Review Article

The Utility of Artificial Intelligence and Machine Learning in the Diagnosis of Takotsubo Cardiomyopathy: A Systematic Review

Helen Huang[1,2], Francesco Perone[2,3], Keith Sai Kit Leung[2,4,5], Irfan Ullah[2,6,7], Quinncy Lee[2], Nicholas Chew[8], Tong Liu[9], Gary Tse[9,10,11]

[1]Faculty of Medicine and Health Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland, [2]Cardiac Electrophysiology Unit, Cardiovascular Analytics Group, PowerHealth Institute, Hong Kong, China, [3]Cardiac Rehabilitation Unit, Rehabilitation Clinic "Villa delle Magnolie", Caserta, Italy, [4]Faculty of Health and Life Sciences, Aston University Medical School, Aston University, Birmingham, UK, [5]Hull University Teaching Hospitals, National Health Service Trust, Yorkshire, UK, [6]Kabir Medical College, Gandhara University, Peshawar, Pakistan, [7]Department of Internal Medicine, Khyber Teaching Hospital, Peshawar, Pakistan, [8]Department of Cardiology, National University Heart Centre, National University Health System, Singapore, [9]Department of Cardiology, Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, China, [10]Kent and Medway Medical School, Canterbury, UK, [11]School of Nursing and Health Studies, Hong Kong Metropolitan University, Hong Kong, China

Abstract

Introduction: Takotsubo cardiomyopathy (TTC) is a cardiovascular disease caused by physical/psychological stressors with significant morbidity if left untreated. Because TTC often mimics acute myocardial infarction in the absence of obstructive coronary disease, the condition is often underdiagnosed in the population. Our aim was to discuss the role of artificial intelligence (AI) and machine learning (ML) in diagnosing TTC. **Methods:** We systematically searched electronic databases from inception until April 8, 2023, for studies on the utility of AI- or ML-based algorithms in diagnosing TTC compared with other cardiovascular diseases or healthy controls. We summarized major findings in a narrative fashion and tabulated relevant numerical parameters. **Results:** Five studies with a total of 920 patients were included. Four hundred and forty-seven were diagnosed with TTC via International Classification of Diseases codes or the Mayo Clinic diagnostic criteria, while there were 473 patients in the comparator group (29 of healthy controls, 429 of myocardial infarction, and 14 of acute myocarditis). Hypertension and smoking were the most common comorbidities in both cohorts, but there were no statistical differences between TTC and comparators. Two studies utilized deep-learning algorithms on transthoracic echocardiographic images, while the rest incorporated supervised ML on cardiac magnetic resonance imaging, 12-lead electrocardiographs, and brain magnetic resonance imaging. All studies found that AI-based algorithms can increase the diagnostic rate of TTC when compared to healthy controls or myocardial infarction patients. In three of these studies, AI-based algorithms had higher sensitivity and specificity compared to human readers. **Conclusion:** AI and ML algorithms can improve the diagnostic capacity of TTC and additionally reduce erroneous human error in differentiating from MI and healthy individuals.

Keywords: Artificial intelligence, diagnostics, precision medicine, takotsubo cardiomyopathy

Introduction

Takotsubo cardiomyopathy (TTC), also known as broken heart syndrome or stress cardiomyopathy, is a condition characterized by apical heart systolic dysfunction with sudden onset and reversibility that mimics acute coronary syndrome (ACS) but without evidence of coronary artery disease (CAD) on angiography.[1] TTC has two clinical forms: one is primary takotsubo syndrome which present in the emergency department as they experience symptoms acutely,[2] whereas secondary takotsubo syndrome present in people who are already hospitalized for other diseases.[3]

Received: 12-10-2023; **Accepted:** 01-03-2024; **Published:** 25-07-2024

Access this article online

Quick Response Code:

Website: journals.lww.com/hhmi

DOI: 10.4103/hm.HM-D-23-00061

Address for correspondence: Ms. Helen Huang, Faculty of Medicine and Health Science, Royal College of Surgeons in Ireland, Dublin 2, D02 YN77, Ireland.
E-mail: helenhuang@rcsi.ie
Prof. Gary Tse,
Department of Cardiology, Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin 300211, China.
Kent and Medway Medical School, Canterbury CT2 7FS, Kent, UK.
School of Nursing and Health Studies, Hong Kong Metropolitan University, Hong Kong 00000, China.
E-mail: garytse@tmu.edu.cn

How to cite this article: Huang H, Perone F, Leung KS, Ullah I, Lee Q, Chew N, *et al*. The utility of artificial intelligence and machine learning in the diagnosis of takotsubo cardiomyopathy: A systematic review. Heart Mind 2024;8:165-76.

TTC is thought to be caused by a number of reasons, such as sympathetic overdrive with elevated catecholamines, coronary spasm, microvascular dysfunction, low estrogen levels, inflammation, or defective myocardial fatty acid metabolism.[4-6] Catecholamine-mediated damage is considered the main cause of TTC pathogenesis, which can be observed in critical or stressed patients.[7,8] The common presentations of TTC are substernal chest pain, shortness of breath, syncopal attack, and changes in the electrocardiogram (ECG) in relation to acute stress.[9,10] Some patients present with tachycardia, low pulse pressure, and low systolic blood pressure (<90 mmHg) in admitted patients.[11]

The incidence of TTC increased dramatically between 2006 and 2012, by a factor of over 20, potentially due to increased recognition and awareness of the condition itself.[12] According to reports, 2% of people who exhibit clinical signs of ACS also have takotsubo syndrome.[13] Almost 6% of all women have TTC who seek immediate angiography after presenting with a suspected ST-elevation myocardial infarction (STEMI).[14] Various diagnostic criteria are used for diagnosing TTC like the International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria), Mayo Clinic criteria, and others.[15] It is important to emphasize, however, that TTC is a diagnosis of exclusion that can only be made after coronary angiography because of the indistinguishable features from acute coronary disease.[16] As a result, patients can be misdiagnosed for mimics of TTC such as ST-elevated myocardial infarction, acute myocardial infarction, or myocarditis.

Recent years have observed the potential applications of artificial intelligence (AI) to augment diagnostic and prognostic utility in various diseases.[17-21] Machine learning (ML) and other AI approaches can be used to distinguish a variety of patterns found in the imaging modalities, including echocardiography.[22] Because AI can automatically analyze aspects from images and data that are beyond human perception, it can be used in echocardiography to detect disease states.[23] Given that the amount of data collected during normal echocardiogram can be challenging for human professionals to interpret in a short amount of time, a significant amount of potentially diagnostic information may go unused.[24] Because AI can automatically analyze aspects from images and data that are beyond human perception, it can be used in echocardiography to detect disease states. As such, the objective of this study is to systematically review preexisting studies implementing the applications of AI and ML in the diagnosis of TTC to determine its applicability in clinical practice and patient care.

Methods

Search strategy

The studies chosen for this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement) guidelines. The protocol is registered in PROSPERO (CRD42023433539). A preliminary search was utilized to carry out the literature search and to determine its uniqueness. Studies were screened based on the modified PICO (Problem, Intervention, Comparison, Outcome) criteria [Table 1].[25]

Inclusion and exclusion criteria

Studies that were included had all the following parameters: (1) patients with diagnosed TTC through International Classification of Diseases-9/10, the Mayo Clinic diagnostic criteria, or InterTAK, (2) studies with patients >18 years of age, and (3) studies comparing the utility of AI- or ML-based algorithms in diagnosing TTC compared to other cardiovascular diseases or healthy controls. All diagnostic tools were considered for the inclusion of this study to ensure adequate representation of studies. We included prospective/retrospective observational studies and cross-sectional studies. We excluded conference abstracts, systematic reviews, narrative reviews, editorials, short communications/letters, book chapters, case studies/series, animal studies, *in vitro* studies involving cell lines, studies with patients <18 years of age, and scientific articles in languages other than English.

Study selection

Two reviewers (HH and KSKL) independently conducted an electronic systematic search in three databases (PubMed, EMBASE, and SCOPUS) from inception until April 8, 2023, without search limitations using a predefined search strategy [Supplementary Table 1]. The studies were carefully exported to the Endnote 2020 library (X9) and screened using Covidence.[26,27] The same reviewers independently screened for title/abstracts and full text, with discrepancies regarding the inclusion of studies being arbitrated by the senior author (GT).

Data extraction and quality assessment

Information in the included studies were extracted into an Excel spreadsheet which included summary characteristics of included studies (title, authors, abstract, published year, journal, and DOI). Full-text papers were retrieved to extract the following information: country of origin, study type, study size of total participants, patient population with TTC, comparator population, baseline characteristics such as sex and mean age, and common comorbidities (i.e., hypertension, diabetes). Then, we summarized the tested imaging parameter and the different AI- or ML-based algorithms utilized in a narrative fashion. We specified whether these diagnostic algorithms were tested compared to either traditional

Table 1: Modified problem, intervention, comparison, and outcome criteria

Categories	Variables
Patient	Adults diagnosed with TTC
Exposure	AI- or ML-assisted approaches in TTC
Comparator	AI- or ML-assisted approaches in other conditions or healthy controls
Outcome	Diagnostic or prognostic utility

AI=Artificial intelligence, ML=Machine learning, TTC=Takotsubo cardiomyopathy

diagnostic modalities such as human readers (i.e., health-care professionals) or different types of AI/ML models in each paper. The study outcomes were assessing the diagnostic efficacy of AI/ML-based approaches in identifying TTC compared to healthy controls or other cardiovascular conditions and tabulated statistical parameters (area under the curve [AUC], sensitivity, specificity, and accuracy) where available. Two authors (HH and KSKL) assembled all available information in a shared Excel spreadsheet. For missing, incorrect, or unreported data, the corresponding authors of the respective papers were contacted via E-mail for clarification. Supplementary material related to the main article was also investigated in such cases. For the quality assessment of included studies in the systematic review, we used the Newcastle–Ottawa Scale for observational studies by two independent reviewers [Supplementary Table 2].[28]

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics and common comorbidities in this paper using the mean and standard deviation for continuous variables, while frequencies and percentages were used for dichotomous variables. To determine significant differences in patient comorbidities, we first pooled event outcomes in the TTC and comparator groups separately and performed a two-tailed Fisher's test based on these two groups. In addition, we performed a conventional two-arm meta-analysis of patient comorbidities using the DerSimonian and Laird random-effects model for study variations with the inverse-variance weighted method.[29] Outcomes were reported as odds ratios (OR) and their corresponding 95% confidence interval (95% CI). Statistical significance was met if the 95% CI of the pooled results did not cross the numeric "1" and the two-tailed $P < 0.05$. The Higgins I-squared (I^2) statistical model was used to assess heterogeneity among studies, with I^2 <75% considered mild-moderate and ≥75% considered high.[30] Regarding the ML algorithms, we reported the AUC, sensitivity, specificity, and accuracy noted in each paper. For papers where accuracy was not reported, we used calculations from positive predictive values and negative predictive values provided in the study. Analyses and visualization of data were done using Prism version 8 (GraphPad, LaJolla, CA, USA) and Microsoft Excel 2021 (Microsoft, Redmond, WA, USA). The meta-analysis was performed using Review Manager software (RevMan) Version 5.4 (The Cochrane Collaboration, Copenhagen, Germany). The graphical abstract was curated using BioRender.[31]

Results

Study selection

The utilization of our predefined search terms [Supplementary Table 1] without restrictions yielded 818 studies, including 83 from PUBMED, 652 from EMBASE, and 83 from SCOPUS. Of these, 44 duplicates were excluded and a further 753 articles were excluded from the initial posttitle and abstract screening based on the inclusion and exclusion criteria. Full-text review was conducted for the remaining 21 studies, of which five studies met the requirement for our systematic review.[32-36] The PRISMA flow diagram is depicted in Figure 1. All five of the included studies were retrospective observational studies, with publication years ranging from 2017 to 2023 [Table 2]. Three studies were conducted in Europe, whilst the remainder of the studies were conducted in the United States and Japan, respectively.

Patient characteristics

A total of 920 participants were included in this systematic review, with a mean sample size of 114.65 (±110.26). Of these, 447 were diagnosed with TTC and constituted around 48% of the study population [Table 2 and Figure 2]. Three studies compared TTC with myocardial infarction (two anterior and one STEMI), two studies compared against healthy controls, and one study compared TTC with acute myocarditis ($n = 473$, 51.4%). Based on the clinical characteristics of the cohort with TTC, 86% of the patients were of female sex ($n = 388$) with a mean age of 68.5 ± 2.3 years. The mean age for the pooled comparison cohort was 60.4 ± 10.2 years, and only two studies – Laumer, 2022, and Zaman, 2021 – reported female sex ($n = 252$).

We further examined the comorbidities of the TTC cohort where available. Hypertension was the most common comorbidity in TTC patients, with 55.4% diagnosed at baseline [Figure 3]. This was followed by 36.5% with a history of smoking, 28.2% diagnosed with hyperlipidemia, 17.9% with diabetes mellitus ($n = 80$), and 9.4% with CAD [Supplementary Table 3].

Table 2: Study characteristics and baseline demographics

Study characteristics				TTC group		Control group		
Study	Year	Country	Study size (*n*)	Sample size (*n*)	Mean age ± SD	Comparator	Sample size (*n*)	Mean age ± SD
Cau *et al*.[33]	2023	Italy	43	18	69.0 ± 11.0	AM and healthy	AM: 14 Healthy: 11	AM: 44.0 ± 16.0 Healthy: 50.0 ± 10.0
Klein *et al*.[34]	2017	Switzerland	39	20	65.3 ± 14.3	Healthy	19	67.4 ± 14.2
Laumer *et al*.[35]	2022	Switzerland	448	224	67.9 ± 11.7	AMI	224	68.7 ± 11.7
Zaman *et al*.[36]	2021	United States	300	140	64.0 ± 13.1	STEMI	160	61.3 ± 13.3
Shimizu *et al*.[32]	2022	Japan	90	45	78.0 ± 12.6	AMI	45	-

TTC=Takotsubo cardiomyopathy, AM=Acute myocarditis, AMI=Acute myocardial infarction, STEMI=ST-segment elevation myocardial infarction, SD=Standard deviation, *n*=number

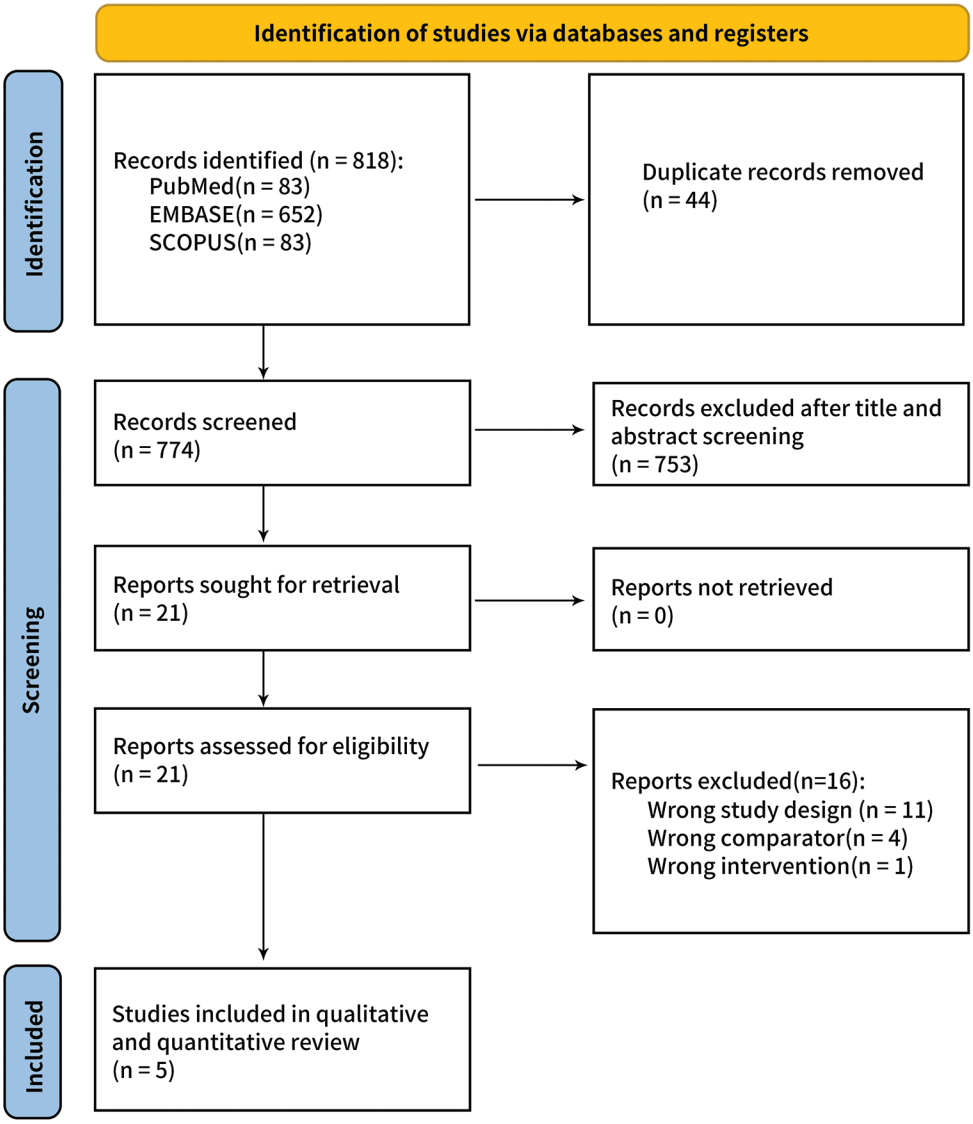


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram

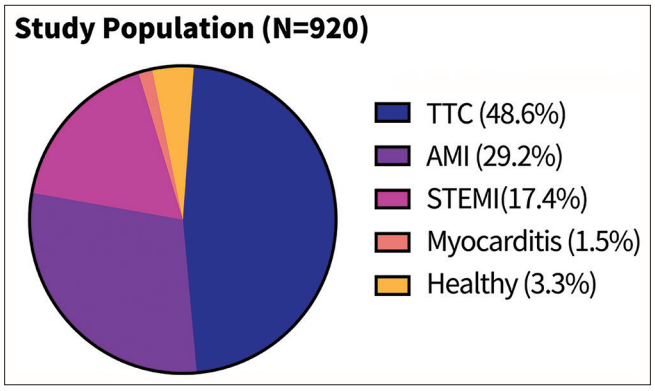


Figure 2: Overview of patient characteristics in included studies. TTC=Takotsubo cardiomyopathy, AMI=Acute myocardial infarction, STEMI=ST-segment elevation myocardial infarction

A previous history of chronic kidney disease was reported in two studies (7.8%). Statistical analyses did not shed significant differences in comorbidities when comparing TTC patients with the comparator group after pooling samples from available studies [Supplementary Table 4]. In addition, the risk of comorbidities between the two groups was comparable [Supplementary Figure 1]. The mean % of left ventricular ejection fraction was recorded at 45.3 ± 9.3 based on three of the included studies, while two studies reported heart rate, systolic blood pressure, and a presentation of ST-segment elevation.

Imaging parameters and applied artificial intelligence algorithms

Table 3 summarizes the utilized imaging parameters and algorithms used for their model on differentiating TTC from the comparator groups. In terms of outcomes, all studies reported the diagnostic utility and there was no data on the prognostic utility of AI.

In Cau *et al.*,[33] five different tree-based ensemble algorithms were applied to noncontrast cardiac magnetic resonance (CMR) scans with late gadolinium enhancements in TTC subjects presenting with chest pain, which were compared to human readers.

Additional analyses revealed that left atrial conduit strains and strain rate were strong indicators for TTC identification.

Klein *et al*.[34] applied a support vector ML algorithm on diffusion-weighted magnetic resonance images (MRI) of the brain to compare TTC patients with healthy controls. Three different diffusion-based measures were compared in TTC patients, which consisted of diffusion tension imaging (DTI), voxel-based manometry (VBM), and resting-state functional magnetic resonance imaging (rsfMRI).

In two studies, deep-learning algorithms that utilized convolutional neural networks were used to discriminate TTC from MI based on transthoracic echocardiography (TTE) images compared to interpretations from human readers such as trained cardiologists. Laumer *et al*.[35] assessed the utility of temporal neural networks based on one-dimensional convolution architectures of different views captured by the TTE (apical two-chamber and four-chamber views). In comparison, Zaman utilized three deep convolution neural networks (DCNNs) and one recurrent neural network (RNN) with a region of interest selection algorithm, allowing them to differentiate TTC from STEMI.

Finally, Shimizu *et al*.[32] utilized a similar approach using 12 different ensemble learning models on 12-lead electrocardiographic microvolt-level measurements. ML models such as light gradient-boosting machine and extra-tree classifiers were compared to traditional statistical models to distinguish TTC from anterior AMI. The differences in the accuracy of these models were observed in 25 different ECG parameters based on lead positions.

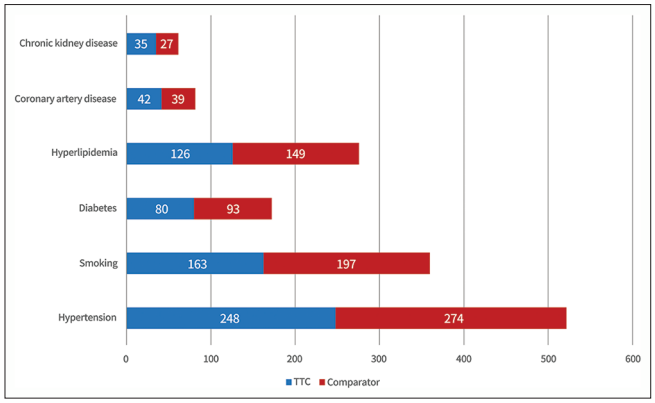


Figure 3: The number (*n*) of patient comorbidities in reported studies

Diagnostic performances of artificial intelligence algorithms

The results from all studies found that AI-based algorithms can increase the diagnostic rate of TTC when compared to the comparator group [Table 4]. In Cau *et al*., the AUC and sensitivity/specificity utilizing the random forest classifier and the gradient-boosting algorithm on CMR images to diagnose

Table 3: Descriptive summary of artificial intelligence algorithms in included studies

	Study				
	Cau *et al*.[33]	**Klein *et al*.[34]**	**Laumer *et al*.[35]**	**Zaman *et al*.[36]**	**Shimizu *et al*.[32]**
Objective/ aim of study	Derive a machine learning model integrating noncontrast CMR parameters to identify TTC in subjects with cardiac chest pain	Identify predictors for the presence of TTC based on different modalities of MRI data	Assess the utility of machine learning systems for automatic discrimination of TTC and AMI	Using deep learning neural networks in the differential diagnosis of TTC and STEMI based on bedside echocardiographic images and videos	Distinguish TTC with Ant-AMI by ML approach of microvolt-level quantitative measurements
Imaging parameter	CMR scans	Diffusion-weighted MRI brain	TTE	TTE	12-lead ECG
Algorithm description	Tree-based ensemble learning ML algorithms	Support vector machine learning algorithm	Deep-learning algorithm using convolutional autoencoder and temporal convolution neural network	Deep convolutional neural networks and recurrent neural networks with ROI selection algorithm	Predictive ML models with ensemble learning procedure
Algorithm models	AdaBoost, Bagging, XGBoost, RF, ExtraTrees	DTI (FA) VBM (GM, WM, CSF) rsfMRI (fALFF, ALFF, ReHo)	Temporal neural network based on one-dimensional time convolution architecture of apical two-chamber and four-chamber views from TTE	DCNN (2D [SCI]), DCNN (2D [MCI]), DCNN (2D+t), RNN	LGB machine, ExtraTrees, AdaBoost, Naive Bayes, GB, RF, LD analysis, DT, K-neighbors, logistics regression, quadratic discriminant analysis
Comparison	Human readers	Between three different forms of MRI sequencing data	Human readers	Human readers	Traditional statistical models

TTC=Takotsubo cardiomyopathy, AMI=Acute myocardial infarction, CMR=Cardiac magnetic resonance, TTE=Transthoracic echocardiography, ECG=Electrocardiogram, ML=Machine-learning, ROI=Regions of interest, AdaBoost=Adaptive boosting, XGBoost=Extreme gradient boosting, RF=Random forests, ExtraTrees=Extreme gradient boosting, DTI=Diffuse tensor imaging, FA=Fractional anisotropy, VBM=Voxel-based morphometry, WM=White matter, CSF=Cerebrospinal fluid, rsfMRI=Resting state functional magnetic resonance imaging, fALFF=Fractional amplitude of low-frequency fluctuations, ReHo=Regional homogeneity, DCNN=Deep convolution neural networks, 2D=Two-dimensional, SCI=Single-channel image, MCI=Multi-channel image, RNN=Recurrent neural network, LGB=Light gradient boosting, GB=Gradient boosting, LD=Linear discriminant, DT=Decision tree

Table 4: Comparison of area under curve, sensitivity, specificity, and accuracy values between machine-learning models

Study	Model	AUC	Sensitivity	Specificity	Accuracy
Cau *et al*.[33]	AdaBoost	0.76	0.691	0.822	-
	Bagging	0.89	0.778	0.846	-
	XGBoost	0.92	0.808	0.874	-
	RF	0.93	0.861	0.869	-
Klein *et al*.[34]	DTI	0.83	0.7857	0.7857	0.7857
	VBM	0.55	0.5789	0.5789	0.5789
	rsfMRI	0.86	0.8125	0.75	0.7812
	All modalities	0.71	0.6667	0.75	0.7083
Laumer *et al*.[35]	Two-chamber and four-chamber	0.79#	0.755	0.741	0.748*
	Two-chamber view		0.739	0.719	0.729*
	Four-chamber view		0.742	0.673	0.666*
Zaman *et al*.[36]	DCNN (2D [SCI])	-	0.67	0.78	0.73
	DCNN (2D [MCI])	-	0.73	0.77	0.75
	DCNN (2D+t)	0.79	0.79	0.8	0.8
	RNN	0.77	0.71	0.79	0.75
Shimizu *et al*.[32]	Light gradient-boosting machine	0.86	0.87	-	0.865
	Extra-tree classifier	0.88	0.83	-	0.832
	AdaBoost classifier	0.87	0.87	-	0.832
	Naive Bayes	0.87	0.81	-	0.821
	Gradient-boosting classifier	0.87	0.87	-	0.821
	Random forest classifier	0.85	0.85	-	0.821
	Linear discriminant analysis	0.844	0.81	-	0.786
	Decision-tree classifier	0.81	0.82	-	0.778
	K-neighbors classifier	0.79	0.85	-	0.776
	Logistic regression	0.80	0.71	-	0.719
	Quadratic discriminant analysis	0.69	0.79	-	0.708

*Calculated from true/false positives and true/false negatives, #AUC based on the performance of the overall ML model. AdaBoost=Adaptive boosting, XGBoost=Extreme gradient boosting, RF=Random forests, ExtraTrees=Extreme gradient boosting, DTI=Diffuse tensor imaging, VBM=Voxel-based morphometry, rsfMRI=Resting state functional magnetic resonance imaging, DCNN=Deep convolution neural networks, 2D=Two-dimensional, SCI=Single-channel image, MCI=Multi-channel image, RNN=Recurrent neural network, AUC=Area under the curve

TTC were higher than 0.90 and 0.80, respectively. This was in comparison to the application of ensemble-based decision tree called AdaBoost (adaptive boosting) on CMR images. For Klein *et al*., there were stark differences in the AUC for DTI (0.83) and rsfMRI (0.86) measures in comparison to VBM (0.55) in the diagnosis of TTC when using MRI imaging techniques.[34] The same trend was true for the sensitivity, specificity, and accuracy in Cau *et al*.'s CMR algorithms and Klein *et al*.'s brain MRI algorithms. Laumer *et al*. identified no significant difference in the AUC, sensitivity, specificity, and accuracy among different apical chamber views captured by TTE images to diagnose TTC. Zaman *et al*. reported that the overall AUC for DCNN was 0.79 compared to RNN which was 0.77 to diagnose TTC captured on TTE compared to STEMI. When comparing DCNN models alone, DCNN (2D [two-dimensional] +t) exhibited higher sensitivity. Finally, Shimizu *et al*. looked at 12 different ML-based models on 12-lead ECG data which were compared to traditional statistical models without ML algorithms.[32] The majority of ML models had a higher AUC than 0.8 in the diagnosis of TTC on ECG data points with the exception of quadratic discriminant analysis and K-neighbors classifier. In terms of sensitivity, all were higher than 0.8 with the exception of the logistic regression and quadratic discriminant analysis.

In three of these studies utilizing CMR (Cau *et al*.) and TTE (Laumer and Zama *et al*.), AI-based algorithms had a higher AUC, sensitivity, and specificity compared to human readers in diagnosing TTC [Table 5]. In Cau *et al*., it was found that all four ML models had a higher AUC and specificity, than a human reader.[33] However, the sensitivity of a human reader diagnosing TTC from CMR images was 0.833, which outperformed AdaBoost (0.69) and Bagging (0.778). By contrast, Laumer *et al*. demonstrated that the AUC and sensitivity of four human readers diagnosing TTC from TTE images were lower than that of temporal neural networks.[35] However, human readers outperformed in specificity compared to the model. Finally, Zaman *et al*. compared the performance of 49 human readers to DCNN (2D+t) and RNN, to which the ML algorithms outperformed other algorithm types for AUC.[36]

Discussion

This is one of the first systematic reviews that elaborate on the utility of AI and ML in the diagnosis of TTC [Central Illustration]. In our cohort, AI and ML show additional and impactful value due to the increased TTC diagnosis rate compared to the comparator group. Based on ventricular segmentation, volume measurements, and an automatic

Table 5: Studies comparing machine-learning models with human readers

Study	Model	AUC	Sensitivity	Specificity
Cau *et al*.[33]	AdaBoost	0.76	0.691	0.822
	Bagging	0.89	0.778	0.846
	XGBoost	0.92	0.808	0.874
	RF	0.93	0.861	0.869
	Human reader	0.52	0.833	0.24
Laumer *et al*.[35]	Two-chamber and four-chamber	0.79#	0.755	0.741
	Two-chamber view		0.739	0.719
	Four-chamber view		0.742	0.673
	Human reader 1	0.73	0.455	0.845
	Human reader 2	0.68	0.464	0.745
	Human reader 3	0.69	0.445	0.809
	Human reader 4	0.74	0.645	0.755
Zaman *et al*.[36]	DCNN (2D+t)	0.79	0.79	0.8
	RNN	0.77	0.71	0.79
	Human reader*	0.699	-	-

**n* = 49, #AUC based on the performance of the overall ML model. AdaBoost=Adaptive boosting, XGBoost=Extreme gradient boosting, RF=Random forest, DCNN=Deep convolution neural networks, 2D=Two-dimensional, RNN=Recurrent neural network, AUC=Area under the curve

evaluation of myocardial function and motion, AI-assisted diagnosis of cardiomyopathies can be made.[33,34] AI and predictive models can assist to distinguish between similar diseases in clinical practice. The potential for improved diagnostic performance, particularly in the early stages of some cardiomyopathies where no clear structural echocardiographic symptoms may be detected by human perception, may be one of the most significant advantages of AI in this sector. ML approach can support the diagnosis of cardiomyopathies by removing interobserver variability, avoiding wrong decisions from inexperienced colleagues or human misjudgments, and guaranteeing faster and higher quality reports, even in the presence of less highly qualified experience.

The utilization of AI is trending in popularity within cardiology, especially in the context of interpreting large datasets from medical imaging reports to improve the classification of related conditions.[37] In general, AI algorithms fall within the realm of data science and include classical programming and ML, with subsequent applications in health care by analyzing electronic health records or making decisions based on evidence-based guidelines.[38] There are multiple ML algorithms that have been developed for prediction-based tasks or pattern recognition including deep learning (DL) and artificial neural networks (ANNs).[39] DL utilizes techniques that learn the optimal features directly from the dataset, allowing for the automatic discovery of latent data relationships that might otherwise be unknown or hidden at the surface level.[37] ANN is a powerful DL algorithm and is a practical modeling tool with the ability to generalize pattern information to new data, producing reliable estimates and solving complex interactions that may not be observed with traditional statistical methods.[40] A deep-dive overview of the different types of algorithms regarding neural networks and ML taxonomy has been covered in Woodman and Mangoni.[41] ML is a field of learning aspects of AI by developing algorithms that best represent a set of data, divided into two significant categories: supervised and unsupervised learning.[28] Supervised learning techniques involve inferring and mapping functions from inputs to outputs such as logistic regression and support vector machines. In contrast, unsupervised learning aims to learn the properties of the inputs' distribution including clustering and density estimation.[42] The development of clinical-based ML algorithms requires the selection of models using neural networks or decision trees, the specification of ML models such as hyperparameter tuning, and the evaluation of model performances.[43] Hyperparameter optimizations control the overall training process for algorithms and are key to model performance within a specific dataset.[43,44] As such, the selection of which measures to prioritize will depend on user preferences and resources. Differences in the quality of data, sample size, and optimized training of datasets can explain the variation in accuracy of different models.[45] As such, it is important to continue research on human datasets with the goal of enhancing output accuracy of ML algorithms for its use as a prediction tool in clinical practice.

Typical clinical presentation of individuals with TTC is characterized by acute chest pain, shortness of breath, or syncope with new ECG modification such as ST-segment elevation or depression, T-wave inversion, and QTc prolongation.[15] Common profile is a woman patient older than 50 years. Key clinical features in the diagnostic assessment of TTC are female sex, emotional or physical stress, and psychiatric or neurologic disorders.[46] Generally, cardiovascular risk factors[47] are not considered in the diagnostic algorithm of TTC.[15] In our cohort, we found that hypertension was the most common comorbidity observed which is in line with previous studies reported in the literature.[47,48] The distribution of comorbidities was similar in both the TTC cohort and comparators and not statistically different, which also demonstrates that it may be difficult to

Key question

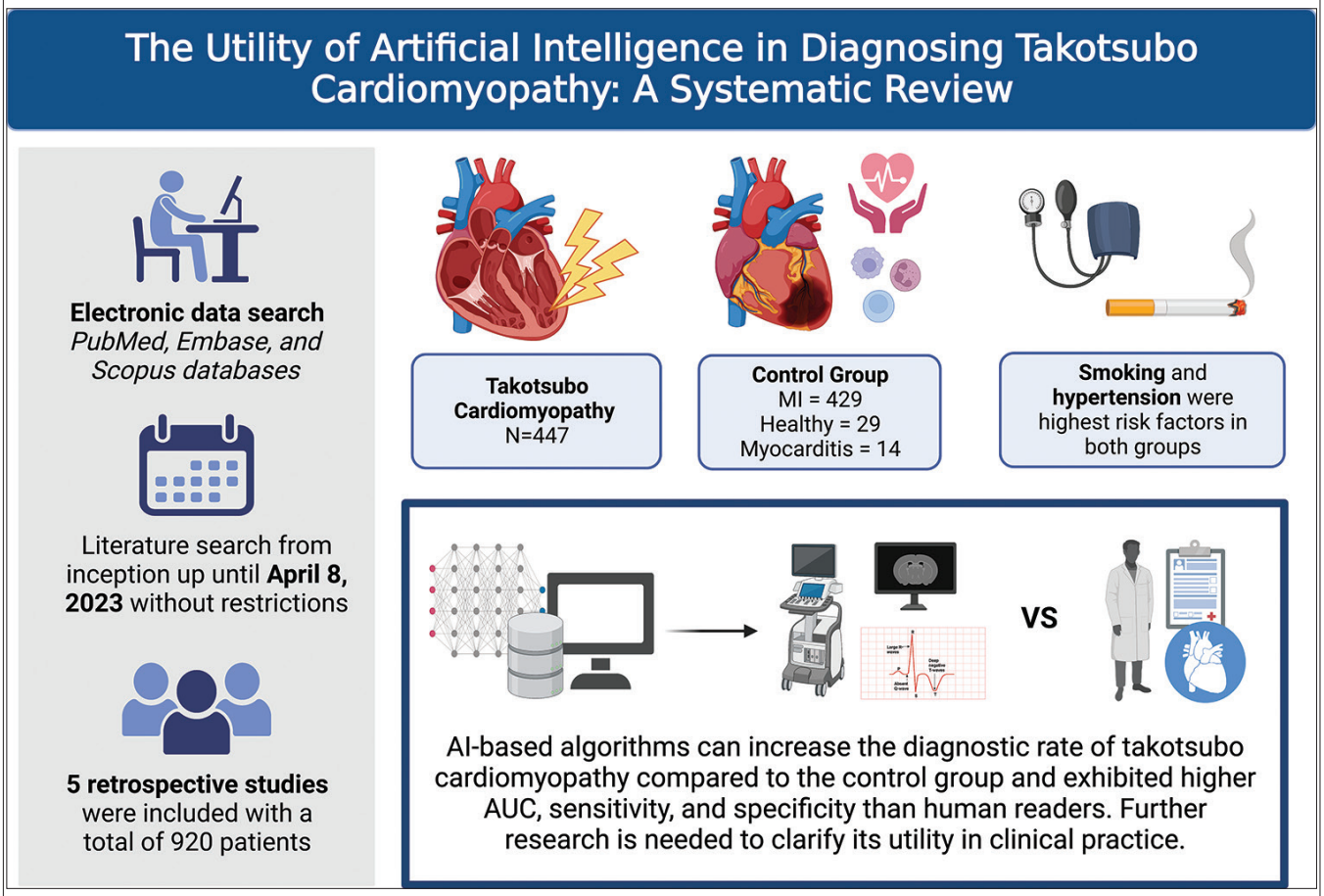
What is the role of artificial intelligence (AI) and machine learning (ML) in the diagnosis of takotsubo cardiomyopathy (TTC) compared to myocardial infarction and healthy controls?

Key finding

Five observational studies reported that AI-based algorithms can increase the diagnostic rate of TTC when compared to healthy controls or myocardial infarction patients. In three of these studies, AI-based algorithms were more sensitive and specific compared to human readers.

Message for readers

AI and ML algorithms can improve the diagnostic capacity of TTC and additionally reduce erroneous human error in differentiating from other cardiovascular conditions. AI is transformative in the field of cardiology, but there is a lack of original studies that exist regarding the key question.



Central Illustration: A summary on the utility of artificial intelligence in takotsubo cardiomyopathy.

distinguish cardiomyopathies compared to other cardiovascular conditions and healthy individuals. Recent work also identified the presence of malignancy as an important of short- and long-term mortality outcomes in TTC.[49]

ECG is the primary investigation to assess individuals with suspected TTC and for the differential diagnosis. In the emergency departments, patients present an ECG with acute changes and ST-segment elevation is the most frequent (44%).[15] Several studies have proposed specific ECG criteria to discriminate TTC from anterior STEMI based on the standard 12-lead ECG.[50-52] ECGs are widely available and often produce raw data that are easily stored in electronic health records and transferred in a digital form, utilized for a variety of cardiovascular conditions during the initial assessment.[53] However, human interpretations of ECG recordings are variable and its reproducibility comes in accordance with levels of expertise and experience for certain disease processes. With currently standardized computer-generated interpretations, there remain limitations regarding the detection of different patterns within an ECG reading when two pathologies present similarly. In the case of TTC, a 12-lead ECG can show similar patterns to a STEMI patient as the degree of ST-elevation/

depression and T-wave inversions vary between conditions.[32,54] However, the findings from Shizimu *et al*. identified in this review suggest that AI-powered ECG interpretations may improve accuracy in diagnosing TTC by identifying possible discriminatory markers on ECG such as normal QRS axis and prolonged QTc intervals to distinguish from AMI. In broader cardiovascular practices, the applications of AI algorithms in ECG interpretations have shown promising results in detecting arrhythmias, ST-segment changes in structural heart disease, and risk prediction for patients at a higher risk of myocardial infarction, stroke, or sudden cardiac death.[53,55-57] Combined, our study suggests that AI-powered ECG is continuously being explored in the context of TTC, but further studies are needed to consolidate these data as this is the only published findings on AI-diagnosed TTC using standard 12-lead ECGs. Given the widespread accessibility of ECGs, understanding the implications of ML algorithms in the interpretation of ECG readings can pave the way to future considerations in diagnosing clinically indistinguishable diseases such as TTC and MI.

In the workup of TTC, echocardiographic imaging is also a key tool to guide toward the diagnosis, follow-up, and, especially, for the differential diagnosis.[2,58] In TTC, regional wall motion abnormalities are independent of the distribution of a single epicardial coronary artery.[59] Indeed, compared to anterior STEMI, individuals with TTC show a circumferential pattern of myocardial dysfunction involving equally and symmetrically the walls supplied by all coronary arteries. In anterior STEMI, wall motion abnormalities are regional and related to the left anterior descending coronary artery as the culprit lesion.[60] While echocardiographic videos are comprehensive in measuring ventricular function, human assessment is limited due to time restriction and may be subject to bias based on experience and personal knowledge. In addition, differences in ML processes and human "judgment calls" may reflect real-life situations of fearing the misdiagnosis of life-threatening pathologies.[61,62] Utilizing DL networks can address these issues by performing real time on individual pixels of data derived from still-frame images and objectively identifying subtle changes in myocardial contractility/function of two indistinguishable pathologies that may go unnoticed by humans.[63] In this context, two of the included studies in this review found that utilizing deep neural learning algorithms outperformed cardiologists by a significant margin when differentiating features of TTC and MI as both conditions vary in contractile function at different time points.[35,36] These findings come in line with previous studies done in cardiovascular practice suggesting improved diagnostic utility in assessing ventricular function and size with AI-employed echocardiograms.[64-67] While future studies should aim to further evaluate differentiating features of TTC on echocardiograms using ML algorithms, such systems emerge as an important tool to deliver precise assessments in cardiology. Perhaps, limitations to routine echocardiography in general may hinder the utility of AI, but a combination of clinical data and biomarkers may improve diagnostic accuracy.

Another type of imaging technique used in the assessment of TTC is CMR. CMR is a unique tool that can further evaluate TTC, adding key information for the characterization of myocardial tissue.[46] The utility of CMR has been extensively investigated in TTC, with guidelines suggesting that TTC patients exhibit a combination of mid-ventricular akinesis and apical sparing, as well as reduced left atrial function, myocardial edema, and absence of gadolinium enhancement.[68-70] In particular, myocardial strain is becoming recognized as a noncontrast quantitative method in CMR assessments that is reliable in diagnosing various cardiovascular diseases processes and TTC.[71] In Cau *et al*.,[33] the application of an ML approach using tree-based ensemble algorithms with noncontrast CMR parameters demonstrated accuracy in diagnosing TTC with further deliberation that left atrial strain is a key imaging marker. Similar methods have been previously investigated in other forms of cardiomyopathy and CAD.[72-76] The utility of AI-powered CMR can additionally be efficient in diagnosing cardiomyopathies as predictions made by models can be made significantly faster than clinicians. In future studies, the integration of DL systems to analyze variables from CMR scans may be beneficial as it had been demonstrated in echocardiograms.

Interestingly, our review also yielded a study testing unconventional imaging techniques such as a brain MRI in the diagnosis of TTC. It is unclear how aberrations on brain imaging could be associated with TTC, but its pathophysiological mechanisms would seem to be linked to excessive sympathetic stimulation with activations of specific brain areas mainly involving the limbic system. In practice, the utility of brain MRIs in TTC is limited given the resource limitations and the lack of clinical indications. Previous studies suggest that patients with TTC exhibit a significant stroke risk in the presence of white matter hyperintensities.[10] The brain–heart interaction is central to the development of TTC, and this could arise from altered neurological networks controlling emotion regulation and autonomic nervous system. Several studies using functional and structural brain MRI have documented these brain alterations such as smaller white matter and gray matter volumes in TTC patients supporting this hypothesis.[6,77,78] Likewise, Klein *et al*.[34] also found a homogeneous neuronal alteration of the emotional-autonomic control system. The evaluation of brain MRIs in its diagnosis is a striking application that could be applicable as an additional clinical feature, given its link to physical and emotional stressors. Published rsfMRI studies found increased connectivity within the orbitofrontal areas that may reflect inefficient emotional regulation in TTC patients.[79] While the application of ML-driven structural MRI measures is considered to be promising in the differentiation of TTC from healthy controls, clinical applicability may be limited in routine cardiovascular care but underscores the importance of the brain–heart axis.

While we shed light on its promising specificity, accuracy, and sensitivity in diagnosing TTC compared to healthy controls, we also acknowledge that more studies should be done to

elaborate on its clinical utility in diagnosing TTC and for other underdiagnosed heart conditions.

At present, challenges and limitations are present in the application of AI and ML in clinical practice. The first issue is related to the data itself, including determining the right dataset needed to optimize algorithms and addressing bias. These challenges are well addressed in a review by Gianfrancesco *et al*., where sources of bias can stem from missing values during data entry, power issues due to inadequate sample size, and errors in measurement due to implicit bias by health-care practitioners and socioeconomic status.[80] The availability of data is key to construct an optimal algorithm and often depends on whether the data are structured, unstructured, semi-structured, or metadata. Structured data are highly organized and easily accessed which can conform to a model following standard order while unstructured data can be more difficult to capture and analyze (i.e., audio files, images, and videos).[45,81] As such, the appropriate algorithms based on these datasets should be considered and thereby guide analyses. For example, classification and regression techniques can facilitate supervised learning while clustering could be considered unsupervised and semi-supervised learning. Holistically, system-related limitations such as data security, infrastructure, integration, and computation may also pose limitations to the widespread use of ML. As discussed by Pastorino *et al*., the increasing use of technology must be facilitated by a stable technological infrastructure to store and converge massive volumes of health-care data such as electronic health records, which are vulnerable to privacy breaches and insecurity.[82] However, administrative and technical safeguards can be implemented to strengthen the privacy of health record databases such as encryption or using gatekeeping techniques with firewalls.[83] Combined, the use of ML is promising in clinical practice, but there must be discussions surrounding the ethical implications of utilizing big data.[84,85]

Our study has several limitations. First, there were limited patient-level data available in the comparator group which may not accurately represent the pooled comparison in comorbidities in our study. In addition to this, we were not able to ascertain the causes of TTC in these studies to perform additional analyses. Second, the overwhelming majority of the comparator group consisted of participants with myocardial infarction and may not accurately represent healthy controls or myocarditis. These limitations could be overcome through further studies on the use of AI and ML in distinguishing TTC from the underrepresented cohorts in our study. Finally, the variability of these algorithms was generalized into AI-based and ML-based techniques, and therefore, the identification of specific clinical features being identified was not possible. To overcome these limitations, further large multicenter studies on the use of AI and ML in TTC diagnosis are needed to ensure reproducibility and generalizability, considering the large heterogeneity of the data.

In conclusion, the applications of AI- and ML-based algorithms are promising in cardiomyopathy research. The integration of AI-based parameters in cardiovascular imaging techniques can improve the early detection and treatment of patients with TTC, with the possibility of shedding light on its use in monitoring the prognosis of certain demographics.

Author contributions

Helen Huang (HH) did the conceptualization of topic and coordination of reading, writing, and editing. All authors contributed to read, write, and edit the original draft. HH and Gary Tse (GT) critically revise the manuscript. HH drafted figures and tables. All authors have given final approval for the current version to be published.

Ethical statement

Ethical statement is not applicable for this article.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

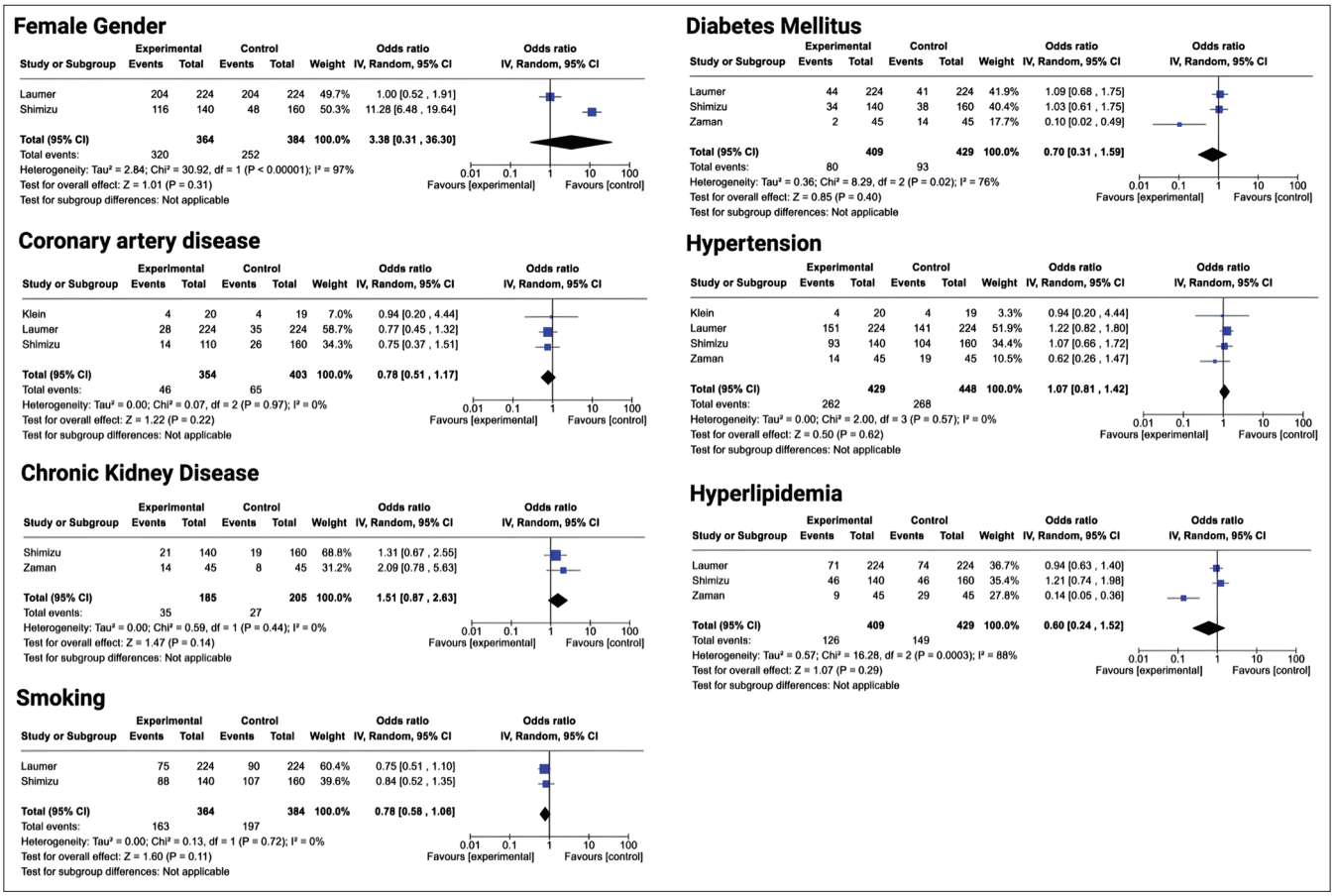
References

1. Medina de Chazal H, Del Buono MG, Keyser-Marcus L, Ma L, Moeller FG, Berrocal D, *et al.* Stress cardiomyopathy diagnosis and treatment: JACC state-of-the-art review. J Am Coll Cardiol 2018;72:1955-71.
2. Lampropoulos K, Giannoulis E, Bazoukis G, Tse G, Triantafyllou E, Triantafyllou A. Reversible stress cardiomyopathy secondary to aneurysmal subarachnoid hemorrhage: A case report. J Emerg Med 2017;53:e129-31.
3. Lyon AR, Citro R, Schneider B, Morel O, Ghadri JR, Templin C, *et al.* Pathophysiology of takotsubo syndrome: JACC state-of-the-art review. J Am Coll Cardiol 2021;77:902-21.
4. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, *et al.* Current state of knowledge on takotsubo syndrome: A position statement from the taskforce on takotsubo syndrome of the heart failure association of the European society of cardiology. Eur J Heart Fail 2016;18:8-27.
5. Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of takotsubo syndrome. Circulation 2017;135:2426-41.
6. Suzuki H, Matsumoto Y, Kaneta T, Sugimura K, Takahashi J, Fukumoto Y, *et al.* Evidence for brain activation in patients with takotsubo cardiomyopathy. Circ J 2014;78:256-8.
7. Tsuchihashi K, Ueshima K, Uchida T, Oh-Mura N, Kimura K, Owa M, *et al.* Transient left ventricular apical ballooning without coronary artery stenosis: A novel heart syndrome mimicking acute myocardial infarction. Angina pectoris-myocardial infarction investigations in Japan. J Am Coll Cardiol 2001;38:11-8.
8. Morel O, Sauer F, Imperiale A, Cimarelli S, Blondet C, Jesel L, *et al.* Importance of inflammation and neurohumoral activation in takotsubo cardiomyopathy. J Card Fail 2009;15:206-13.
9. Ghadri JR, Ruschitzka F, Lüscher TF, Templin C. Takotsubo cardiomyopathy: Still much more to learn. Heart 2014;100:1804-12.
10. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, *et al.* Clinical features and outcomes of takotsubo (stress) cardiomyopathy. N Engl J Med 2015;373:929-38.
11. Prokudina ES, Kurbatov BK, Zavadovsky KV, Vrublevsky AV,

Naryzhnaya NV, Lishmanov YB, *et al.* Takotsubo syndrome: Clinical manifestations, etiology and pathogenesis. Curr Cardiol Rev 2021;17:188-203.

12. Minhas AS, Hughey AB, Kolias TJ. Nationwide trends in reported incidence of takotsubo cardiomyopathy from 2006 to 2012. Am J Cardiol 2015;116:1128-31.
13. Akashi YJ, Nef HM, Lyon AR. Epidemiology and pathophysiology of takotsubo syndrome. Nat Rev Cardiol 2015;12:387-97.
14. Redfors B, Vedad R, Angerås O, Råmunddal T, Petursson P, Haraldsson I, *et al.* Mortality in takotsubo syndrome is similar to mortality in myocardial infarction – A report from the SWEDEHEART registry. Int J Cardiol 2015;185:282-9.
15. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, *et al.* International expert consensus document on takotsubo syndrome (Part I): Clinical characteristics, diagnostic criteria, and pathophysiology. Eur Heart J 2018;39:2032-46.
16. Cusmà-Piccione M, Longobardo L, Oteri A, Manganaro R, Di Bella G, Carerj S, *et al.* Takotsubo cardiomyopathy: Queries of the current era. J Cardiovasc Med (Hagerstown) 2018;19:624-32.
17. Bazoukis G, Bollepalli SC, Chung CT, Li X, Tse G, Bartley BL, *et al.* Application of artificial intelligence in the diagnosis of sleep apnea. J Clin Sleep Med 2023;19:1337-63.
18. Li XM, Gao XY, Tse G, Hong SD, Chen KY, Li GP, *et al.* Electrocardiogram-based artificial intelligence for the diagnosis of heart failure: A systematic review and meta-analysis. J Geriatr Cardiol 2022;19:970-80.
19. Chung CT, Lee S, King E, Liu T, Armoundas AA, Bazoukis G, *et al.* Clinical significance, challenges and limitations in using artificial intelligence for electrocardiography-based diagnosis. Int J Arrhythmia 2022;23:24.
20. Chung CT, Bazoukis G, Lee S, Liu Y, Liu T, Letsas KP, *et al.* Machine learning techniques for arrhythmic risk stratification: A review of the literature. Int J Arrhythmia 2022;23:10.
21. Bazoukis G, Stavrakis S, Zhou J, Bollepalli SC, Tse G, Zhang Q, *et al.* Machine learning versus conventional clinical methods in guiding management of heart failure patients-a systematic review. Heart Fail Rev 2021;26:23-34.
22. Sehly A, Jaltotage B, He A, Maiorana A, Ihdayhid A, Rajwani A, *et al.* Artificial intelligence in echocardiography: The time is now. Rev Cardiovasc Med 2022;23:256.
23. Nedadur R, Wang B, Tsang W. Artificial intelligence for the echocardiographic assessment of valvular heart disease. Heart 2022;108:1592-9.
24. Yoon YE, Kim S, Chang HJ. Artificial intelligence and echocardiography. J Cardiovasc Imaging 2021;29:193-204.
25. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. Environ Int 2018;121:1027-31.
26. Kellermeyer L, Harnke B, Knight S. Covidence and rayyan. J Med Libr Assoc 2018;106:580.
27. EndNote X9 version. Clarivate, 1500 Spring Garden Street, Fourth Floor, Philadelphia, PA 19130. Released July 2018. Available from: https://endnote.com/. [Last accessed on 2023 Jun 10].
28. Xu M, Tantisira KG, Wu A, Litonjua AA, Chu JH, Himes BE, *et al.* Genome wide association study to predict severe asthma exacerbations in children using random forests classifiers. BMC Med Genet 2011;12:90.
29. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015;45:139-45.
30. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
31. Created with BioRender.com. Available from: https://www.biorender.com/. [Last accessed on 2023 Jun 10].
32. Shimizu M, Suzuki M, Fujii H, Kimura S, Nishizaki M, Sasano T. Machine learning of microvolt-level 12-lead electrocardiogram can help distinguish takotsubo syndrome and acute anterior myocardial infarction. Cardiovasc Digit Health J 2022;3:179-88.
33. Cau R, Pisu F, Porcu M, Cademartiri F, Montisci R, Bassareo P, *et al.* Machine learning approach in diagnosing takotsubo cardiomyopathy: The role of the combined evaluation of atrial and ventricular strain, and parametric mapping. Int J Cardiol 2023;373:124-33.
34. Klein C, Hiestand T, Ghadri JR, Templin C, Jäncke L, Hänggi J. Takotsubo syndrome – Predictable from brain imaging data. Sci Rep 2017;7:5434.
35. Laumer F, Di Vece D, Cammann VL, Würdinger M, Petkova V, Schönberger M, *et al.* Assessment of artificial intelligence in echocardiography diagnostics in differentiating takotsubo syndrome from myocardial infarction. JAMA Cardiol 2022;7:494-503.
36. Zaman F, Ponnapureddy R, Wang YG, Chang A, Cadaret LM, Abdelhamid A, *et al.* Spatio-temporal hybrid neural networks reduce erroneous human "judgement calls" in the diagnosis of takotsubo syndrome. EClinicalMedicine 2021;40:101115.
37. Theodosiou AA, Read RC. Artificial intelligence, machine learning and deep learning: Potential resources for the infection clinician. J Infect 2023;87:287-94.
38. Feng J, Phillips RV, Malenica I, Bishara A, Hubbard AE, Celi LA, *et al.* Clinical artificial intelligence quality improvement: Towards continual monitoring and updating of AI algorithms in healthcare. NPJ Digit Med 2022;5:66.
39. Georgevici AI, Terblanche M. Neural networks and deep learning: A brief introduction. Intensive Care Med 2019;45:712-4.
40. Shahid N, Rappon T, Berta W. Applications of artificial neural networks in health care organizational decision-making: A scoping review. PLoS One 2019;14:e0212356.
41. Woodman RJ, Mangoni AA. A comprehensive review of machine learning algorithms and their application in geriatric medicine: Present and future. Aging Clin Exp Res 2023;35:2363-97.
42. Rowe M. An introduction to machine learning for clinicians. Acad Med 2019;94:1433-6.
43. Black JE, Kueper JK, Williamson TS. An introduction to machine learning for classification and prediction. Fam Pract 2023;40:200-4.
44. Pfob A, Lu SC, Sidey-Gibbons C. Machine learning in medicine: A practical introduction to techniques for data pre-processing, hyperparameter tuning, and model comparison. BMC Med Res Methodol 2022;22:282.
45. Sarker IH. Machine learning: Algorithms, real-world applications and research directions. SN Comput Sci 2021;2:160.
46. Pei Q, Mbabazi N, Zou L, Zhang J, Yin H, Li B, *et al.* Mechanisms of myocardial stunning in stress-induced cardiomyopathy. Cardiovasc Innov Appl 2022;7:1.
47. Liang J, Zhang J, Xu Y, Teng C, Lu X, Wang Y, *et al.* Conventional cardiovascular risk factors associated with takotsubo cardiomyopathy: A comprehensive review. Clin Cardiol 2021;44:1033-40.
48. Pelliccia F, Parodi G, Greco C, Antoniucci D, Brenner R, Bossone E, *et al.* Comorbidities frequency in takotsubo syndrome: An international collaborative systematic review including 1109 patients. Am J Med 2015;128:654.e11-9.
49. Guo S, Xie B, Tse G, Roever L, Xia Y, Li G, *et al.* Malignancy predicts outcome of takotsubo syndrome: A systematic review and meta-analysis. Heart Fail Rev 2020;25:513-22.
50. Tamura A, Watanabe T, Ishihara M, Ando S, Naono S, Zaizen H, *et al*. A new electrocardiographic criterion to differentiate between takotsubo cardiomyopathy and anterior wall ST-segment elevation acute myocardial infarction. Am J Cardiol 2011;108:630-3.
51. Kosuge M, Ebina T, Hibi K, Morita S, Okuda J, Iwahashi N, *et al.* Simple and accurate electrocardiographic criteria to differentiate takotsubo cardiomyopathy from anterior acute myocardial infarction. J Am Coll Cardiol 2010;55:2514-6.
52. Ogura R, Hiasa Y, Takahashi T, Yamaguchi K, Fujiwara K, Ohara Y, *et al.* Specific findings of the standard 12-lead ECG in patients with 'takotsubo' cardiomyopathy: Comparison with the findings of acute anterior myocardial infarction. Circ J 2003;67:687-90.
53. Attia ZI, Harmon DM, Behr ER, Friedman PA. Application of artificial intelligence to the electrocardiogram. Eur Heart J 2021;42:4717-30.
54. Frangieh AH, Obeid S, Ghadri JR, Imori Y, D'Ascenzo F, Kovac M, *et al.* ECG criteria to differentiate between takotsubo (stress) cardiomyopathy and myocardial infarction. J Am Heart Assoc 2016;5:e003418.
55. Makimoto H, Höckmann M, Lin T, Glöckner D, Gerguri S, Clasen L, *et al.* Performance of a convolutional neural network derived from an ECG database in recognizing myocardial infarction. Sci Rep 2020;10:8445.

56. Martínez-Sellés M, Marina-Breysse M. Current and future use of artificial intelligence in electrocardiography. J Cardiovasc Dev Dis 2023;10:175.
57. Siontis KC, Noseworthy PA, Attia ZI, Friedman PA. Artificial intelligence-enhanced electrocardiography in cardiovascular disease management. Nat Rev Cardiol 2021;18:465-78.
58. Chiang LL, Tsang SL, Lee JX, Gong M, Liu T, Tse G, *et al.* Takotsubo cardiomyopathy with low ventricular ejection fraction and apical ballooning predicts mortality: A systematic review and meta-analysis. Heart Fail Rev 2021;26:309-18.
59. Citro R, Okura H, Ghadri JR, Izumi C, Meimoun P, Izumo M, *et al.* Multimodality imaging in takotsubo syndrome: A joint consensus document of the European Association of Cardiovascular Imaging (EACVI) and the Japanese Society of Echocardiography (JSE). Eur Heart J Cardiovasc Imaging 2020;21:1184-207.
60. Citro R, Rigo F, Ciampi Q, D'Andrea A, Provenza G, Mirra M, *et al.* Echocardiographic assessment of regional left ventricular wall motion abnormalities in patients with tako-tsubo cardiomyopathy: Comparison with anterior myocardial infarction. Eur J Echocardiogr 2011;12:542-9.
61. Ahuja AS. The impact of artificial intelligence in medicine on the future role of the physician. PeerJ 2019;7:e7702.
62. Darcy AM, Louie AK, Roberts LW. Machine learning and the profession of medicine. JAMA 2016;315:551-2.
63. Poplin R, Varadarajan AV, Blumer K, Liu Y, McConnell MV, Corrado GS, *et al.* Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. Nat Biomed Eng 2018;2:158-64.
64. Muraki R, Teramoto A, Sugimoto K, Sugimoto K, Yamada A, Watanabe E. Automated detection scheme for acute myocardial infarction using convolutional neural network and long short-term memory. PLoS One 2022;17:e0264002.
65. Tabassian M, Alessandrini M, Herbots L, Mirea O, Pagourelias ED, Jasaityte R, *et al.* Machine learning of the spatio-temporal characteristics of echocardiographic deformation curves for infarct classification. Int J Cardiovasc Imaging 2017;33:1159-67.
66. Vidya KS, Ng EY, Acharya UR, Chou SM, Tan RS, Ghista DN. Computer-aided diagnosis of myocardial infarction using ultrasound images with DWT, GLCM and HOS methods: A comparative study. Comput Biol Med 2015;62:86-93.
67. Narang A, Bae R, Hong H, Thomas Y, Surette S, Cadieu C, *et al.* Utility of a deep-learning algorithm to guide novices to acquire echocardiograms for limited diagnostic use. JAMA Cardiol 2021;6:624-32.
68. Eitel I, Behrendt F, Sareban M, Schuler G, Gutberlet M, Thiele H. The utility of cardiovascular magnetic resonance imaging in takotsubo cardiomyopathy (apical ballooning) for differential diagnosis, pathophysiological insights and additional findings. J Cardiovasc Magn Reson 2009;11 Suppl 1:023.
69. Plácido R, Cunha Lopes B, Almeida AG, Rochitte CE. The role of cardiovascular magnetic resonance in takotsubo syndrome. J Cardiovasc Magn Reson 2016;18:68.
70. Bratis K. Cardiac magnetic resonance in takotsubo syndrome. Eur Cardiol 2017;12:58-62.
71. Scatteia A, Baritussio A, Bucciarelli-Ducci C. Strain imaging using cardiac magnetic resonance. Heart Fail Rev 2017;22:465-76.
72. Chong JH, Abdulkareem M, Petersen SE, Khanji MY. Artificial intelligence and cardiovascular magnetic resonance imaging in myocardial infarction patients. Curr Probl Cardiol 2022;47:101330.
73. Zhang N, Yang G, Gao Z, Xu C, Zhang Y, Shi R, *et al.* Deep learning for diagnosis of chronic myocardial infarction on nonenhanced cardiac cine MRI. Radiology 2019;291:606-17.
74. Larroza A, Materka A, López-Lereu MP, Monmeneu JV, Bodí V, Moratal D. Differentiation between acute and chronic myocardial infarction by means of texture analysis of late gadolinium enhancement and cine cardiac magnetic resonance imaging. Eur J Radiol 2017;92:78-83.
75. Overmars LM, van Es B, Groepenhoff F, De Groot MC, Pasterkamp G, den Ruijter HM, *et al.* Preventing unnecessary imaging in patients suspect of coronary artery disease through machine learning of electronic health records. Eur Heart J Digit Health 2022;3:11-9.
76. Gopalakrishnan V, Menon PG, Madan S. cMRI-BED: A novel informatics framework for cardiac MRI biomarker extraction and discovery applied to pediatric cardiomyopathy classification. Biomed Eng Online 2015;14 Suppl 2:S7.
77. Hiestand T, Hänggi J, Klein C, Topka MS, Jaguszewski M, Ghadri JR, *et al.* Takotsubo syndrome associated with structural brain alterations of the limbic system. J Am Coll Cardiol 2018;71:809-11.
78. Khan H, Gamble DT, Rudd A, Mezincescu AM, Abbas H, Noman A, *et al.* Structural and functional brain changes in acute takotsubo syndrome. JACC Heart Fail 2023;11:307-17.
79. Sabisz A, Treder N, Fijałkowska M, Sieminski M, Fijałkowska J, Naumczyk P, *et al.* Brain resting state functional magnetic resonance imaging in patients with takotsubo cardiomyopathy an inseparable pair of brain and heart. Int J Cardiol 2016;224:376-81.
80. Gianfrancesco MA, Tamang S, Yazdany J, Schmajuk G. Potential biases in machine learning algorithms using electronic health record data. JAMA Intern Med 2018;178:1544-7.
81. Arbet J, Brokamp C, Meinzen-Derr J, Trinkley KE, Spratt HM. Lessons and tips for designing a machine learning study using EHR data. J Clin Transl Sci 2020;5:e21.
82. Pastorino R, De Vito C, Migliara G, Glocker K, Binenbaum I, Ricciardi W, *et al.* Benefits and challenges of big data in healthcare: An overview of the European initiatives. Eur J Public Health 2019;29:23-7.
83. Basil NN, Ambe S, Ekhator C, Fonkem E. Health records database and inherent security concerns: A review of the literature. Cureus 2022;14:e30168.
84. Tse G, Lee Q, Chou OH, Chung CT, Lee S, Chan JS, *et al.* Healthcare big data in Hong Kong: Development and implementation of artificial intelligence-enhanced predictive models for risk stratification. Curr Probl Cardiol 2024;49:102168.
85. Wu D, Nam R, Leung KSK, Waraich H, Purnomo A, Chou AHI, *et al.* Population-based clinical studies using routinely collected data in Hong Kong, China: A systematic review of trends and established local practices. CVIA 2023;8.



Supplementary Figure 1: Forest plot of comorbidities in takotsubo cardiomyopathy versus the comparator group

Supplementary Table 1: Search term strategy

Search term	PubMed	EMBASE	SCOPUS
"broken heart syndrome" or "stress cardiomyopathy" or "takotsubo syndrome" or "takotsubo cardiomyopathy" or "takotsubo cardiomyopath*" or "takotsubo" or "stress induced cardiomyopathy"	15,365	11,918	1,309
.("Artificial intelligence" OR "machine learning" OR "Deep learning" OR "AI" OR "ML" OR "DL")	768,736	2,162,798	7,302,540
("diagnos*" OR "prognos*")	6,658,122	8,847,150	12,721,376
1 and 2	224	904	107
1 and 2 and 3	83	652	83

Supplementary Table 2: Newcastle–Ottawa Scale for quality assessment and bias assessment of observational studies

NOS items	Cau *et al*.[33]	Klein *et al*.[34]	Laumer *et al*.[35]	Zaman *et al*.[36]	Shimizu *et al*.[32]
Selection					
Representativeness of exposed cohort	1	1	1	1	1
Selection of the nonexposed cohort	1	1	1	1	1
Ascertainment of exposure	1	1	1	1	1
Demonstration that outcome of interest was not present at the start of the study	1	1	1	1	1
Comparability					
Main factor	1	1	1	1	1
Additional factors	1	1	1	1	0
Outcome					
Assessment of outcomes	1	1	1	1	1
Sufficient follow-up time	0	0	0	0	0
Adequate follow-up time	0	0	0	0	0
Total	7	7	7	7	6

Score of 6+ was considered an adequate quality study. NOS=Newcastle–Ottawa Scale

Supplementary Table 3: Baseline characteristics of takotsubo cardiomyopathy group

Study	Female, *n* (%)	CAD, *n* (%)	HTN, *n* (%)	DM, *n* (%)	HL, *n* (%)	Smoking, *n* (%)	HR, mean (SD)	LVEF %, mean (SD)
Cau *et al*.[33]	17 (94.4)	-	-	-	-	-	-	58.71 (8.9)
Klein *et al*.[34]	20 (100.0)	4 (23.5)	-	-	-	-	74.6 (13.9)	44.9 (13.8)
Laumer *et al*.[35]	204 (91.1)	38 (18.3)	141 (63.9)	44 (19.8	71 (32.8)	75 (34.8)	-	39.85 (10.46)
Zaman *et al*.[36]	116 (82.9)	16 (11.4)	93 (66.4)	34 (24.3)	46 (32.9)	88 (65.7)	86.83 (19.02)	-
Shimizu *et al*.[32]	31 (69.0)	-	14 (31.0)	2 (4.0)	9 (20.0)		-	-

The number (*n*) and percentages (%) are taken from the respective studies. CAD=Coronary artery disease, HTN=Hypertension, DM=Diabetes mellitus, HL=Hyperlipidemia, HR=Heart rate, LVEF=Left ventricular ejection fraction, SD=Standard deviation

Supplementary Table 4: Differences in comorbidities of takotsubo cardiomyopathy versus comparator group

	TTC		Comparator group		*P*
	Total patients, *n* (%)	Total sample, *n* (%)	Total patients, *n* (%)	Total sample, *n* (%)	
Gender	473 (48.6)	920	447 (51.4)	920	0.2629
CAD	42 (10.9)	384	39 (9.7)	403	0.639
HTN	248 (60.6)	409	274 (63.8)	429	0.3543
DM	80 (19.6)	409	93 (21.7)	429	0.4947
CKD	35 (18.9)	185	27 (13.29)	205	0.1291
HL	126 (44.7)	409	149 (34.7)	429	0.2394
Smoking	163 (44.7)	364	197 (51.3)	384	0.0792

Total sample (*n*) and percentage (%) for TTC and comparator groups with comorbidities are based on the total sum from a subset of included studies that reported comorbidities. A two-tailed exact Fisher's test was used for the *P* values, which was considered statistically significant if $P<0.05$. CAD=Coronary artery disease, HTN=Hypertension, DM=Diabetes mellitus, CKD=Chronic kidney disease, HL=Hyperlipidemia, TTC=Takotsubo cardiomyopathy