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Review

Perspectives on Resolving Diagnostic Challenges between Myocardial Infarction and Takotsubo Cardiomyopathy Leveraging Artificial Intelligence

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Abstract: Background: cardiovascular diseases, including acute myocardial infarction (AMI) and takotsubo cardiomyopathy (TTC), are significant causes of morbidity and mortality worldwide. Timely differentiation of these conditions is essential for effective patient management and improved outcomes. Methods: We conducted a review focusing on studies that applied artificial intelligence (AI) techniques to differentiate between acute myocardial infarction (AMI) and takotsubo cardiomyopathy (TTC). Inclusion criteria comprised studies utilizing various AI modalities, such as deep learning, ensemble methods, or other machine learning techniques, for discrimination between AMI and TTC. Additionally, studies employing imaging techniques, including echocardiography, cardiac magnetic resonance imaging, and coronary angiography, for cardiac disease diagnosis were considered. Publications included were limited to those available in peer-reviewed journals. Exclusion criteria were applied to studies not relevant to the discrimination between AMI and TTC, lacking detailed methodology or results pertinent to the AI application in cardiac disease diagnosis, not utilizing AI modalities or relying solely on invasive techniques for differentiation between AMI and TTC, and non-English publications. Results: The strengths and limitations of AI-based approaches are critically evaluated, including factors affecting performance, such as reliability and generalizability. The review delves into challenges associated with model interpretability, ethical implications, patient perspectives, and inconsistent image quality due to manual dependency, highlighting the need for further research. Conclusions: This review article highlights the promising advantages of AI technologies in distinguishing AMI from TTC, enabling early diagnosis and personalized treatments. However, extensive validation and real-world implementation are necessary before integrating AI tools into routine clinical practice. It is vital to emphasize that while AI can efficiently assist, it cannot entirely replace physicians. Collaborative efforts among clinicians, researchers, and AI experts are essential to unlock the potential of these transformative technologies fully.

Keywords: artificial intelligence; acute myocardial infarction (AMI); takotsubo cardiomyopathy (TTC); diagnostic differentiation; machine learning algorithms; echocardiogram

1. Introduction

Takotsubo cardiomyopathy (TTC), also known as stress cardiomyopathy, apical ballooning syndrome, or "broken heart syndrome", is an abrupt catecholamine-induced myocardial inflammation that primarily affects elderly women after experiencing significant stress [1]. It is a short-term, reversible systolic abnormality of the apical left ventricle that resembles a myocardial infarction (MI) but is not due to coronary artery disease (CAD) [2]. Myocardial infarction (MI), also known as a "heart attack", occurs when the blood supply to a region of the myocardium is reduced or completely stopped. MI can be "silent" and go unnoticed, or it can be a catastrophic occurrence that results in hemodynamic decline and untimely death [3]. These two disorders present with equivalent symptoms, such as chest discomfort, dyspnea, electrocardiogram (ECG) abnormalities, and increased cardiac biomarkers [4].

Takotsubo cardiomyopathy (TTC) is becoming more common, which may be due to the increasing prevalence of modern-day stressors, as well as the clinical cardiology community's increased knowledge and detection of the disorder. Studies from different parts of the world have reported that 85–90% of the patients with TTC are women, aged 65–70 years [5]. Takotsubo cardiomyopathy accounts for roughly 2–3% of all acute coronary syndrome patients and 5–6% of female patients, albeit it may be underappreciated and underdiagnosed, particularly in patients with co-existing coronary artery disease [6]. Dana et al. looked over the previous decade, and researchers discovered that takotsubo cardiomyopathy (TTC) accounted for approximately 7% of patients first diagnosed with MI [7]. Several studies have shown that long-term mortality is comparable to that of acute coronary syndrome, with all-cause death occurring in 5.6% of patients per year. Redfors et al. recently revealed that long-term mortality for takotsubo syndrome is comparable to that of patients with non-ST-segment elevation myocardial infarction [6] but lower than that of patients with ST-segment elevation myocardial infarction. Although the exact prevalence is unknown, up to 0.7–2.5% of all patients presenting with an initial clinically diagnosed acute coronary syndrome (ACS) may have TTC, and the overall incidence is likely to be underestimated [8].

Acute detection of takotsubo cardiomyopathy (TTC) is crucial due to differences in care. However, it is challenging given the similarity in clinical presentation, ECG, and cardiac biomarkers characteristics with myocardial infarction [9]. Currently, emergency coronary angiography and ventriculography are eventually needed to confirm the diagnosis [10]. Early differentiation between the two conditions can impact the timing of coronary angiography and the choice of antiplatelet/anticoagulation regimen, especially in patients with multiple comorbidities, such as those experiencing physical stressors like subarachnoid hemorrhage or hemorrhagic stroke, known common causes of TTC [11].

Additionally, patients often mistake TTC for myocardial infarction due to the resemblance in signs and symptoms [11]. From the patient's perspective, the pain experienced in TTC is comparable to that of myocardial infarction [12]. The key distinction is that TTC is associated with emotional stress onset, while MI is usually sudden in onset. In recent years, the application of artificial intelligence (AI) and machine learning algorithms in cardiovascular diagnostics has gained significant interest. This review article specifically focuses on AI's role in distinguishing between myocardial infarction and takotsubo cardiomyopathy, given their clinical similarities. By summarizing existing studies, we aim to highlight AI's potential benefits and limitations in differentiating these two conditions, contributing to improved patient outcomes, and advancing precision medicine in cardiology.

2. Methodology

The literature review was collaboratively conducted by all authors using electronic databases such as PubMed, Google Scholar, Medline, and IEEE Xplore. Search terms included "artificial intelligence", "machine learning", "cardiovascular diagnostics", "myocardial infarction", and "Takotsubo cardiomyopathy". Inclusion criteria focused on studies from the last decade discussing artificial intelligence in cardiovascular diagnostics, parameters for differentiating MI from TTC, and prevalence of TTC. Studies involving human subjects to diagnose myocardial dysfunction using artificial intelligence and reporting relevant metrics were included. Authors were assigned subsections related to different diagnostic approaches. Relevant studies were then compared, and those meeting the criteria were included. The exclusion criteria were implemented to eliminate non-peer-reviewed sources, books, and studies of lower quality, emphasizing a rigorous approach to underscore the role of artificial intelligence in differentiating between the two cardiovascular conditions.

3. Artificial Intelligence in Healthcare

Artificial intelligence (AI) is a field within computer science that possesses the ability to analyze detailed medical information [13]. It is centered around computers acquiring knowledge from data and imitating human cognitive processes [14]. By enhancing learning capabilities, AI is revolutionizing the future of healthcare by offering decision-support systems on a large scale [14]. The capacity of AI to uncover significant correlations within datasets can be harnessed in various clinical scenarios, such as diagnosis, treatment, and prognosis [13,14].

4. Machine Learning in Diagnostics

Within the broader domain of artificial intelligence (AI), machine learning (ML) is a subset that focuses on developing algorithms and models capable of automatically learning and improving from experience without being explicitly programmed [15,16].

The machine learning system operates by combining the principles of both statistics and computer science [16]. This convergence is driven by the unique computational challenges associated with constructing statistical models from massive datasets [17]. The primary subtypes of ML are supervised learning (SL), unsupervised learning (UL), and deep learning (DL). This categorization is determined by the presence or absence of labeled training samples [18], enabling computers to gain knowledge and generate predictions from data [12,15].

4.1. Supervised Machine Learning

Supervised learning (SL) is the predominant machine learning approach employed in medical research [14]. It is clinically applied for the diagnosis and prognosis of diseases and serves the purpose of predicting specific outcomes or accurately classifying cases based on known reference data. In supervised learning, the model is trained using a dataset that contains labeled examples. This training process empowers the model to make predictions on new, unlabeled data [19]. The primary focus of SL lies in addressing classification and regression-based challenges [20] and the modeling methods utilized are support vector machines (SVMs), artificial neural networks (ANNs), and random forests (RFs) [21]. However, supervised learning also comes with limitations, including the requirement of a substantial amount of labeled data for training and the need for validation.

4.2. Unsupervised Machine Learning

Unsupervised learning (UL) is primarily concerned with pattern recognition, making it well-suited for modeling disease mechanisms and uncovering hidden patterns within genotype or phenotype data [14,18]. It utilizes an unlabeled dataset to train the model and reveal intrinsic patterns or relationships within the data. The identified patterns often need to undergo evaluation for their usefulness, either through human analysis or by applying them to a supervised learning task. While supervised learning primarily tackles classification and regression problems, unsupervised learning focuses more on clustering and dimensionality reduction modeling techniques [21,22].

4.3. Deep Learning

Deep learning (DL) has emerged as a prominent subset of machine learning, aiming to mimic human brain capabilities, particularly in computer vision, where neural networks outperformed other techniques in image analysis [20]. Notably, in 2012, during the ImageNet Large-Scale Visual Recognition Challenge (ILSVRC), a deep learning model (specifically, a convolutional neural network) achieved outstanding performance by reducing the error rate to half compared to the other models in the image classification task [23]. These convolutional neural networks (CNNs) are a specific type of deep learning technique, capable of automatically learning a set of feature detectors from a labeled dataset [24]. The application of deep learning (DL) in the field of medical imaging for processing and analyzing data has gained pivotal popularity lately [25].

Although AI is being increasingly applied in healthcare, many research efforts primarily focus on cancer, nervous system disorders, and cardiovascular diseases due to their substantial impact as leading causes of disability and mortality [14]. Improved extraction of clinical insights and their integration into well-trained and validated systems have paved the way for early diagnosis in numerous conditions. This progress allows for the timely detection of various ailments by utilizing valuable clinical knowledge and integrating it into the system effectively [26]. Figure 1 presents the attributes and limitations associated with various machine learning methodologies.

Machine Learning Approaches

Category	Supervised Machine Learning	Unsupervised Machine Learning	Deep Learning
Definition	Algorithm learns from labeled training data to make predictions or classifications	Algorithm identifies patterns or structures in unlabeled data without explicit labels	Neural networks with multiple layers learn hierarchical representations from raw data
Data Requirement	Requires labeled data with input features and corresponding target labels	Works with unlabeled or partially labeled data with input features only	Processes raw data without explicit labeling, but typically requires large amounts of data
Learning Approach	Address classification and regression challenges using labeled data	Discover patterns and relationships in unlabeled data	Utilize neural networks to learn hierarchical representations
Application in Medical field	Diagnosis, prognosis, classification tasks; Examples: Risk prediction for cardiovascular events, ECG analysis for detecting arrhythmia	Applied in Clustering, identification Of disease phenotypes Examples: identify the subtype of heart failure, Grouping cardiac MRI data based on patterns	Automated image recognition and analysis Example: interpretation of Echocardiography, cardiac MRI, detection of atherosclerotic plaques
Modeling Methods	Support Vector Machine (SVM), Artificial Neural Network (ANN), Random Forest (RF)	Clustering algorithms , dimensionality reduction Techniques	Convolutional Neural Networks (CNNs) for image analysis, Recurrent Neural Networks (RNNs) for time series data
Limitations	Require a substantial amount of labeled data, need for validation	Relies on Human analysis or applying to supervised learning tasks for evaluation	Demands computational resources, large amounts of data, and poses interpretability challenges

Figure 1. Machine learning approaches.

5. Significance of Distinguishing MI from Takotsubo Cardiomyopathy

Cardiovascular diseases are responsible for the highest mortality rates in both the United States and worldwide. Based on the NHANES 2013 to 2016 data [27,28], the overall prevalence of cardiovascular disease among adults aged 20 years and above is 48.0%, equivalent to 121.5 million individuals in 2016. Globally in 2016, approximately

17.6 million deaths were attributed to cardiovascular disease (CVD), with a 14.5% increase compared to 2006. The data exhibited a progressive rise in the occurrence of cardiovascular disease (CVD) as individuals advanced in age, evident in both males and females [27]. As a result, it is of utmost importance to develop timely and accurate techniques for diagnosing these life-threatening conditions.

Acute myocardial infarction (MI) and takotsubo cardiomyopathy (TTC) are two cardiovascular emergencies that exhibit striking clinical similarities in their presentations. Distinguishing between the two conditions in the emergency room can be extremely challenging, especially given the limited time available for prompt diagnosis and treatment [9,12]. Figure 2 illustrates the clinical similarities and distinctions between acute myocardial infarction and takotsubo cardiomyopathy.

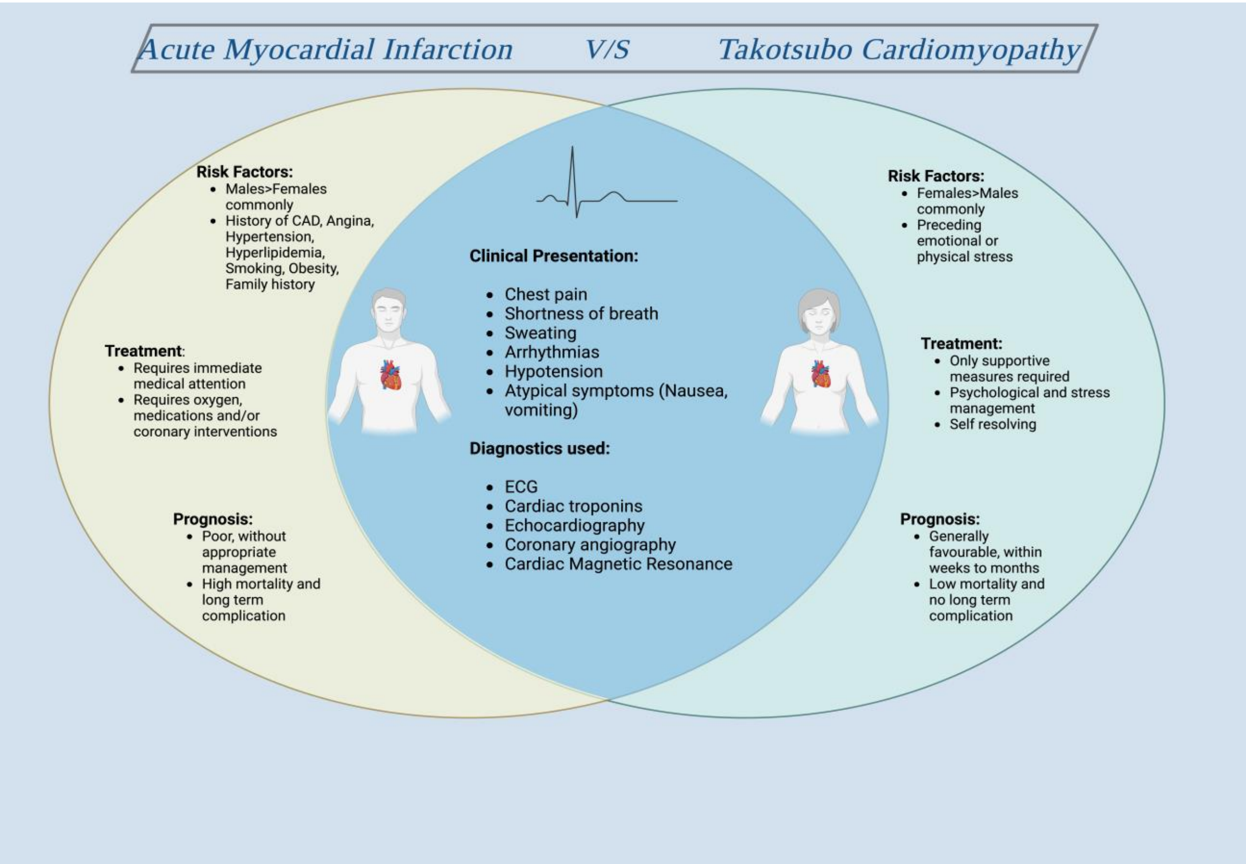

Figure 2. Comparison of acute myocardial infarction (MI) and takotsubo cardiomyopathy (TTC).

Hence, it is crucial to consider takotsubo syndrome (TTC) as a potential alternative diagnosis in patients presenting with chest pain and suspected acute coronary syndrome (ACS), especially when there is a history of intense emotional or physical stress [28]. A cohort study conducted by Frangieh AH, Obeid S et al. compared the clinical presentations and triggers, concluding that there were no significant differences observed between the groups, except for patients with a specific emotional trigger [11].

6. Current Diagnostic Approaches for Myocardial Infarction and Takotsubo Cardiomyopathy

6.1. Cardiac Biomarkers

6.1.1. N-Terminal Pro-B-Type Natriuretic Peptide, Troponin, CK, CK-MB, and Myoglobin

Cardiac biomarkers, such as troponin levels, are crucial for identifying myocardial injury and differentiating between MI and TTC. In MI, troponin levels are elevated due to ongoing myocardial damage caused by ischemia. In TTC, troponin levels may also increase [29], although the rise is typically modest compared to MI. Consequently, relying solely on troponin levels may not be sufficient for distinguishing the two conditions. During the acute phase of takotsubo cardiomyopathy (TTC), significantly elevated levels of serum brain natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) can be detected [29–32]. In the majority of cases, cardiac biomarkers, such as troponin (Tn), creatine kinase (CK), and CK-MB, are slightly elevated [33–35]. While cardiac biomarkers currently lack the specificity [36] needed for a definitive differentiation between takotsubo cardiomyopathy (TTC) and acute coronary syndrome (ACS), they can still be helpful in distinguishing between the two conditions. In challenging situations where obtaining a coronary angiogram is difficult, particularly in high-risk bleeding patients, cardiac biomarkers can be useful in identifying TTC and avoiding unnecessary antithrombotic therapy [4]. According to a study, differentiation between TTC and ACS was achieved using the ratio of peak levels of NT-proBNP (ng/L) to TnT (μg/L) [32]. Relying solely on biomarkers, such as natriuretic peptides (NPs) and troponin levels, for differentiation between the two conditions is limited due to the wide range of elevation observed and the significant overlap between TTC and ACS.

6.1.2. Soluble Suppression of Tumorigenicity 2 (sST2)

sST-2 levels were significantly higher in TTC patients compared to patients with ICMP in a relatively small study. A receiver operating characteristic (ROC) analysis showed that SST-2 was a valuable diagnostic biomarker for identifying TTC when compared to ICMP [37].

6.1.3. Soluble Urokinase Plasminogen Activator Receptor (suPAR)

Elevated suPAR levels have been associated with the development of atherosclerotic lesions and the destabilization of plaque [38,39]. Baseline serum plasma levels of suPAR were highest in patients with ischemic cardiomyopathy (ICMP), but there were no significant differences observed when compared to takotsubo cardiomyopathy (TTC) patients.

6.1.4. Heart-Type Fatty Acid Binding Protein (H-FABP)

In addition to its role as a marker for ischemia and early myocardial damage, H-FABP also serves as a parameter for assessing myocardial stress [40]. Interestingly, in a relatively small study, it was observed that the highest plasma levels of H-FABP were found in patients with dilated cardiomyopathy (DCMP), followed by levels in patients with ischemic cardiomyopathy (ICMP), and with a significant difference, lower levels were seen in patients with takotsubo cardiomyopathy (TTC). This finding suggests a potential clinical utility of H-FABP as a marker for distinguishing between DCMP and TTC [37]. Given that myocardial stunning is the underlying pathogenesis in takotsubo cardiomyopathy (TTC), it appears that TTC patients exhibit lower levels of myocardial stress compared to clinically compensated dilated cardiomyopathy (DCMP) patients [41].

6.1.5. Growth/Differentiation Factor-15 (GDF-15)

GDF-15 is a stress-responsive biomarker of cardiac and vascular disease and has been shown to be up-regulated in the presence of oxidative stress and inflammation. This aligns with previous findings indicating that inflammation and oxidative stress play significant roles in the pathogenesis of takotsubo cardiomyopathy (TTC) [42,43]. GDF-15 exhibited the highest levels in takotsubo cardiomyopathy (TTC) compared to ischemic cardiomyopathy (ICMP), dilated cardiomyopathy, the combined group of ICMP [37], and ACS [44], indicating its potential value in differential diagnosis.

6.2. Electrocardiography ECG

Timely and expeditious electrocardiographic (ECG) testing is essential for individuals presenting with chest pain. It is important to note that women may exhibit atypical symptoms, such as abdominal pain or dizziness, and elderly patients may present primarily with shortness of breath during a myocardial infarction (MI) episode [45–47]. The ECG is highly specific for MI (95% to 97%) but lacks sensitivity (approximately 30%).

The primary objective should be to identify individuals requiring urgent coronary angiography. The majority of takotsubo cardiomyopathy (TTC) patients (80%) display abnormal ECG findings, including ST-segment elevation, T-wave inversion, and transient Q waves [48–50], although this may be an overrepresentation. Like acute myocardial infarction (AMI), the ECG in TTC can reveal localized and dynamic ischemic changes, evolving over time.

A study by Toshiaki et al. assessed ST-segment elevation frequencies in all 12 leads, including treating lead aVR as lead aVR. Compared to anterior AMI, Takotsubo cardiomyopathy exhibited less ST-segment elevation and a higher prevalence of no abnormal Q waves, indicating less myocardial damage. In TTC, ST-segment elevation was more extensive, involving regions beyond the anterior wall. Notably, ST-segment elevation in lead aVR was more frequent in TTC than in AMI, indicating a unique pattern. Lead aVR faces the apical and inferolateral regions, not directly captured by the standard 12 leads, which may explain the diffuse ST-segment elevation observed in TTC, representing widespread wall-motion abnormalities centered around the apex. Conversely, ST-segment elevation in lead V1, reflecting right ventricular anterior and para-septal regions, was rare in TTC due to limited wall-motion abnormalities in that area. These findings suggest that the presence of ST-segment shift in leads aVR and V1 may help differentiate between TTC and anterior AMI in patients admitted within 6 h of symptom onset, although the study sample size was small [51]. In another study [11], patients with MI showed a higher prevalence of ST depression in all ECG leads except aVR. In contrast, TTC cases displayed a higher prevalence of ST-elevation in lead aVR compared to MI. Additionally, T-wave inversion was more commonly seen in TTC, particularly in the lateral and anterior leads. The same study [11] concluded that ST-depression was more prevalent in ST-elevation myocardial infarction (STEMI) compared to TTC across all leads, except for lead aVR, where ST elevation was more common in TTC [11,52]. Conversely, T-wave inversion was observed more frequently in TTC, affecting more than five leads, particularly in the lateral and anterior leads. The study had a large sample size and benefited from being a multicenter registry but had limitations due to its retrospective design and not distinguishing between typical and atypical forms of TTC [11]. Furthermore, in patients with pre-existing conditions like left bundle branch block and pacemakers, the presence of ST-segment elevation and progressive T-wave inversion on ECG might not be reliable criteria for distinguishing between these conditions [53].

Takotsubo cardiomyopathy is often under-recognized and significantly impacts the diagnosis of acute coronary syndromes. Physicians need to be attentive to this condition, as no previous articles have comprehensively analyzed a substantial number of reported TTC cases or conducted literature reviews encompassing all aspects discussed regarding the early stages of the disease [54].

6.3. Cardiac Imaging Techniques

Imaging techniques combined with artificial intelligence (AI) have shown promising results in differentiating myocardial infarction from takotsubo cardiomyopathy.

AI algorithms can be trained to analyze various imaging modalities, such as echocardiography, cardiac MRI, coronary angiography, or nuclear imaging scans, to identify specific patterns and features unique to each condition.

6.3.1. Echocardiography

Also referred to as cardiac ultrasound, echocardiography is presently the most employed noninvasive imaging technique for evaluating patients with diverse cardiovascular conditions [55].

It is essential for identifying the structural and functional abnormalities of the heart. Additionally, it enables the evaluation of intracardiac hemodynamics, providing valuable insights into the heart's performance [55]. Regardless of the significant diagnostic and prognostic benefits of echocardiography, the interpretation and analysis of echo images still heavily rely on the manual efforts of cardiac sonographers [56,57]. Consequently, this can lead to decreased accuracy and efficiency in generating echo reports [57].

Implementing artificial intelligence and machine learning techniques for analyzing echo data has the potential to significantly alleviate the variability and burden related to manual image measurements [56].

This automated approach can drastically reduce the reliance on manual efforts for interpretation and analysis, thereby reducing the risk of human error and optimizing the overall efficiency of reports [57].

A cohort study conducted by Fabian Laumer et al. [57] included 448 patients of TTC (224 patients) and AMI (224 patients), with the purpose of investigating whether machine learning methods applied to echocardiograms could aid in distinguishing these two conditions. The study incorporated clinical data and transthoracic echocardiogram findings from patients diagnosed with acute myocardial infarction (AMI) as well as takotsubo cardiomyopathy (TTC) [58]. A real-time deep learning system was developed for the automated interpretation of echocardiographic images and the study also trained a machine learning system to distinguish between TTC and AMI. The results clearly demonstrated that the system outperformed manual interpretation by a panel of cardiologists, indicating the potential for the future development of fully automated computer-aided decision support systems in the field of echocardiography.

Nicolas et al. conducted a comparative study to assess LV systolic function using a two-dimensional strain in takotsubo cardiomyopathy (TTC) [59]. They studied 42 women divided into three groups: TTC patients (group 1), coronary artery disease patients (group 2), and healthy individuals (group 3). They found that TTC patients showed lower systolic peak velocity, strain, and strain rate compared to healthy individuals ($p < 0.04$). However, LV ejection fractions significantly improved during follow-up ($p < 0.0001$) and all velocity values increased significantly on day 7 compared to the acute phase ($p \leq 0.01$). The study suggested that two-dimensional speckle-tracking echocardiography is a reliable tool for assessing circular dysfunction in TTC patients and monitoring LV functional recovery. They concluded that in the post-acute phase, TTC may mimic LV systematic dysfunction in coronary artery disease, leading to potential misdiagnosis, and this technique is valuable for monitoring LV functional recovery [59].

Another study conducted by Rodolfo Citro et al. [60] compared the echocardiographic distribution of regional wall motion abnormalities (RWMA) between patients with takotsubo cardiomyopathy (TTC) and anterior ST-elevation myocardial infarction (ant-STEMI). They examined 37 TTC and 37 ant-STEMI patients during hospital admission using echocardiography. Results showed that TTC patients had a lower left ventricular ejection fraction and a higher wall motion score index compared to ant-STEMI patients. RWMA in TTC patients involved multiple coronary artery territories, while ant-STEMI patients predominantly showed involvement in the left anterior descending coronary artery territory. The study proposed specific cut-off values to predict TTC based on the number of territories with RWMA. They found that TTC patients exhibit a unique pattern of contractility, with symmetrical RWMA extending equally into the territory of the distribution of all coronary arteries [60]. While these studies demonstrate the usefulness of AI in cardiovascular diagnostics, it is important to emphasize that deep learning algorithms are designed to complement cardiologists' decision-making, not replace it. They serve as valuable tools for providing rapid and accurate analyses of echocardiographic data.

6.3.2. Cardiac MRI

In takotsubo cardiomyopathy, MRI findings usually show the absence of late enhancement on delayed contrast sequences, which sets it apart from anterior ST-elevation myocardial infarction (STEMI). Even in cases of anterior STEMI with no reflow or microvascular obstruction, most patients exhibit evidence of necrosis in the wall, which is not typically observed in takotsubo cardiomyopathy. Although some isolated published cases have described small areas of late enhancement in the apical segment in takotsubo cardiomyopathy, this characteristic finding of absent late enhancement on delayed contrast sequences remains a key differentiating factor [61]. Further research and studies in the radiology field could provide more comprehensive insights into the MRI findings of takotsubo cardiomyopathy and its differentiation from other cardiac conditions [62,63].

6.3.3. Coronary Angiography

Coronary angiography can rule out significant coronary artery blockages in cases where the symptoms might be like MI. This helps in accurately diagnosing TTC and avoiding unnecessary interventions like angioplasty or stent placement, which are typically required for coronary artery blockages seen in MI. While coronary angiography is an essential tool for diagnosing coronary artery disease and evaluating heart vessel abnormalities, it may not be sufficient to differentiate between MI and TTC. A comprehensive evaluation, including patient history, clinical presentation, and additional imaging techniques, is necessary for an accurate diagnosis and appropriate management. AI can analyze coronary angiography images to evaluate the presence and severity of coronary artery disease. AI algorithms can identify differences in the extent and location of coronary artery lesions between MI and TTC. AI can analyze coronary angiography images to evaluate the presence and severity of coronary artery disease. AI algorithms can identify differences in the extent and location of coronary artery lesions between MI and TTC. The diagnosis of takotsubo cardiomyopathy is currently confirmed using invasive coronary angiography, but it is rarely the initial diagnosis upon hospital admission. In the majority of cases, no significant coronary artery stenoses are observed during the angiography. Left ventriculography is a valuable technique for diagnosing and categorizing the condition, as it typically reveals the distinct shape of the left ventricle resembling a Japanese octopus pot, characterized by a round bottom and a narrow neck. About 30% of cases display predominantly mid-ventricular hypokinesis, while there is also a less common basal or "inverted" form [64]. In most stress cardiomyopathy cases, angiography typically does not reveal any obstructive lesions, and only a small number of cases may show minimal medication-inducible vasospasm [61]. Nevertheless, there is increasing clinical evidence suggesting the presence of a possible vasogenic/coronary vascular component. Some studies have reported incidents of single and multifocal coronary vasospasm on angiography, as well as improvements in coronary perfusion with the resolution of myopathy. Additionally, other research has found evidence of plaque rupture/thrombosis in patients with stress cardiomyopathy [65–67]. Patients with stress cardiomyopathy consistently exhibit features of microvascular dysfunction, including impaired endothelium-dependent vasodilation, excessive vasoconstriction, and abnormalities in myocardial perfusion [61,66]. The diagnosis of takotsubo cardiomyopathy is based on various factors, including clinical presentation, changes in electrocardiograms, elevated cardiac biomarkers, and characteristic findings from imaging studies, especially echocardiography. In some cases, coronary angiography may also be conducted to rule out significant coronary artery disease [68]. Figure 3 represents the different perspectives on utilizing artificial intelligence in diagnosing acute myocardial infarction and takotsubo cardiomyopathy.

In medical facilities where primary percutaneous intervention (PCI) is available for both ST-elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI), the likelihood of diagnosing takotsubo cardiomyopathy (TTC) increases when patients undergo early invasive management. However, in institutions without intervention capabilities, relying on first-line fibrinolysis for STEMI, maintaining a high level of suspicion for TTC remains crucial. It is essential to note that suspicion of TTC should not impede the administration of fibrinolytic therapy when it is indicated [54].

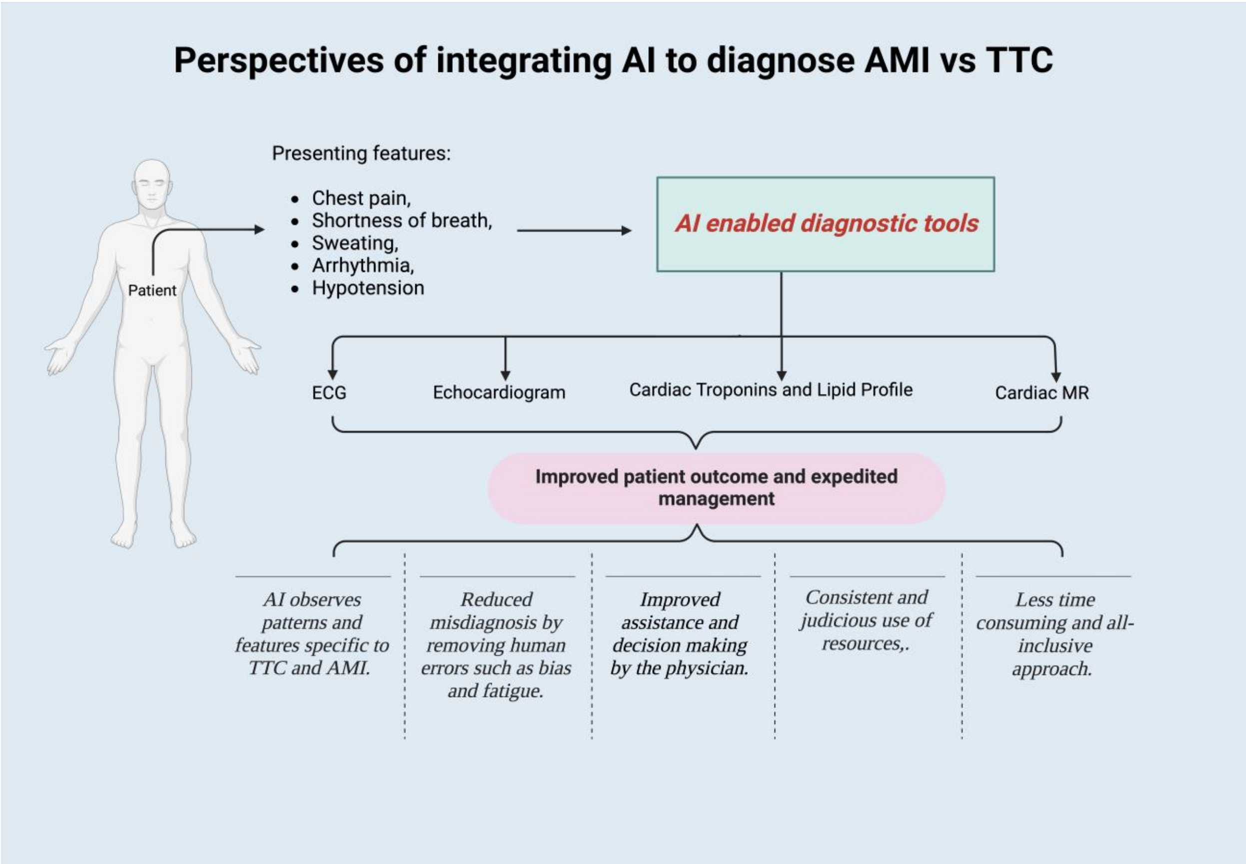

Figure 3. Integrating AI to cardiovascular diagnostics.

6.4. InterTak Score

In a retrospective single-center study to validate a scoring system, a score of ≥50 correctly diagnosed TTC in 85% of cases, while a score of ≤31 correctly diagnosed ACS in 92% of cases. The results confirmed the good accuracy of the score, when using a cut-off value of 45 points, sensitivity was 75%, and specificity was 95% for TTC. However, due to the low prevalence of TTC in the admitted patient population, the sample size was limited, and the statistical significance of certain parameters included in the InterTAK score could not be established. This limits the generalizability of the findings. A prospective approach would be more promising in further evaluating the scoring system and overcoming these limitations [4].

Along with these diagnostic tests, the integration of AI with the InterTAK Diagnostic Score [12] can also smoothly predict TTC in the emergency department. The InterTAK Diagnostic Score can be quickly calculated using seven clinical parameters during the admission process. Points are assigned to each clinical parameter, depending on their diagnostic importance, as follows:

- Female sex—25 points (TTC: the disease shows a strong preponderance toward the female sex, with ~90% of all patients being women [69]).
- Emotional trigger—24 points (emotional and physical trigger factors are typical features of TTC [70].
- Physical trigger—13 points [71].
- Absence of ST-segment depression except in lead aVR—12 points (ST-segment depression is a common finding in AMI, but uncommon in TTC) [4,11,69,71].
- QTc prolongation—6 points (an ECG hallmark of TTC patients) [4,11,69,71].
- Psychiatric disorders—11 points (prevalence of neurologic or psychiatric disorders is twice as high in TTC compared with AMI) [69].

- Neurologic disorders—9 points.

Table 1, depicted below, provides a comparative analysis outlining various diagnostic methods, along with their reliability and accuracy in distinguishing between myocardial infarction (MI) and takotsubo cardiomyopathy (TTC).

Table 1. Comparative analysis outlining various diagnostic methods.

Diagnostic Method	Findings in MI	Findings in TTC	Notes
Troponin, CK, CK-MB, Myoglobin	Elevated levels of troponin, CK-MB, myoglobin	Modest elevation, typically lower than MI	Biomarkers lack specificity, useful in high-risk bleeding patients. May not be solely relied upon to distinguish between the two conditions.
NT-proBNP	Variable levels	Significantly elevated levels noted in acute phase	Can be used as an additional tool to distinguish between ACS and TTC in early stages.
sST2	Elevated	Elevated	Measurement of sST2 used for risk stratification
suPAR	Elevated	No notable distinction.	Elevated levels associated with atherosclerotic lesions and plaque destabilization.
H-FABP	Elevated	Not Elevated	Useful in distinguishing CMP and TTC
GDF-15	Elevated	Significantly Elevated	Useful in differentiating CMP AND TTC
Electrocardiography (ECG)	ST-segment elevation more extensive. Obtain posterior leads V7 to V9 for posterior infarction, pathologic Q waves frequently noted.	Diffuse ST elevation in lead aVR is noted frequently. T-wave inversion in anterior and lateral leads seen more commonly. Pathologic Q waves are uncommon.	Highly specific for MI (95–97%) but lacks sensitivity (30%). ECG can be used to identify location of infarct. ECG in 80% TTC patients show nonspecific findings. ST-segment shift in leads aVR and V1 may help differentiate between TTC and anterior AMI. Not a sole reliable criterion to differentiate
Echocardiography	Detects Wall motion abnormalities based on area of infarct, cavity size, EF, and associated conditions and complications.	Reveals distinct LV shape resembling a Japanese octopus pot. Mid-ventricular hypokinesis is seen	Most-employed noninvasive imaging technique for differentiation
Cardiac MRI	Late enhancement on delayed contrast Most patients exhibit evidence of necrosis in the wall	Absence of late enhancement No evidence of necrosis	Absence of late enhancement on MRI is a key differentiating factor for TTC.
Coronary Angiography	Significant coronary artery blockages	No coronary artery stenosis	Rule out coronary artery blockages, helping diagnose TTC from MI.
InterTak Score	A score of $\leq$31	A score of $\geq$50	Sensitivity 75%, specificity 95%. Rapidly determined in ER using clinical parameters

7. Discussion

Artificial intelligence (AI) and machine learning (ML) are revolutionizing the field of healthcare and medicine by aiding medical professionals. A recent analysis revealed a consistent rise in the quantity of FDA-approved AI/ML-enabled medical devices in the United States, starting from the initial approval in 1995. An apparent increase in the acceptance of these devices began in 2018. The FDA has approved 691 AI/ML-enabled medical devices as of the latest update on 19 October 2023 [72]. According to the significant findings from numerous studies in the past, we suggest the idea of integrating AI and ML algorithms in the field of cardiology to distinguish patients with TTC and AMI and reduce the burden on our healthcare ecosystem. In this article, we propose coalescing AI and ML algorithms with already existing tools to help differentiate AMI and TTC in emergency settings. Consequently, this will aid in improving patient outcomes and time-effectiveness, while simultaneously reducing the overall cost and unnecessary interventions.

A retrospective study by Sainath et al. used a lipid profile to differentiate TTC from AMI [73]. In that study, ten TTC patients' fasting serum lipoprotein levels were compared with forty, age and sex-matched myocardial infarction (MI) patients. The main results of this study were: (a) the TTC group had significantly higher HDL-C (p = 0.008), lower LDL-C (p = 0.0002), and lower triglycerides (p < 0.0001) compared to age and sex-matched MI patients and (b) hyperalphalipoproteinemia or mild hypotriglyceridemia was noted in 40% of the TTC patients.

Caroline et al. conducted another study using ECG changes and discovered distinct differences in the evolution of the ECGs among their group of patients [74]. The subjects were compared head-to-head for ECG changes in the early phase of post-acute TTC versus AMI in age- and gender-matched subjects, which is especially relevant to the QTc interval, which is gender-dependent. On the presenting (day 0) ECG, a lesser number of total abnormal leads were observed (most likely due to the lack of reciprocal changes, as shown by Kosuge et al.), as well as a comparable number of leads with ST elevation, less magnitude of ST elevation, and fewer Q waves, in the takotsubo patients [51]. In addition, they reported more ST elevation in the takotsubo patients; however, the two groups were not gender-matched [51]. The lesser magnitude of ST elevation and the more frequent absence of Q waves in TTC suggest myocardial necrosis, which was confirmed by the CMR findings of the absence of late gadolinium enhancement [74]. When looking at how the ECG changed over time, the first thing that stood out was that the T-wave inversion in TTC seemed to get deeper and/or more widespread in the first 4 days after the acute event. Secondly, there was an obvious pattern of opposite directional change in the daily increasing mean QTc in TTC, contrasting with the gradual shortening towards normal values in the AMI group. This is the first study comparing age and gender-matched populations, and since the normal QTc is different in women (≤450 ms) compared to men (≤440 ms) in those aged 40–69, this is an important finding [75]. Migliore et al. also described several patients with deep T-wave inversion in a TTC-like pattern associated with significant myocardial edema and reversible LV dysfunction of different causes [76,77]. Marra then demonstrated a correlation between regional myocardial edema and T-wave inversion in patients with takotsubo syndrome [78]. These characteristics can be used in the future to further add to diagnostic certainty.

The first-line imaging modality for evaluating TTC is transthoracic echocardiography (TTE) [79]. TTE provides useful information about multiple cardiac parameters and is also helpful in identifying patients at higher risk of adverse outcomes [80,81]. The "apical" and "mid-ventricular" ballooning types make up the vast majority of TTC. Myocardial dysfunction outside of the confines of a single coronary artery characterizes both types [60,79,82–84]. This circumferential pattern of myocardial dysfunction represents a hallmark for diagnosing TTC [79]. RV involvement, such as in "biventricular" ballooning, reinforces the diagnostic suspicion of TTC and has been associated with adverse in-hospital outcomes [34,85]. During the acute phase of TTC, echocardiography can assist in monitoring the spontaneous recovery of systolic function, which is typical of TTC [86]. Dynamic left ventricular outflow tract obstruction (LVOTO) and transient moderate-to-severe mitral regurgitation (MR) have shown prevalence of about 12.8% to 25% and about 20 to 25% of TTC patients, respectively [85,87,88]. Since the presence of LVOTO and MR simultaneously can have severe implications, early echocardiographic diagnosis becomes important for appropriate therapeutic management. Using 3D echocardiography, small thrombi can be detected in TTC patients [83,89]. Although left ventricular free wall rupture is a rare finding (<1%) in TTC, it can lead to higher mortality. Early echocardiographic detection and rapid surgery have become important for positive outcomes [90]. Thus, echocardiography, in combination with machine learning tools, can surely and rapidly differentiate TTC from AMI.

Marco et al. proposed using ECG and echocardiographic parameters, as well as two new indexes, to distinguish TTC from AMI based on ventricular involvement and the inferior-apex ratio (IAR) and the inferior-lateral-apex ratio (ILAR) [91]. The results showed that IAR and ILAR can easily measure impaired contractility that goes beyond the apex and affects the mid-inferior and inferior-lateral walls. This makes it easy to tell the difference between TTC and extensive anterior STEMI without doing anything invasive [91].

In another retrospective study, Riccardo et al. compared five different non-contrast cardiac magnetic resonance (CMR) models based on machine learning to traditional CMR models based on gadolinium in three groups [92]. The results proved that the tree-based ensemble machine learning algorithm showed a sensitivity of 92% (95% CI 78–100), specificity of 86% (95% CI 80–92), and area under the ROC of 0.94 (95% CI 0.90–0.99) in diagnosing TTC. Hence, supporting the use of machine learning to diagnose TTC with good accuracy.

Along with these diagnostic tests, integrating AI with the InterTAK Diagnostic Score can also smoothly predict TTC in the emergency department [12]. The InterTAK Diagnostic Score can be quickly calculated using seven clinical parameters during the admission process in the emergency department. Results by Jbyudyta Samul-Jastrzębska et al. confirmed the good accuracy of the score. When using a cut-off value of 45 points, sensitivity was 75% and specificity was 95% for TTC [4]. When patients with a score of $\geq$50 were diagnosed with TTC, 85% were correctly diagnosed. When patients with a score of 31 were diagnosed with ACS, 92% of them were correctly identified. Noticeably, the InterTAK Diagnostic Score should be considered in symptomatic patients with no ST-segment elevation [50,93].

The gold standard test for atherosclerotic coronary artery disease (CAD) is coronary angiography. Being an invasive procedure, Tavakol et al. mentioned the specific patient-dependent and procedure-related complications that are inherent to the test [94]. The severity of complications may vary greatly, from small issues with immediate consequences to life-threatening circumstances that may result in irreparable harm. The patient might have heparin-induced thrombocytopenia or an allergic response to the contrast material. It is costly and has hazards, such as problems at the vascular access site and nephropathy brought on by the contrast agent [95]. A hematoma, retroperitoneal hemorrhage, pseudoaneurysm, dissection, or arteriovenous fistula may all result from local vascular damage. Infections and sepsis result from improper sterilization. Rarely, thrombosis, cholesterol emboli, and mortality have also been reported, along with conduction abnormalities. The patient's chance of developing cancer rises due to extended radiation exposure. So, it makes sense to choose non-invasive procedures over invasive ones.

8. Limitations Using AI to Distinguish TTC from AMI

Although AI and machine learning models come with unparalleled positive perspectives, they also have their own limitations and challenges. Both TTC and AMI require prompt and appropriate management. Any delay can lead to adverse outcomes in either condition. Hence, overcoming technical and logistical challenges can be complex.

Firstly, devising the algorithm for an AI diagnostic model often requires an extensive amount of data, good informatics skills, and an appropriate definition of the reference standard [96]. TTC is a relatively rare disease, and most of the studies regarding the clinical applications of AI have been retrospective. AI algorithms must still be validated in large, multicenter studies [97].

Secondly, AI is constantly developing and evolving. Thus, models continually change over time, requiring frequent updating and regular training. Also, some diagnostic methodologies, such as the echocardiogram, are technician-dependent, impacting the clinical application of AI as a result of vendor-dependent setup differences. The frequent inability to obtain optimal image quality or precise views can also have an impact on AI clinical applications as a result of vendor-dependent setup differences [98].

Another significant problem in devising the algorithm is overfitting. It occurs when the algorithm is excessively tailored to the training sample rather than finding relevant features and relations. Hence, it makes almost perfect predictions on it, but at the price of generalization, therefore decreasing its performance on other populations. This issue can be solved by the inclusion of more data or subtle modifications to the training set [99]. Additionally, large amounts of low-quality data are often used, limiting the potential of classifiers, as they may find patterns that are not useful in real-life clinical practice [100]. In these scenarios, preprocessing by another operator may, conversely, increase the burden on healthcare professionals.

9. Ethical Challenges in Using AI to Distinguish TTC from AMI

AI also brings some ethical and legal challenges with it. The primary ethical challenges that are faced to realize the full potential of AI in healthcare are discussed as follows.

9.1. Informed Consent to Use

Patients may not feel comfortable providing their data for studies of AI applications, limiting future prospective trials and studies. The need to investigate conditions under which the principles of informed consent should be used in the field of clinical AI. To what degree are clinicians obligated to educate patients about the intricacies of AI and the specific ML techniques employed by the system, the types of data inputs utilized, and the potential presence of biases or other limitations in the data being utilized? When are clinicians required to inform patients about the utilization of AI? Answering these concerns becomes more problematic when the AI utilizes "black-box" methods, which might arise from non-interpretable machine-learning methodologies that clinicians find extremely tricky to comprehend entirely [92,101].

9.2. Safety and Transparency

The used datasets need to be reliable and valid. The better the training dataset is, the better the performance of AI will be [102]. In addition, the algorithms often need further refinement to generate accurate results. For this, vast amounts of data and, thus, more data sharing will be necessary [102]. In general, it always depends on the particular AI and its tasks as to how much data will be required.

For patient safety as well as patient confidence, some amount of transparency must be ensured. Although it would be great for all data and algorithms to be openly accessible to the public, there are valid concerns, like safeguarding against data breaches and minimizing cybersecurity risks. Using third-party or governmental audits may serve as a viable solution for this issue [103].

9.3. Algorithmic Fairness and Biases

Any ML system or human-trained algorithm will only be as trustworthy, effective, and fair as the data that it is trained with. AI also bears a risk for biases and, hence, discrimination. Additionally, these studies often have small sample sizes since TTC is a very rare diagnosis and needs a larger number of subjects to validate the results [26]. Therefore, it is vital that AI makers are aware of this risk and minimize potential biases at every stage in the process of product development [103].

10. Future Perspective Harnessing AI for Transformative Healthcare in Cardiology

In the rapidly evolving landscape of healthcare, the integration of artificial intelligence (AI) holds immense potential for revolutionizing cardiology. To fully unlock the benefits of AI, a multi-faceted approach encompassing education, regulation, and technological infrastructure is essential.

10.1. Educational Awareness as a Catalyst for Transformation

For AI to seamlessly integrate into cardiology, a comprehensive educational framework is imperative. This involves not only training scientists and physicians, but also educating the broader public about AI and its applications. Universities are beginning to adapt by incorporating medical engineering, computational sciences, coding, and algorithmics into their curricula. Short courses and postgraduate degrees focused on AI in healthcare further empower professionals to navigate the intricacies of this innovative technology. Well-educated physicians play a pivotal role, not only in fostering the adoption of innovative applications, but also in raising awareness about ethical and privacy considerations.

10.2. Regulatory Frameworks for Trust and Safety

The nascent nature of AI in healthcare necessitates robust regulatory frameworks to ensure safety, efficacy, and ethical use. Regulatory bodies, such as the FDA and the European Union, have taken steps to establish guidelines for AI-based medical devices [104,105]. Continuous updates and upgrades of AI products should be subject to periodic evaluations to prevent drift over time, ensuring ongoing reliability and adherence to clinical standards.

10.3. AI in Cardiology: Transforming Patient Care

Cardiologists are poised to witness a paradigm shift in their daily practice as AI becomes an integral part of cardiovascular care. From effective phenotyping of patients to the design of predictive models for various diseases, AI offers the potential to enhance non-invasive diagnostics and reduce the reliance on costly and invasive tests for conditions like coronary artery disease (CAD). Future cardiologists armed with AI insights will be able to provide personalized risk assessments, enabling early intervention and preventive measures.

10.4. Digital Transformation and AI Integration

AI's role extends beyond the realm of healthcare into the broader digital transformation sweeping across the world. The wealth of digital data, particularly from Electronic Health Records (EHR), combined with advancements in computer technology and the internet, creates an environment ripe for AI growth [106]. Integrating AI in cardiac care spans diverse areas, including cardiac imaging, risk prediction, daily decision-making processes, such as diagnosis and treatment, and the development of algorithms aligned with clinical guidelines. One such example of harnessing AI is using a commercially available smartwatch sensor to monitor atrial fibrillation in the population, and the findings were comparable to the traditional insertable cardiac monitor arm in the study [107].

10.5. Future Research

For a promising future, building effective AI solutions requires extensive research and trials. Access to extensive, high-quality datasets, infrastructure, and related technologies is crucial. The importance of collaborative efforts to gather, curate, and share datasets to drive innovation in cardiac care cannot be emphasized enough.

Embracing these future perspectives ensures that AI becomes a transformative force in cardiology, enhancing patient care, streamlining diagnostics, and empowering healthcare professionals to make informed, accurate decisions in an increasingly digital healthcare landscape.

11. Patient-Centered Perspectives

Artificial Intelligence (AI) is rapidly transforming the field of cardiology, introducing innovative approaches to diagnose, predict, and treat cardiovascular diseases. This paradigm shift is not only driven by technological advancements, but also holds immense promise for enhancing patient-centered care. The synergy between these perspectives emphasizes the transformative potential of AI in shaping the future of personalized and effective cardiovascular medicine.

11.1. Patient Experience

- Using AI promises greater diagnostic precision and efficacy by analyzing extensive patient and clinical data, reducing misdiagnosis due to human errors and clinician fatigue.
- Faster diagnostics with the assistance of AI algorithms provide consistent and standardized interpretations of the data. This will speed up the management process and improve efficiency by rapidly expediting the diagnostic process and analyzing data faster than manual methods [108]. Additionally, reducing wait times and alleviating patient anxiety.

11.2. Patient–Physician Interaction

- AI aids communication, facilitating informed discussions between patients and physicians.
- Time-efficient AI tools allow physicians to focus on meaningful interactions, contributing to better decision-making.
- AI algorithms reduce clinician burden and decrease fatigue by expediting the diagnostic process.

11.3. Patient Outcomes

- Early detection, personalized care pathways, and remote monitoring enhance patient well-being.
- Continuous monitoring and follow-up optimize long-term health.

Artificial intelligence has the power to revolutionize the field of cardiology, offering new and innovative ways to diagnose, predict, and treat cardiovascular diseases. By leveraging AI technologies, we can improve the accuracy and efficiency of diagnosis, develop personalized treatment plans, and, ultimately, improve patient outcomes. By harnessing the power of AI to analyze complex datasets and identify patterns and trends, we have the potential to achieve more precise and effective cardiovascular care. Ultimately, the use of AI in cardiology offers a unique opportunity to transform the way we approach patient care and promote equitable healthcare outcomes, paving the way for a future of more personalized and effective cardiovascular medicine.

The development of novel technologies is needed to benefit patients by improving diagnostic accuracy and providing personalized therapy that is focused on extending the quantity and quality of life.

12. Conclusions

The amalgamation of machine learning methods with already existing modalities has shown success in differentiating AMI from takotsubo cardiomyopathy. Importantly, while AI shows promise, more extensive studies are required in the future for thorough validation and implementation. A collective effort of AI experts, doctors, and regulatory bodies is indispensable for the secure and reliable use of machine learning technology for diagnosis and patient care. AI cannot entirely replace a physician but can serve as an assistant to the physician.

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References

1. Horowitz, J.D.; Nguyen, T.H. Differentiating Tako-tsubo cardiomyopathy from myocardial infarction. *Eur. Soc. Cardiol.* **2014**, *13*, N7.
2. Amin, H.Z.; Amin, L.Z.; Pradipta, A. Takotsubo Cardiomyopathy: A Brief Review. *J. Med. Life* **2020**, *13*, 3–7. [CrossRef] [PubMed]
3. Ojha, N.; Dhamoon, A.S.; Chapagain, R. Myocardial Infarction (Nursing). In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2024. Available online: http://www.ncbi.nlm.nih.gov/pubmed/33760446 (accessed on 18 July 2023).
4. Samul-Jastrzębska, J.; Roik, M.; Wretowski, D.; Łabyk, A.; Ślubowska, A.; Bizoń, A.; Paczyńska, M.; Kurnicka, K.; Pruszczyk, P.; Ciurzyński, M. Evaluation of the InterTAK Diagnostic Score in differentiating Takotsubo syndrome from acute coronary syndrome. A single center experience. *Cardiol. J.* **2021**, *28*, 416–422. [CrossRef] [PubMed]
5. Y-Hassan, S.; Tornvall, P. Epidemiology, pathogenesis, and management of takotsubo syndrome. *Clin. Auton. Res.* **2018**, *28*, 53–65. [CrossRef] [PubMed]
6. Singh, T.; Khan, H.; Gamble, D.T.; Scally, C.; Newby, D.E.; Dawson, D. Takotsubo Syndrome: Pathophysiology, Emerging Concepts, and Clinical Implications. *Circulation* **2022**, *145*, 1002–1019. [CrossRef] [PubMed]
7. Meng, L.-P.; Zhang, P. Takotsubo cardiomyopathy misdiagnosed as acute myocardial infarction under the Chest Pain Center model: A case report. *World J. Clin. Cases* **2022**, *10*, 2616–2621. [CrossRef] [PubMed]
8. Carita, P.; Fazio, G. Takotsubo cardiomyopathy. *Counc. Cardiol. Pract.* **2010**, *8*. Available online: https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-8/Takotsubo-cardiomyopathy (accessed on 17 July 2023).
9. Hinojos, A.; Vanhecke, T.E.; Enright, S.; Elg, N.; Gifft, K.; Marengo, B.; Rao, S. Takotsubo Cardiomyopathy and Non-ST-Segment Elevation Myocardial Infarction: Predictors of Left Ventricular Dysfunction. *Clin. Med. Insights Cardiol.* **2017**, *11*, 117954681771610. [CrossRef] [PubMed]
10. Dahal, S.; Budoff, M.J.; Roy, S.K. Coronary Computed Tomography Angiography for Evaluation of Chest Pain in the Emergency Department. *Tex. Heart Inst. J.* **2022**, *49*, e217550. [CrossRef]
11. Frangieh, A.H.; Obeid, S.; Ghadri, J.; Imori, Y.; D'Ascenzo, F.; Kovac, M.; Ruschitzka, F.; Lüscher, T.F.; Duru, F.; Templin, C.; et al. ECG Criteria to Differentiate Between Takotsubo (Stress) Cardiomyopathy and Myocardial Infarction. *J. Am. Heart Assoc.* **2016**, *5*, e003418. [CrossRef]
12. Templin, C.; Ghadri, J.R.; Diekmann, J.; Napp, L.C.; Bataiosu, D.R.; Jaguszewski, M.; Cammann, V.L.; Sarcon, A.; Geyer, V.; Neumann, C.A.; et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *N. Engl. J. Med.* **2015**, *373*, 929–938. [CrossRef]
13. Holmes, J.; Sacchi, L.; Bellazzi, R. Artificial intelligence in medicine. *Ann. R. Coll. Surg. Engl.* **2004**, *86*, 334–338.
14. Noorbakhsh-Sabet, N.; Zand, R.; Zhang, Y.; Abedi, V. Artificial Intelligence Transforms the Future of Health Care. *Am. J. Med.* **2019**, *132*, 795–801. [CrossRef] [PubMed]
15. Deo, R.C. Machine Learning in Medicine. *Circulation* **2015**, *132*, 1920–1930. [CrossRef]
16. Mitchell, T.M. *Machine Learning*; McGraw-Hill series in Computer Science; Nachdr.; McGraw-Hill: New York, NY, USA, 2013; ISBN 978-0-07-042807-2.
17. Hastie, T.; Tibshirani, R.; Friedman, J.H. *The Elements of Statistical Learning: Data Mining, Inference, and Prediction*, 2nd ed.; Springer Series in Statistics; Corrected at 12th Printing 2017; Springer: New York, NY, USA, 2009; ISBN 978-0-387-84857-0.
18. Petegrosso, R.; Li, Z.; Kuang, R. Machine learning and statistical methods for clustering single-cell RNA-sequencing data. *Brief. Bioinform.* **2019**, *21*, 1209–1223. [CrossRef] [PubMed]
19. Pruneski, J.A.; Pareek, A.; Kunze, K.N.; Martin, R.K.; Karlsson, J.; Oeding, J.F.; Kiapour, A.M.; Nwachukwu, B.U.; Williams, R.J. Supervised machine learning and associated algorithms: Applications in orthopedic surgery. *Knee Surg. Sports Traumatol. Arthrosc.* **2022**, *31*, 1196–1202. [CrossRef]
20. Eraslan, G.; Avsec, Ž.; Gagneur, J.; Theis, F.J. Deep learning: New computational modelling techniques for genomics. *Nat. Rev. Genet.* **2019**, *20*, 389–403. [CrossRef]
21. Handelman, G.S.; Kok, H.K.; Chandra, R.V.; Razavi, A.H.; Lee, M.J.; Asadi, H. eDoctor: Machine learning and the future of medicine. *J. Intern. Med.* **2018**, *284*, 603–619. [CrossRef] [PubMed]
22. Yan, J.; Wang, X. Unsupervised and semi-supervised learning: The next frontier in machine learning for plant systems biology. *Plant J.* **2022**, *111*, 1527–1538. [CrossRef]

23. Russakovsky, O.; Deng, J.; Su, H.; Krause, J.; Satheesh, S.; Ma, S.; Huang, Z.; Karpathy, A.; Khosla, A.; Bernstein, M.; et al. ImageNet Large Scale Visual Recognition Challenge. *Int. J. Comput. Vis.* **2015**, *115*, 211–252. [CrossRef]
24. Yamashita, R.; Nishio, M.; Do, R.K.G.; Togashi, K. Convolutional neural networks: An overview and application in radiology. *Insights Imaging* **2018**, *9*, 611–629. [CrossRef] [PubMed]
25. Cai, L.; Gao, J.; Zhao, D. A review of the application of deep learning in medical image classification and segmentation. *Ann. Transl. Med.* **2020**, *8*, 713. [CrossRef] [PubMed]
26. Jiang, F.; Jiang, Y.; Zhi, H.; Dong, Y.; Li, H.; Ma, S.; Wang, Y.; Dong, Q.; Shen, H.; Wang, Y. Artificial intelligence in healthcare: Past, present and future. *Stroke Vasc. Neurol.* **2017**, *2*, 230–243. [CrossRef] [PubMed]
27. Benjamin, E.J.; Muntner, P.; Alonso, A.; Bittencourt, M.S.; Callaway, C.W.; Carson, A.P.; Chamberlain, A.M.; Chang, A.R.; Cheng, S.; Das, S.R.; et al. Heart Disease and Stroke Statistics—2019 Update: A Report from the American Heart Association. *Circulation* **2019**, *139*, e56–e528. [CrossRef] [PubMed]
28. Assad, J.; Femia, G.; Pender, P.; Badie, T.; Rajaratnam, R. Takotsubo Syndrome: A Review of Presentation, Diagnosis and Management. *Clin. Med. Insights Cardiol.* **2022**, *16*, 117954682110657. [CrossRef] [PubMed]
29. Doyen, D.; Moceri, P.; Chiche, O.; Schouver, E.; Cerboni, P.; Chaussade, C.; Mansencal, N.; Ferrari, E. Cardiac biomarkers in Takotsubo cardiomyopathy. *Int. J. Cardiol.* **2014**, *174*, 798–801. [CrossRef] [PubMed]
30. Nguyen, T.H.; Neil, C.J.; Sverdlov, A.L.; Mahadavan, G.; Chirkov, Y.Y.; Kucia, A.M.; Stansborough, J.; Beltrame, J.F.; Selvanayagam, J.B.; Zeitz, C.J.; et al. N-Terminal Pro-Brain Natriuretic Protein Levels in Takotsubo Cardiomyopathy. *Am. J. Cardiol.* **2011**, *108*, 1316–1321. [CrossRef]
31. Pilgrim, T.M.; Wyss, T.R. Takotsubo cardiomyopathy or transient left ventricular apical ballooning syndrome: A systematic review. *Int. J. Cardiol.* **2008**, *124*, 283–292. [CrossRef]
32. Fröhlich, G.M.; Schoch, B.; Schmid, F.; Keller, P.; Sudano, I.; Lüscher, T.F.; Noll, G.; Ruschitzka, F.; Enseleit, F. Takotsubo cardiomyopathy has a unique cardiac biomarker profile: NT-proBNP/myoglobin and NT-proBNP/troponin T ratios for the differential diagnosis of acute coronary syndromes and stress induced cardiomyopathy. *Int. J. Cardiol.* **2012**, *154*, 328–332. [CrossRef]
33. Bonaca, M.P.; Morrow, D.A. Defining a Role for Novel Biomarkers in Acute Coronary Syndromes. *Clin. Chem.* **2008**, *54*, 1424–1431. [CrossRef]
34. Akashi, Y.J.; Nef, H.M.; Möllmann, H.; Ueyama, T. Stress Cardiomyopathy. *Annu. Rev. Med.* **2010**, *61*, 271–286. [CrossRef] [PubMed]
35. Bielecka-Dabrowa, A.; Mikhailidis, D.P.; Hannam, S.; Rysz, J.; Michalska, M.; Akashi, Y.J.; Banach, M. Takotsubo cardiomyopathy—The current state of knowledge. *Int. J. Cardiol.* **2010**, *142*, 120–125. [CrossRef]
36. Randhawa, M.S.; Dhillon, A.S.; Taylor, H.C.; Sun, Z.; Desai, M.Y. Diagnostic Utility of Cardiac Biomarkers in Discriminating Takotsubo Cardiomyopathy from Acute Myocardial Infarction. *J. Card. Fail.* **2014**, *20*, 2–8. [CrossRef]
37. Topf, A.; Mirna, M.; Bacher, N.; Paar, V.; Motloch, L.J.; Ohnewein, B.; Larbig, R.; Grueninger, J.; Hoppe, U.C.; Lichtenauer, M.; et al. Analysis of Selected Cardiovascular Biomarkers in Takotsubo Cardiomyopathy and the Most Frequent Cardiomyopathies. *Front. Cardiovasc. Med.* **2021**, *8*, 700169. [CrossRef]
38. Mekonnen, G.; Corban, M.T.; Hung, O.Y.; Eshtehardi, P.; Eapen, D.J.; Al-Kassem, H.; Rasoul-Arzrumly, E.; Gogas, B.D.; McDaniel, M.C.; Pielak, T.; et al. Plasma soluble urokinase-type plasminogen activator receptor level is independently associated with coronary microvascular function in patients with non-obstructive coronary artery disease. *Atherosclerosis* **2015**, *239*, 55–60. [CrossRef]
39. Olson, F.J.; Thurison, T.; Ryndel, M.; Høyer-Hansen, G.; Fagerberg, B. Soluble urokinase-type plasminogen activator receptor forms in plasma as markers of atherosclerotic plaque vulnerability. *Clin. Biochem.* **2010**, *43*, 124–130. [CrossRef]
40. Ye, X.; He, Y.; Wang, S.; Wong, G.T.; Irwin, M.G.; Xia, Z. Heart-type fatty acid binding protein (H-FABP) as a biomarker for acute myocardial injury and long-term post-ischemic prognosis. *Acta Pharmacol. Sin.* **2018**, *39*, 1155–1163. [CrossRef] [PubMed]
41. Huang, C.-H.; Vatner, S.F.; Peppas, A.P.; Yang, G.; Kudej, R.K. Cardiac nerves affect myocardial stunning through reactive oxygen and nitric oxide mechanisms. *Circ. Res.* **2003**, *93*, 866–873. [CrossRef] [PubMed]
42. Scally, C.; Abbas, H.; Ahearn, T.; Srinivasan, J.; Mezincescu, A.; Rudd, A.; Spath, N.; Yucel-Finn, A.; Yuecel, R.; Oldroyd, K.; et al. Myocardial and Systemic Inflammation in Acute Stress-Induced (Takotsubo) Cardiomyopathy. *Circulation* **2019**, *139*, 1581–1592. [CrossRef]
43. George, M.; Jena, A.; Srivatsan, V.; Muthukumar, R.; Dhandapani, V. GDF 15—A Novel Biomarker in the Offing for Heart Failure. *Curr. Cardiol. Rev.* **2016**, *12*, 37–46. [CrossRef]
44. Stiermaier, T.; Adams, V.; Just, M.; Blazek, S.; Desch, S.; Schuler, G.; Thiele, H.; Eitel, I. Growth differentiation factor-15 in Takotsubo cardiomyopathy: Diagnostic and prognostic value. *Int. J. Cardiol.* **2014**, *173*, 424–429. [CrossRef]
45. Alquézar-Arbé, A.; Sanchís, J.; Guillén, E.; Bardají, A.; Miró, Ò.; Ordóñez-Llanos, J. Cardiac troponin measurement and interpretation in the diagnosis of acute myocardial infarction in the emergency department: A consensus statement. *Emerg. Rev. Soc. Espanola Med. Emerg.* **2018**, *30*, 336–349.
46. Perera, M.; Aggarwal, L.; Scott, I.A.; Logan, B. Received care compared to ADP-guided care of patients admitted to hospital with chest pain of possible cardiac origin. *Int. J. Gen. Med.* **2018**, *11*, 345–351. [CrossRef]

47. Riley, R.F.; Miller, C.D.; Russell, G.B.; Soliman, E.Z.; Hiestand, B.C.; Herrington, D.M.; Mahler, S.A. Usefulness of Serial 12-Lead Electrocardiograms in Predicting 30-Day Outcomes in Patients with Undifferentiated Chest Pain (the ASAP CATH Study). *Am. J. Cardiol.* **2018**, *122*, 374–380. [CrossRef] [PubMed]
48. Hurst, R.T.; Prasad, A.; Askew, J.W.; Sengupta, P.P.; Tajik, A.J. Takotsubo cardiomyopathy: A unique cardiomyopathy with variable ventricular morphology. *JACC Cardiovasc. Imaging* **2010**, *3*, 641–649. [CrossRef]
49. Yoshikawa, T. Takotsubo cardiomyopathy, a new concept of cardiomyopathy: Clinical features and pathophysiology. *Int. J. Cardiol.* **2015**, *182*, 297–303. [CrossRef]
50. Ghadri, J.-R.; Wittstein, I.S.; Prasad, A.; Sharkey, S.; Dote, K.; Akashi, Y.J.; Cammann, V.L.; Crea, F.; Galiuto, L.; Desmet, W.; et al. International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. *Eur. Heart J.* **2018**, *39*, 2047–2062. [CrossRef]
51. Kosuge, M.; Ebina, T.; Hibi, K.; Morita, S.; Okuda, J.; Iwahashi, N.; Tsukahara, K.; Nakachi, T.; Kiyokuni, M.; Ishikawa, T.; et al. Simple and accurate electrocardiographic criteria to differentiate takotsubo cardiomyopathy from anterior acute myocardial infarction. *J. Am. Coll. Cardiol.* **2010**, *55*, 2514–2516. [CrossRef]
52. Bybee, K.A.; Motiei, A.; Syed, I.S.; Kara, T.; Prasad, A.; Lennon, R.J.; Murphy, J.G.; Hammill, S.C.; Rihal, C.S.; Wright, R.S. Electrocardiography cannot reliably differentiate transient left ventricular apical ballooning syndrome from anterior ST-segment elevation myocardial infarction. *J. Electrocardiol.* **2007**, *40*, 38.e1–38.e6. [CrossRef]
53. Mechanic, O.J.; Gavin, M.; Grossman, S.A. Acute Myocardial Infarction. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2024. Available online: http://www.ncbi.nlm.nih.gov/books/NBK459269/ (accessed on 20 July 2023).
54. Sanchez-Jimenez, E.F. Initial clinical presentation of Takotsubo cardiomyopathy with-a focus on electrocardiographic changes: A literature review of cases. *World J. Cardiol.* **2013**, *5*, 228. [CrossRef]
55. Akkus, Z.; Aly, Y.H.; Attia, I.Z.; Lopez-Jimenez, F.; Arruda-Olson, A.M.; Pellikka, P.A.; Pislaru, S.V.; Kane, G.C.; Friedman, P.A.; Oh, J.K. Artificial Intelligence (AI)-Empowered Echocardiography Interpretation: A State-of-the-Art Review. *J. Clin. Med.* **2021**, *10*, 1391. [CrossRef] [PubMed]
56. Zamzmi, G.; Hsu, L.-Y.; Li, W.; Sachdev, V.; Antani, S. Harnessing Machine Intelligence in Automatic Echocardiogram Analysis: Current Status, Limitations, and Future Directions. *IEEE Rev. Biomed. Eng.* **2020**, *14*, 181–203. [CrossRef] [PubMed]
57. Laumer, F.; Di Vece, D.; Cammann, V.L.; Würdinger, M.; Petkova, V.; Schönberger, M.; Schönberger, A.; Mercier, J.C.; Niederseer, D.; Seifert, B.; et al. Assessment of Artificial Intelligence in Echocardiography Diagnostics in Differentiating Takotsubo Syndrome from Myocardial Infarction. *JAMA Cardiol.* **2022**, *7*, 494–503. [CrossRef] [PubMed]
58. Alsharqi, M.; Woodward, W.J.; Mumith, J.A.; Markham, D.C.; Upton, R.; Leeson, P. Artificial intelligence and echocardiography. *Echo Res. Pract.* **2018**, *5*, R115–R125. [CrossRef] [PubMed]
59. Mansencal, N.; Abbou, N.; Pillière, R.; El Mahmoud, R.; Farcot, J.-C.; Dubourg, O. Usefulness of two-dimensional speckle tracking echocardiography for assessment of tako-tsubo cardiomyopathy. *Am. J. Cardiol.* **2009**, *103*, 1020–1024. [CrossRef] [PubMed]
60. Citro, R.; Rigo, F.; Ciampi, Q.; D'Andrea, A.; Provenza, G.; Mirra, M.; Giudice, R.; Silvestri, F.; Di Benedetto, G.; Bossone, E. 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*, 542–549. [CrossRef]
61. Kurisu, S.; Sato, H.; Kawagoe, T.; Ishihara, M.; Shimatani, Y.; Nishioka, K.; Kono, Y.; Umemura, T.; Nakamura, S. Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: A novel cardiac syndrome mimicking acute myocardial infarction. *Am. Heart J.* **2002**, *143*, 448–455. [CrossRef]
62. Cummings, K.W.; Bhalla, S.; Javidan-Nejad, C.; Bierhals, A.J.; Gutierrez, F.R.; Woodard, P.K. A pattern-based approach to assessment of delayed enhancement in nonischemic cardiomyopathy at MR imaging. *RadioGraphics* **2009**, *29*, 89–103. [CrossRef]
63. Gerbaud, E.; Montaudon, M.; Leroux, L.; Corneloup, O.; Dos Santos, P.; Jaïs, C.; Coste, P.; Laurent, F. MRI for the diagnosis of left ventricular apical ballooning syndrome (LVABS). *Eur. Radiol.* **2008**, *18*, 947–954. [CrossRef]
64. Hurst, R.T.; Askew, J.W.; Reuss, C.S.; Lee, R.W.; Sweeney, J.P.; Fortuin, F.D.; Oh, J.K.; Tajik, A.J. Transient midventricular ballooning syndrome: A new variant. *J. Am. Coll. Cardiol.* **2006**, *48*, 579–583. [CrossRef]
65. Kumar, G.; Holmes, D.R.; Prasad, A. "Familial" apical ballooning syndrome (Takotsubo cardiomyopathy). *Int. J. Cardiol.* **2010**, *144*, 444–445. [CrossRef] [PubMed]
66. Ibanez, B.; Navarro, F.; Cordoba, M.; M-Alberca, P.; Farre, J. Tako-tsubo transient left ventricular apical ballooning: Is intravascular ultrasound the key to resolve the enigma? *Heart* **2005**, *91*, 102–104. [CrossRef]
67. Ito, K.; Sugihara, H.; Katoh, S.; Azuma, A.; Nakagawa, M. Assessment of Takotsubo (ampulla) cardiomyopathy using99mTc-tetrofosmin myocardial SPECT—Comparison with acute coronary syndrome. *Ann. Nucl. Med.* **2003**, *17*, 115–122. [CrossRef]
68. Pineda, A.R.B.; Gudi, T.R.; Montecino, R.M.B.; Cornejo, C.L.G.; Bonilla, F.R.B.; Gonzalez, J.N.; Aggarwal, P.; Chao, A.G.; Pariyar, B.; Robles, P.C.M.; et al. An Overview of Takotsubo Cardiomyopathy, a Potential Mimic of Acute Myocardial Infarction. *J. Cardiol. Cardiovasc. Ther.* **2023**, *18*, 555993. [CrossRef]
69. Ghadri, J.R.; Sarcon, A.; Diekmann, J.; Bataiosu, D.R.; Cammann, V.L.; Jurisic, S.; Napp, L.C.; Jaguszewski, M.; Scherff, F.; Brugger, P.; et al. Happy heart syndrome: Role of positive emotional stress in takotsubo syndrome. *Eur. Heart J.* **2016**, *37*, 2823–2829. [CrossRef]
70. Kosuge, M.; Kimura, K. Electrocardiographic findings of takotsubo cardiomyopathy as compared with those of anterior acute myocardial infarction. *J. Electrocardiol.* **2014**, *47*, 684–689. [CrossRef] [PubMed]

71. Looi, J.-L.; Wong, C.-W.; Lee, M.; Khan, A.; Webster, M.; Kerr, A.J. Usefulness of ECG to differentiate Takotsubo cardiomyopathy from acute coronary syndrome. *Int. J. Cardiol.* **2015**, *199*, 132–140. [CrossRef]
72. Joshi, G.; Jain, A.; Araveeti, S.R.; Adhikari, S.; Garg, H.; Bhandari, M. FDA-Approved Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices: An Updated Landscape. *Electronics* **2024**, *13*, 498. [CrossRef]
73. Gaddam, S.; Nimmagadda, K.C.; Nagrani, T.; Naqi, M.; Wetz, R.V.; Weiserbs, K.F.; McCord, D.; Ghavami, F.; Gala, B.; Lafferty, J.C. Serum lipoprotein levels in takotsubo cardiomyopathy vs. myocardial infarction. *Int. Arch. Med.* **2011**, *4*, 14. [CrossRef]
74. Scally, C.; Choo, W.; Rudd, A.; Neil, C.; Siddiqi, N.; Mezincescu, A.M.; Wilson, H.M.; Frenneaux, M.; Horgan, G.; Broadhurst, P.; et al. The early dynamic of ECG in Takotsubo syndrome presenting with ST-elevation: A comparison with age and gender-matched ST-elevation myocardial infarction. *Int. J. Cardiol.* **2020**, *320*, 7–11. [CrossRef]
75. Rautaharju, P.M.; Mason, J.W.; Akiyama, T. New age- and sex-specific criteria for QT prolongation based on rate correction formulas that minimize bias at the upper normal limits. *Int. J. Cardiol.* **2014**, *174*, 535–540. [CrossRef] [PubMed]
76. Migliore, F.; Zorzi, A.; Perazzolo Marra, M.; Iliceto, S.; Corrado, D. Myocardial edema as a substrate of electrocardiographic abnormalities and life-threatening arrhythmias in reversible ventricular dysfunction of takotsubo cardiomyopathy: Imaging evidence, presumed mechanisms, and implications for therapy. *Heart Rhythm.* **2015**, *12*, 1867–1877. [CrossRef] [PubMed]
77. Migliore, F.; Zorzi, A.; Marra, M.P.; Basso, C.; Corbetti, F.; De Lazzari, M.; Tarantini, G.; Buja, P.; Lacognata, C.; Thiene, G.; et al. Myocardial edema underlies dynamic T-wave inversion (Wellens' ECG pattern) in patients with reversible left ventricular dysfunction. *Heart Rhythm.* **2011**, *8*, 1629–1634. [CrossRef] [PubMed]
78. Perazzolo Marra, M.; Zorzi, A.; Corbetti, F.; De Lazzari, M.; Migliore, F.; Tona, F.; Tarantini, G.; Iliceto, S.; Corrado, D. Apicobasal gradient of left ventricular myocardial edema underlies transient T-wave inversion and QT interval prolongation (Wellens' ECG pattern) in Tako-Tsubo cardiomyopathy. *Heart Rhythm.* **2013**, *10*, 70–77. [CrossRef] [PubMed]
79. Citro, R.; Piscione, F.; Parodi, G.; Salerno-Uriarte, J.; Bossone, E. Role of echocardiography in takotsubo cardiomyopathy. *Heart Fail. Clin.* **2013**, *9*, 157–166. [CrossRef]
80. Citro, R.; Pontone, G.; Pace, L.; Zito, C.; Silverio, A.; Bossone, E.; Piscione, F. Contemporary Imaging in Takotsubo Syndrome. *Heart Fail. Clin.* **2016**, *12*, 559–575. [CrossRef] [PubMed]
81. Citro, R.; Okura, H.; Ghadri, J.R.; Izumi, C.; Meimoun, P.; Izumo, M.; Dawson, D.; Kaji, S.; Eitel, I.; Kagiyama, N.; 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). *J. Echocardiogr.* **2020**, *18*, 199–224. [CrossRef] [PubMed]
82. Prasad, A.; Lerman, A.; Rihal, C.S. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): A mimic of acute myocardial infarction. *Am. Heart J.* **2008**, *155*, 408–417. [CrossRef] [PubMed]
83. Citro, R.; Lyon, A.R.; Meimoun, P.; Omerovic, E.; Redfors, B.; Buck, T.; Lerakis, S.; Parodi, G.; Silverio, A.; Eitel, I.; et al. Standard and advanced echocardiography in takotsubo (stress) cardiomyopathy: Clinical and prognostic implications. *J. Am. Soc. Echocardiogr.* **2015**, *28*, 57–74. [CrossRef]
84. Citro, R.; Rigo, F.; D'Andrea, A.; Ciampi, Q.; Parodi, G.; Provenza, G.; Piccolo, R.; Mirra, M.; Zito, C.; Giudice, R.; et al. Echocardiographic correlates of acute heart failure, cardiogenic shock, and in-hospital mortality in tako-tsubo cardiomyopathy. *JACC Cardiovasc. Imaging* **2014**, *7*, 119–129. [CrossRef]
85. Citro, R.; Bossone, E.; Parodi, G.; Rigo, F.; Nardi, F.; Provenza, G.; Zito, C.; Novo, G.; Vitale, G.; Prota, C.; et al. Independent Impact of RV Involvement on In-Hospital Outcome of Patients with Takotsubo Syndrome. *JACC Cardiovasc. Imaging* **2016**, *9*, 894–895. [CrossRef]
86. El Mahmoud, R.; Mansencal, N.; Pilliére, R.; Leyer, F.; Abbou, N.; Michaud, P.; Nallet, O.; Digne, F.; Lacombe, P.; Cattan, S.; et al. Prevalence and characteristics of left ventricular outflow tract obstruction in Tako-Tsubo syndrome. *Am. Heart J.* **2008**, *156*, 543–548. [CrossRef]
87. Parodi, G.; Del Pace, S.; Salvadori, C.; Carrabba, N.; Olivotto, I.; Gensini, G.F. Left ventricular apical ballooning syndrome as a novel cause of acute mitral regurgitation. *J. Am. Coll. Cardiol.* **2007**, *50*, 647–649. [CrossRef] [PubMed]
88. Grabowski, M.; Piatkowski, R.; Scislo, P.; Kochanowski, J.; Filipiak, K.J.; Opolski, G. Real-time three-dimensional echocardiography in transient left apical ballooning syndrome. *Int. J. Cardiol.* **2008**, *129*, e69–e70. [CrossRef] [PubMed]
89. Kudaiberdiev, T.; Akhmedova, I.; Imanalieva, G.; Abdildaev, I.; Jooshev, K.; Ashimov, J.; Mirzabekov, A.; Gaybildaev, J. Surgical treatment of left ventricular wall rupture, regarded as a consequence of Takotsubo cardiomyopathy. *SAGE Open Med. Case Rep.* **2017**, *5*, 2050313X1668921. [CrossRef]
90. Iskander, M.; Abugroun, A.; Shehata, K.; Iskander, F.; Iskander, A. Takotsubo Cardiomyopathy-Induced Cardiac Free Wall Rupture: A Case Report and Review of Literature. *Cardiol. Res.* **2018**, *9*, 244–249. [CrossRef] [PubMed]
91. Berti, M.; Pernigo, M.; Dinatolo, E.; Cozza, F.; Cuccia, C. Differentiating typical Tako-tsubo syndrome from extensive anterior STEMI: Look behind the anterior wall. *Echocardiography* **2022**, *39*, 1299–1306. [CrossRef]
92. Available online: http://petrieflom.law.harvard.edu/resources/article/petrie-flom-center-launches-pmail-project (accessed on 17 February 2024).
93. Ghadri, J.-R.; Wittstein, I.S.; Prasad, A.; Sharkey, S.; Dote, K.; Akashi, Y.J.; Cammann, V.L.; Crea, F.; Galiuto, L.; Desmet, W.; et al. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. *Eur. Heart J.* **2018**, *39*, 2032–2046. [CrossRef]
94. Tavakol, M.; Ashraf, S.; Brener, S.J. Risks and complications of coronary angiography: A comprehensive review. *Glob. J. Health Sci.* **2011**, *4*, 65–93. [CrossRef]

95. Sirajuddin, A.; Mirmomen, S.M.; Kligerman, S.J.; Groves, D.W.; Burke, A.P.; Kureshi, F.; White, C.S.; Arai, A.E. Ischemic Heart Disease: Noninvasive Imaging Techniques and Findings. *RadioGraphics* **2021**, *41*, E990–E1021. [CrossRef]
96. Manrai, A.K.; Patel, C.J.; Ioannidis, J.P.A. In the Era of Precision Medicine and Big Data, Who Is Normal? *JAMA* **2018**, *319*, 1981–1982. [CrossRef]
97. Buzaev, I.V.; Plechev, V.V.; Nikolaeva, I.E.; Galimova, R.M. Artificial intelligence: Neural network model as the multidisciplinary team member in clinical decision support to avoid medical mistakes. *Chronic Dis. Transl. Med.* **2016**, *2*, 166–172. [CrossRef] [PubMed]
98. Zhou, J.; Du, M.; Chang, S.; Chen, Z. Artificial intelligence in echocardiography: Detection, functional evaluation, and disease diagnosis. *Cardiovasc. Ultrasound* **2021**, *19*, 29. [CrossRef]
99. Seetharam, K.; Shrestha, S.; Sengupta, P.P. Artificial Intelligence in Cardiovascular Medicine. *Curr. Treat. Options Cardiovasc. Med.* **2019**, *21*, 25. [CrossRef]
100. Chang, Y.; Paul, A.K.; Kim, N.; Baek, J.H.; Choi, Y.J.; Ha, E.J.; Lee, K.D.; Lee, H.S.; Shin, D.; Kim, N. Computer-aided diagnosis for classifying benign versus malignant thyroid nodules based on ultrasound images: A comparison with radiologist-based assessments: CAD for malignancy of thyroid nodules on ultrasound images. *Med. Phys.* **2016**, *43*, 554–567. [CrossRef] [PubMed]
101. Yu, K.-H.; Beam, A.L.; Kohane, I.S. Artificial intelligence in healthcare. *Nat. Biomed. Eng.* **2018**, *2*, 719–731. [CrossRef]
102. Appen, What Is Training Data? Appen. Available online: https://www.appen.com/blog/training-data (accessed on 17 February 2024).
103. Gerke, S.; Minssen, T.; Cohen, G. Ethical and legal challenges of artificial intelligence-driven healthcare. In *Artificial Intelligence in Healthcare*; Elsevier: Amsterdam, The Netherlands, 2020; pp. 295–336, ISBN 978-0-12-818438-7.
104. European Commission. *Regulatory Framework Proposal on Artificial Intelligence*; European Commission: Brussels, Belgium, 2022.
105. Food and Drug Administration (United States). Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD). April, 2019. Available online: https://apo.org.au/node/228371 (accessed on 17 February 2024).
106. Innovation at ACC | The Future of AI: Fight, Flight, or Lead? American College of Cardiology. Available online: https://www.acc.org/latest-incardiology/articles/2020/02/01/24/42/http://www.acc.org/latest-in-cardiology/articles/2020/02/01/24/42/innovation-at-acc-the-future-of-ai-fight-flight-or-lead (accessed on 17 February 2024).
107. Wasserlauf, J.; You, C.; Patel, R.; Valys, A.; Albert, D.; Passman, R. Smartwatch Performance for the Detection and Quantification of Atrial Fibrillation. *Circ. Arrhythmia Electrophysiol.* **2019**, *12*, e006834. [CrossRef]
108. Karakuş, G.; Değirmencioğlu, A.; Nanda, N.C. Artificial intelligence in echocardiography: Review and limitations including epistemological concerns. *Echocardiography* **2022**, *39*, 1044–1053. [CrossRef]