predicted in-hospital mortality (OR 6.93, 95% CI 2.54–18.93) in TCM patients.⁶⁶ However, another study of 7510 TCM patients found that sepsis was not associated with in-hospital outcomes in TCM patients ($P = 0.67$) after adjustment for demographics and risk factors.³⁶

In addition, in a study with approximately 7.1 million patients with sepsis, 10 746 of them were found to have TCM. The authors found that TCM was associated with lower in-hospital mortality in sepsis patients (OR 0.58, 95% CI 0.51–0.65).³⁷

Chronic obstructive pulmonary disease

Approximately 10.1% to 18.7% TCM patients are diagnosed with chronic obstructive pulmonary disease (COPD).^{123–125} COPD has also been reported as a trigger of TCM, especially in the acute exacerbation phase.¹²⁶

There are few studies on the association between COPD and outcomes in TCM patients (*Table 5*). One retrospective study by Khera *et al.* found that COPD was not associated with in-hospital mortality in patients with TCM.⁶⁶ However, some other studies found that COPD predicted poor in-hospital outcomes in TCM patients. In a study of 3139 TCM patients from the NIS database, Li *et al.* found that TCM patients with COPD had greater inpatient mortality (OR 2.93, 95% CI 1.39–6.15) and a higher risk of complications, including acute respiratory failure (OR 3.25, 95% CI 2.45–4.32) and cardiogenic shock (OR 1.76, 95% CI 1.1–2.81). The result was generated after patients were propensity-matched in a 1:2 target ratio (678 patients in the COPD-TCM group and 1070 in the non-COPD-TCM group) to avoid bias.¹¹² Another study of 14 639 TCM patients found that COPD was associated with greater in-hospital mortality (OR 1.444, 95% CI 1.140–1.829).³⁰ In addition, a study by Kato *et al.* found that compared with those without lung disease, TCM patients with acute pulmonary triggers had greater 5 year mortality (HR 2.12, 95% CI 1.33–3.38), whereas chronic lung disease had no effect on mortality.¹²⁷

Hyperlipidaemia

Approximately 15.9% to 52% of TCM patients have comorbid hyperlipidaemia (HLD).^{8,35,36,41} There is little evidence available regarding the association between TCM outcome and HLD (*Table 5*). One study of 11 193 TCM patients found that HLD was not associated with in-hospital mortality in TCM patients ($P = 0.1474$).⁶⁶ One study of 144 TCM patients also found that HLD was not associated with in-hospital mortality.⁸⁵ However, one recent retrospective study found that TCM patients with HLD had better in-hospital outcomes than those without HLD. Those with comorbid HLD had less in-hospital mortality (OR 0.46, 95% CI 0.24–0.89) and fewer severe in-hospital complications such as cardiogenic shock (OR 0.59, 95% CI 0.39–0.88) and acute respiratory failure (OR 0.73, 95% CI 0.56–0.95). However, the rates of cardiac arrest, ventricular arrhythmia, and acute kidney injury did not differ significantly between the two groups (1162 patients with HLD and 1162 patients without HLD), the author attributed this result to statin use, the protection of low-density lipoprotein cholesterol binding lipopolysaccharide in sepsis, and underlying malnutrition in patients without HLD.¹²⁸ More research is needed to study the association between TCM and HLD.

Anaemia

A common chronic disease, anaemia, has been associated with poor outcome in TCM patients. About 12.7–22.82% of TCM patients have comorbid anaemia.^{29,98,129,130}

There are a few studies of the association between anaemia and the prognosis of TCM. One study of 4733 TCM patients found that anaemia was associated with more in-hospital complications, such as cardiogenic shock (OR 3.14, 95% CI 2.12–4.64), ventricular arrhythmias (OR 1.88, 95% CI 1.20–2.95), acute kidney injury (OR 1.95, 95% CI 1.51–2.52), and acute respiratory failure (OR 1.93, 95% CI 1.49–2.50), although in-hospital mortality was not different between patients with and without anaemia.¹²⁹ Another study with a small sample of 126 TCM patients associated anaemia with long-term mortality (OR 3.93, 95% CI 1.02–2.08) during a median follow-up time of 4.4 years.¹³¹ Given the current evidence, we believe anaemia is associated with a poor prognosis in TCM patients. Future studies should focus on the optimal treatment for anaemia and the best threshold of transfusion in TCM patients.

Treatment

Evidence-based medical therapy for TCM patients is lacking. TCM patients are routinely treated with supportive care, routine complication management, and conventional medical therapy, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and β -blockers. The evidence that using such medications translates into a survival benefit for TCM patients is limited.

Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

In addition to inhibiting the renin-angiotensin-aldosterone system and decreasing sympathetic system activation, ACEIs and ARBs also serve as direct and indirect antioxidants and can decrease nitrate tolerance and endothelial dysfunction, which in turn inhibits coronary artery spasm.¹³² In theory, ACEIs/ARBs use may benefit TCM patients.

The association between ACEIs/ARBs use and the outcomes of TCM is not certain. Some studies have found that TCM patients who receive ACEIs/ARBs have better outcomes.^{8,72} One study found that TCM patients who prescribed ACEIs/ARBs at discharge had less 1 year mortality than those without (33.6% vs. 36.6%, $P = 0.001$).⁸ Another study of 326 TCM patients found those with ACEIs/ARBs had less long-term cardiac mortality (46.7% vs. 70.7%, $P = 0.048$), although the all-cause mortality difference was not statistically significant ($P = 0.743$).⁷² Other studies, on the other hand, have found that ACEIs/ARBs use was not associated with in-hospital outcomes⁸⁴ or long-term outcomes^{52,133} in TCM patients.

Some evidence suggests that ACEIs/ARBs use is beneficial for preventing TCM recurrence. A meta-analysis of 31 studies

and 1664 TCM patients showed that TCM patients receiving ACEIs/ARBs at discharge was correlated with a lower TCM recurrence rate ($P = 0.016$, $r = -0.45$) during long-term follow-up (mean 24.5 months).¹³⁴

β -Blockers

In theory, given that the two most widely accepted mechanisms of TCM are sympathetic nervous system overactivation and catecholamine surge, β -blockers may be able to prevent or reduce the severity of cardiac complications in TCM by counteracting the catecholamine effect. Although they are commonly prescribed for TCM patients during hospitalization and at discharge, the efficacy of β -blockers against TCM remains uncertain.

Although β -blockers could relieve ventricular discordance by blocking the adrenergic system in TCM patients with an elevated intraventricular pressure gradient,¹³⁵ they do not reduce the short-term mortality rate in TCM patients according to our literature review (Table 6).^{84,88,136} A retrospective outcome study found that those who received early β -blocker administration (i.e. starting within the first 2 days of admission; 422 patients) had similar inpatient ($P = 0.703$), 15 day ($P = 1.000$), and 30 day mortality ($P = 0.747$) to those who did not receive any β -blockers during hospitalization (1668 patients).¹³⁶ Another study by Kato *et al.* found that β -blocker use before admission was associated with a higher rate of in-hospital complications (pulmonary oedema, cardiogenic shock, sustained VT or VF, complete atrioventricular block, thromboembolism, cardiac rupture, and cardiac death) (OR 16.9, 95% CI 1.57–181.7).⁸⁸

The effect of β -blockers on the long-term outcome of TCM is still uncertain (Table 6). Our literature review revealed that the majority of studies found β -blocker administration not to be associated with long-term TCM outcome.^{8,52,133,134,137} For example, one meta-analysis of 31 studies from Singh *et al.* found that discharging TCM patients with β -blockers had no significant effect on the recurrence of TCM ($P = 0.28$) during an average of 24.5 months' follow-up.¹³⁴ In addition, one study with a sample size of 711 found that TCM patients with cardiogenic shock who were prescribed β -blockers at discharge had a lower 1 year mortality rate (HR 0.52, 95% CI 0.44–0.79) than patients who were not prescribed such medications. There was also no significant benefit of β -blockers for TCM patients without cardiogenic shock ($P = 0.853$).⁴¹

Calcium channel blockers

Calcium channel blockers are commonly used to treat cardiovascular diseases, especially hypertension and arrhythmia, and can be categorized as dihydropyridine CCBs (which have

a greater effect on reducing systemic vascular pressure) and non-dihydropyridine CCBs (which have a greater negative effect on cardiac conduction and contractility). Although the indications for the two types of CCBs differ, they both have counteractive effects on coronary vasospasm and microcirculatory dysfunction, which are thought to be the pathophysiologic causes of TCM.^{138,139}

Overall, the evidence of CCBs' effects on TCM outcome is limited. A retrospective study using multivariate logistic regression analysis found that TCM patients who were not taking CCBs at admission had a relatively delayed (more than 10 days) recovery from left ventricular systolic dysfunction to normal contraction compared with those taking CCBs (14 patients with dihydropyridine CCB and 2 patients with non-dihydropyridine CCB) (OR 22.2, 95% CI 3.08–291.5).¹¹³ The study was limited by its small sample size and its retrospective design.

Statins

Statins are one of the most frequently used medical therapies for primary and secondary prevention of cardiovascular disease.¹⁴⁰ The benefits of statins for the cardiovascular system have been widely accepted,¹⁴¹ including not only cholesterol biosynthesis reduction¹⁴² but also endothelial function improvement¹⁴³ and inflammation reduction.¹⁴⁴

However, our literature review did not find strong evidence of any short-term or long-term benefit of statins for TCM patients.^{52,84,133,145} A retrospective study by Dias *et al.*, involving 146 participants who received statins during hospitalization, found that statin use was not associated with major adverse cardiovascular events in TCM patients after multivariate analysis ($P = 0.8$).⁸⁴ A meta-analysis of 511 TCM patients, including 203 patients prescribed statins at discharge, found that statin use was not associated with TCM reoccurrence during long-term follow-up (range, 24 to 30 months; $P = 0.95$).¹⁴⁵

Heterogeneity of studies

An increasing number of studies are examining the prognosis of TCM, especially with the rise of administrative databases and multicentre registries. However, these studies have substantial bias and heterogeneity. As Table 7 shows, administrative database and multicentre/single-centre registry studies differ in several ways.

First, the identification and diagnostic criteria of TCM differ significantly among these studies. ICD-9 and ICD-10 codes were widely used to identify TCM in studies based on administrative databases, while other specific diagnostic criteria, such as the Mayo and ESC criteria, were used in multicentre registries and single-centre studies. Although

Table 6 Clinical studies on the effects of drugs in TCM patients

Drug	Author (year)	Diagnostic criteria	Sample size	Type of study	Follow-up	Mortality	Analysis strategy	Risk of bias
β -blocker	Isogai <i>et al.</i> (2016)	ICD-10	2110	Retrospective	15 days in-hospital 30 days in-hospital In-hospital	β -blocker vs. Non- β -blocker No difference	Multivariable logistic regression	High
	Almendro-Delia <i>et al.</i> (2018)	Modified Mayo criteria	711	Prospective	In-hospital 1 year	No difference TCM with cardiogenic shock: HR 0.52 (95% CI 0.44–0.79), P = 0.011 TCM without cardiogenic shock: No difference	Multivariate Cox regression	Moderate

CI, confidence interval; HR, hazard ratio; ICD, International Classification of Diseases; NA, not applicable; TCM, Takotsubo cardiomyopathy.

previous studies showed that the discharge diagnosis of TCM by ICD code has a high accuracy and positive predictive value,¹³ the validity of using the ICD code for TCM identification in public databases, such as the NIS, is lacking and infeasible because the data are deidentified, which compromises findings from these databases.

Second, many studies, both administrative database and multicentre/single-centre registry studies, which aimed to study different prognostic factors with various follow-up times in TCM patients, potentially have overlap among their patient samples. For example, many institutes and research groups that contributed to International Takotsubo Registry have also published prognostic studies based on their own patient cohorts. In addition, some studies used the same sample of TCM patients to study different factors, although the variables in the multivariable model and follow-up times were different.

Third, the quality and sample size of these studies varied substantially. For example, studies based on administrative databases (e.g. the NIS database) usually have a large (over 3000) or moderate (1000 to 3000) sample of TCM patients but a high overall risk of bias. The limitation of database studies is the omission of certain potentially important variables, such as therapeutic schedules and laboratory and imaging findings, which may also be associated with the prognosis of TCM patients. In contrast, studies from multicentre or single-centre registries have moderate or smaller samples (<1000), but they nonetheless have sufficient data to build the multivariable model with less bias. Thus, excluding studies from administrative databases means omitting a large number of TCM patients. Similarly, excluding studies from multicentre registries means excluding some high-quality studies and reduces the credibility of the results.

Fourth, the follow-up times were different between the two types of studies. Administrative databases often offer only in-hospital information, so these data can only be used to examine associations between risk factors and short-term outcomes in TCM patients. In contrast, many multicentre and single-centre registries have both short-term and long-term follow-up data. Therefore, the association between risk factors and TCM prognosis shown in the two types of studies may be different because of the different follow-up times.

As a result, a statistical meta-analysis would be challenging and inappropriate if it included all types of studies. Although one could use stricter inclusion criteria (e.g. by including only studies with specific TCM criteria) and exclusion criteria (e.g. excluding any potential duplicate studies) to synthesize the data, that would result in the exclusion of a significant portion of studies of several prognostic factors. So we describe the outcomes from different studies comprehensively to show the effects of as many risk factors as possible on patients with TCM.

Table 7 Differences between studies based on administrative databases and multicentre/single-centre registries

Variable	Administrative databases	Multicentre/single-centre registries
Study type	Retrospective	Retrospective or prospective
Diagnosis criteria	ICD code	Mayo criteria, ESC criteria (2016), In-TAK criteria, or Madias criteria
Sample size	Large (>3000) or moderate (1000–3000)	Moderate (1000–3000) or small (<1000)
Variables included	Less data: age, sex, race, and some comorbidities selected by ICD code	More data: age, sex, race, comorbidities, therapeutic schedule, laboratory, and imaging findings
Follow-up time	In-hospital	In-hospital and long-term

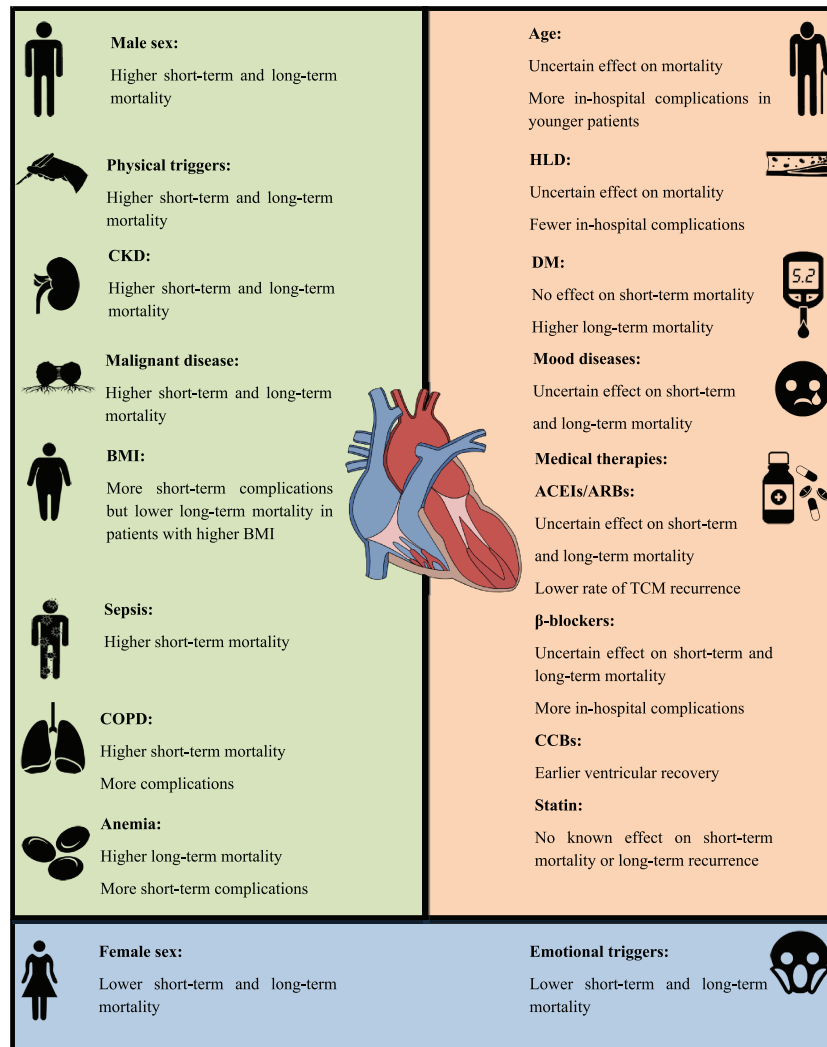
ESC, European Society of Cardiology; ICD, International Classification of Diseases; In-TAK, International Takotsubo.

Limitations

Our review also had limitations. First, the patient populations and potential predictors assessed were heterogeneous (e.g.

the diagnostic criteria for TCM patients and the method of identifying each prognostic factor differed among these studies), which may have affected the interpretation and generalizability of the results. Second, because of the substantial heterogeneity among studies, we only reported findings from

Figure 2 Prognostic factors of Takotsubo cardiomyopathy. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; CCBs, calcium channel blockers; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HLD, hyperlipidaemia.



each study without performing meta-analysis. Third, certain risk factors, such as COPD and anaemia, were examined in only a few studies, which could affect the certainty of the evidence.

Conclusion

Although they are widely recognized, the risk factors and treatments' effect on the outcome of TCM remain largely uncertain (*Figure 2*). The bulk of the evidence suggests that male sex, physical triggers, and certain comorbidities such as CKD, malignant disease, higher BMI, sepsis, COPD, and anaemia are associated with poor TCM prognosis. However, the association of race, DM, mood disorders, HLD, and medical therapies with TCM prognosis remains unclear. Further systemic review and meta-analysis are needed to integrate findings from previous studies and to address the inconsistencies among many risk factors. Randomized controlled trials are warranted to determine whether these risk factors require early intervention and to identify the appropriate methods to intervene.

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Conflict of interest

None declared.

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