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Health technology assessment in cardiovascular diseases

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Health technology assessment in cardiovascular diseases

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Editorial: Health technology assessment in cardiovascular diseases

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Editorial on the Research Topic
Health technology assessment in cardiovascular diseases

According to World Health Organization (WHO), cardiovascular diseases (CVD) remains the number one killer in developing as well as developed countries, accounting for 17.9 million deaths each year (32% of the total deaths), with an expected increase to 23.6 million by 2030[1]. With the chronic nature of the condition, CVD not only has long-term clinical consequences but also a substantial economic burden on both health systems and patients. The CVD cost globally was approximately US$ 863 billion in 2010 and is estimated to rise by 22% (around US$ 1,044 billion) by 2030 (1). Cost estimate for coronary heart disease (CHD) and stroke can be as high as 5,000 US$ per episode (2). Moreover, an epidemiological shift with the disease affecting the younger population at large has made the situation more alarming. These have paved the way for investing in inventing, designing, and implementing approaches and healthcare technologies (HCTs) for improving diagnosis, treatment, and prognosis of CVD with substantial efforts being directed toward the assessment of these technological support solutions.

Over the last few decades, the advancement in medical technologies has touched almost all spheres of life with health care innovations aiding clinicians and health care professionals (HCP) in decision making. HCTs have become one of the fastest growing global markets with an estimated size of 857.58 US$ billion by 2030[2]. Unfortunately, adopting these new technologies can put a huge financial burden on the healthcare system. Hence, it is imperative to identify and adopt technologies and interventions which can contribute significantly to the prevention and management of the disease and provide economically, socially, and contextually acceptable alternatives through systematic, ethical, unbiased, transparent, and robust methods of innovation. These evidence-supported approaches can guide policy decisions for both developing and developed economies. The goal is to support the interventions for a sustainable health system. Health Technology Assessment (HTA) is a relatively new concept in developing countries. It is defined as a form of policy research that supports an evidence-based decision for the use of any technological innovation aiming to improve health outcomes. It recommends the incorporation of innovation in the policy on the bases of clinical efficacy, economic effectiveness,

1 https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

2 https://www.ibef.org/industry/information-technology-india

and social and ethical implications of the HCTs. Areas in which HTA could be applied in the state and national contexts are new equipment procurement, new drug procurement, development of clinical practice guidelines/protocols for common diseases, screening of societal problems for the development of products/processes/prototypes, and prioritizing interventions that represent the greatest value to address the problem within a limited budget.

As per an estimate, the CVD technology market will exceed 40US$ billion by 2030[3]. The HCTs shall form the basis of innovations in all the domains of the solutions ranging from imaging (CT, PET, and MRI), AI-supported prediction and diagnostic tools, genetic and novel biomarkers, non-invasive tools, novel surgical approaches, and drug discovery, to name a few. Along with the rise in the global burden of the disease, there is an expected proportionate increase in the market size and hence the need for rational decision-making with regard to the choice of the solution adopted by the HCPs. HTA is an extension of evidence-based medicine (EBM), critically considering cost-effectiveness analysis with ethical and societal factors into consideration, making it a suitable research method for tailoring contextual policy decisions.

Understanding the need for HTA, various countries have adopted resolutions on linking HTA evaluation with the decision-making process. Countries have established their own administrative bodies for HTA which guide, conduct, and recommend HTA studies based on the felt need of the population and health care budgets of their country and/or the state. The WHO has also directed efforts to broaden the use of HTA across the globe including achieving the sustainable development goal of universal health coverage[4].

This Research Topic covers health technology assessment topics in the field of cardiovascular diseases. The authors have presented their work in the area of CVD technologies and programs that include innovations, medical technologies, programs, and drugs.

The use of artificial intelligence (AI), machine learning (ML), and deep learning (DL) is an important application of data sciences in medical sciences, especially in HTA. In this edition, the use of ML is evaluated for predicting hypotension while DL is used in contextual setup for diagnosing atrial fibrillation. ML is evaluated across 3 countries for predicting the development of hypertension in another original study. A study by Islam, Talukder et al. applies six common ML-based classifiers viz. decision tree (DT), random forest (RF), gradient boosting machine (GBM), extreme gradient boosting (XGBoost), logistic regression (LR), and linear discriminant analysis (LDA) to predict hypertension and its risk factors in 8,18,603 participants, of which 82,748 (10.11%) had hypertension. The ML models perform well to predict hypertension and its associated factors in South Asians. If these models are employed on an open-source platform, they can be scaled up to benefit millions of patients.

Kumar et al. in the CACHET-CADB study, was a subpart of the REAFEL study to optimize the diagnosis of atrial fibrillation using an AI/ML-based algorithm. In contrast to the existing databases apart from the ECG, CACHET-CADB also provides the continuous recording of patients' contextual data such as activities, body positions, movement accelerations, symptoms, stress level, and sleep quality. This can help to develop and evaluate algorithms for patient-operated wearable ECG, thereby making longitudinal ambulatory monitoring more economically robust and feasible. Similarly, another study conducted by Zhao A. et al., provides a systematic summary of articles providing the accuracy of ML-based algorithms for predicting acute hypotension. The authors report the accuracy of algorithms from 70–96% with a sample size ranging from 12–3,825 participants identified from 35 original studies.

A review from the Himalayan country of Nepal delves into the felt need of the same (Adhikari et al.). The use of a modified Delphi approach in a smart home system to improve the self-management behavior of the patients is explored. The prevalence of DM (4.4–18.8%) and HTN (17.2–70.0%) is reported in most of the studies, covering the other aspects of HTA of DM/HTN. Islam, Nourse et al. provide consensus-based recommendations for functions of a smart home system for self-management of chronic heart failure in the community. Through the Delphi method, a consensus is obtained among 15 experts through two rounds of discussion, and a 34-item smart home system is designed to support people with chronic heart failure for self-management and clinical support.

A cost-effectiveness analysis of pharmacist-managed warfarin therapy in patients with prosthetic valves was evaluated in the Egyptian population which has the potential to bring the down the costs of patient care (Batran et al.). The pharmacist-managed warfarin therapy strategy is proven to provide a significantly better anticoagulation control and to be a cost-saving approach in Egyptian patients.

Electrography-based technologies are explored for the prediction of a variety of cardiovascular conditions. The use of speckled tracking in echocardiography has the potential to predict coronary artery disease and in research from Taipei Medical University, Chaichuum et al. attempts to show a correlation between average longitudinal strain and SR of the segmental myocardium supplied by 170 coronary arteries by calculating vessel myocardium strain (VMS) and strain rate (VMSR) to predict significant coronary artery stenosis in angiographically proven CAD patients. A VMS and VMSR higher than 16.9 ± 4.9 and 1.2 ± 0.3, respectively, predicts mild or no coronary artery stenosis. Zhao T. et al., show that electrocardiographic indicators can be useful for the individualized treatment of pediatric vasovagal syncope (VVS). Various ECG indicators such as HRV, Pd, QTd, Tp-Te interval, Tp-Te/QT, T-wave amplitude and shape, immediate heart rate change, DC, and VLP can be useful tools for VVS due to their easy availability and cost-effective nature. Similarly, Guo et al. show the potential utility of electrocardiographic variables for screening for hypertrophic cardiomyopathy (HCM). From 423 patients' data, 30 ECG features were studied and all except an abnormal Q wave are found to be significantly different between the HCM patients and non-HCM patients. A model using two ECG features - T wave inversion (TWI) and the amplitude of S wave in lead V1 (SV1) was developed for HCM prediction and it is found to have good discrimination power (c-statistics of >0.75). Another study (Tang et al.) shows a correlation between QT interval on ECG with depression and anxiety. The study uses data from 61 patients from China and suggests the potential utility of QT interval for the prediction of depression and anxiety.

Jiang et al. in their research, show how the use of Galectin-3 can be used to predict hospitalization in heart failure with preserved ejection fraction (HFpEF) with a moderate diagnostic value (AUC:

3 https://www.dicardiology.com/content/cardiovascular-disease-technology-market-will-exceed-40-billion-2030

4 https://www.who.int/teams/health-product-policy-and-standards/assistive-and-medical-technology/medical-devices/assessment

0.763) which is better than that of interventricular thickness or E/A ratio. A novel method of Pulsed field ablation (PFA) is studied and discussed by Bi et al.. This preclinical study finds that biphasic asymmetric pulses can reduce muscle contractions and drop ablation threshold and that this method can be adapted due to its safe and cost-effective outcomes.

Another article (3) discusses the role of a left ventricular assist device as a destination therapy and comments on its cost-effectiveness in the United Kingdom. The authors suggest that it can be an economic alternative considering the limited availability of donor organs for heart transplants. Two other commentaries [(4); Rawal et al.] discuss the role and cost-effectiveness of statin for primary prevention and Rivaroxaban with or without aspirin in coronary artery disease patients.

The advancement in healthcare technologies is headed toward a major revamp with data sciences and healthcare technology assessment (HTA) driving the next potential revolution in not only early diagnosis and treatment but also in prognostication and primordial prevention in times to come and this edition on HTA tries to envisage and bring the same to the forefront.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Diagnostic Value of Serum Concentration of Galectin-3 in Patients With Heart Failure With Preserved Ejection Fraction

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Background: Although the predictive value of galectin-3 for heart failure with preserved ejection fraction has been demonstrated, the diagnostic value remains unclear. The present study was performed to address this issue.

Hypothesis: Galectin-3 has diagnostic value for heart failure with preserved ejection fraction.

Methods: This is a diagnostic experiment. We conducted an observational study of 223 patients with combined symptoms of heart failure and diseases that can lead to heart failure with preserved ejection fraction. Patients were grouped into the heart failure group and control group in accordance with the 2016 European Society of Cardiology heart failure guidelines for heart failure with preserved ejection fraction. Baseline information and serum galectin-3 concentration were assessed within 24 h after admission.

Results: Serum galectin-3 concentration was significantly higher in the heart failure group compared with the control group. Binary logistic regression analysis showed that higher galectin-3 concentration was associated with the occurrence of heart failure with preserved ejection fraction. The area under the curve of galectin-3 was 0.763, indicating that galectin-3 has moderate diagnostic value for heart failure with preserved ejection fraction. Galectin-3 >15.974 ng/mL identified heart failure with preserved ejection fraction with 76.0% sensitivity and 71.9% specificity.

Conclusions: There was a correlation between galectin-3 and heart failure with preserved ejection fraction, and galectin-3 was an independent predictor of heart failure with preserved ejection fraction. The diagnostic value of galectin-3 for heart failure with preserved ejection fraction was moderate (AUC: 0.763, 95% CI: 0.696–0.821, $P < 0.01$, and the sensitivity is 76.0% while the specificity is 71.9% at the threshold 15.974 ng/mL) and was higher than that of interventricular septal thickness or E/A ratio.

Keywords: galectin-3, diagnosis, diagnostic value, heart failure, heart failure with preserved ejection fraction

INTRODUCTION

Heart failure is a well-known and severe cardiovascular syndrome that continues to cause substantial death. According to the 2018 cardiovascular survey report, despite the gradual decline in population mortality rate, heart disease continues to account for a high proportion of deaths, ranking first among all causes of death, and the absolute number will continue to rise (1, 2). Among the different forms of heart failure, heart failure with preserved ejection fraction (HFPEF) has gradually become the most prevalent (3). Recent studies suggested that approximately three-quarters of older adults have HFPEF (4–6). HFPEF was defined as a subform of heart failure by the European Society of Cardiology (ESC) in 2008 and has attracted much attention as it is difficult to diagnose and treat. Epidemiological data show that HFPEF is characterized by high morbidity and mortality (7, 8). A long-term follow-up study of HFPEF suggested that <2% of patients developed heart failure with reduced ejection fraction, and such changes were not associated with mortality in the study population (9). This suggests that HFPEF has a unique pathophysiological basis and requires unique approaches for diagnosis and treatment. The Framingham heart study (10) reported that the rate of mortality from HFPEF is 22–29%, which is slightly lower than that from heart failure with reduced ejection fraction. Kitzman et al. (11) reported that patients suffer from heart failure before left ventricular ejection fraction drops to 50%, and this occurs in all patients with combined systolic and diastolic heart failure. Therefore, it is necessary to identify a reliable method for early identification of HFPEF. Presently, there are many methods for diagnosing HFPEF, such as ultrasonic detection, use of serum B-type natriuretic peptide (BNP) levels, or the combination of multiple diagnostic procedures, which are generally relatively complicated, and with which the specificity and sensitivity cannot be satisfied simultaneously (3, 12). And an early stage of HFpEF can be easily missed (13). We hypothesized that measurement of a biological indicator involved in the pathophysiological pathway of HFPEF can significantly improve the diagnostic efficiency.

Galectin-3 is a soluble β-galactoside-binding lectin secreted by activated cardiac macrophages and is involved in the pathophysiological processes of inflammation and fibrosis (14). It can induce proliferation of cardiac fibroblasts, leading to deposition of collagen in the heart, which can lead to ventricular dysfunction, a process that has been demonstrated in animal studies (15–17). In animal studies, serum galectin-3 level was significantly increased in animal models with volume and (or) stress overload (18), artificially increasing the level of galectin-3 in animals can promote the occurrence of myocardial fibrosis (19). A large number of studies have found that serum galectin-3 level was significantly elevated in either acute or chronic heart failure patients (20). In population studies, patients with higher basal galectin-3 level were more likely to lead to new-onset heart failure (15, 21, 22). And heart failure patients with higher basal galectin-3 level had poorer outcomes (including higher mortality, higher readmission rates, etc.) (23–25). Therefore, galectin-3 has been identified as a prognostic factor for heart failure, especially HFpEF (25–28). The 2013 US guidelines have recommended galectin-3 using for heart failure risk stratification (29), although it has not been used clinically (30–35).

Although the mechanism of action of galectin-3 in the progression of heart failure has been clarified, determining how to use this biomarker still requires investigation. Studies are exploring the diagnostic value of galactose lectin 3 in heart failure, for example: Kanukurti et al. obtained the diagnostic threshold of 10.1 ng/mL, and suggested that galectin-3 and NT-proBNP should be combined for the diagnosis of HFpEF (36); another study mentioned that the cut-off value of 17.8 ng/ml for galectin-3 to diagnose heart failure (37). However, the sample size of the previous studies was small, and the cut-off point value fluctuated greatly. At the same time, mature, stable and cheap assay for galectin-3 has been reported (20). So, what was the reason for galectin-3 still not been used in clinical practice? As far as we concerned, one most important reason was that there is a large discrepancy in current reports regarding diagnostic threshold in heart failure, especially in HFpEF (35–37). Therefore, we conducted the present study to determine the diagnostic value of galectin-3 level for HFPEF and to establish the threshold.

MATERIALS AND METHODS

Study Design and Patient Selection

This is a diagnostic experiment. We conducted an observational study of 223 patients with combined symptoms of heart failure and diseases that can lead to HFPEF such as hypertension, coronary heart disease, and atrial fibrillation. Patients who met these conditions were consecutively admitted to the Department of Cardiovascular Internal Medicine of No.1 Affiliate Hospital of Shantou University Medical College from July 2018 to September 2018.

According to ESC guidelines for heart failure, the upper limit for normal level of BNP in the non-acute setting is 35 pg/mL, while that for N-terminal pro-BNP (NT-proBNP) is 125 pg/mL; in the acute setting, higher values should be used [BNP, 100 pg/mL; NT-proBNP, 300 pg/mL]. The diagnostic value of BNP applies similarly to heart failure with reduced ejection fraction and HFPEF. On average, the values are lower for HFPEF than for heart failure with reduced ejection fraction (38). Echocardiography plays an important role in the diagnosis of heart failure, accounting for two of the four diagnostic criteria for HFPEF. Therefore, we compared the diagnostic value of galectin-3 with that of ultrasonic diagnostic indexes for HFPEF. The diagnostic value of these two indices was significantly higher than that of BNP.

The diagnostic criteria for HFPEF include the following:

(1) Typical symptoms of heart failure;
(2) Typical signs of heart failure;
(3) Small left ventricle with normal or slightly reduced left ventricular ejection fraction (≥50%);
(4) The presence of left ventricular structural changes (such as left ventricular hypertrophy or left atrial enlargement) and/or left ventricular diastolic dysfunction. Key functional alterations are an E/e' ratio ≥13.

Patients diagnosed with HFPEF in accordance with the above criteria were eligible for inclusion in the experimental group (HF group). Otherwise, patients were included in the control group. Nineteen subjects with left ventricular ejection fraction<50%, five combined with acute coronary syndrome, and seven who suffered from malignant tumors were excluded. Patients were systematically characterized and clinical data upon admission were recorded in detail. All patients underwent echocardiography upon admission by a skilled echocardiologist. On admission, we assessed several variables, including demographic features, such as age, sex, history of hypertension (including duration of hypertension and pressure level), diabetes, coronary artery disease, atrial fibrillation, New York Heart Association (NYHA) basal functional status, and

TABLE 1 | Baseline demographic and clinical features of the study population.

Variables	All subjects ($n = 192$)	HF group ($n = 96$)	Control group ($n = 96$)	Statistical value
Female	92 (47.9%)	52 (54.2%)	40 (41.7%)	0.112
Age, y	66.00 (15.000)	69.00 (19.000)	63.00 (14.000)	0.062
Medical history				
CHD	65 (33.9%)	33 (34.4%)	32 (33.3%)	1.000
Hypertension	157 (81.8%)	75 (78.1%)	82 (85.4%)	0.262
Blood pressure level				0.694
Level 1	23 (12.0%)	8 (8.3%)	15 (15.6%)	
Level 2	48 (25.0%)	26 (27.1%)	22 (22.9%)	
Level 3	86 (44.8%)	41 (42.7%)	45 (46.9%)	
Time of HBP, y	4.00 (9.000)	3.00 (9.000)	4.00 (9.000)	0.803
Diabetes,	57 (29.7%)	31 (32.3%)	26 (27.1)	0.528
Atrial fibrillation	16 (8.3%)	11 (11.5%)	5 (5.2%)	0.190
NYHA classification				0.070
NYHAI	107 (55.7%)	48 (50.0%)	59 (61.5%)	
NYHAII	69 (35.9%)	37 (38.5%)	32 (33.3%)	
NYHA III	11 (5.7%)	7 (7.3%)	4 (4.2%)	
NYHA IV	5 (2.6%)	4 (4.2%)	1 (1.0%)	
Drug therapy history				
No. of drugs	2.00 (1.000)	2.00 (2.000)	2.00 (1.000)	0.437
ACEI,	59 (30.7%)	29 (30.2%)	30 (31.3%)	1.000
ARB	43 (22.4%)	23 (24.0%)	20 (20.8%)	0.729
CCB	98 (51.0%)	48 (50.0%)	50 (52.1%)	0.885
β-Blocker	79 (41.1%)	42 (43.8%)	37 (38.5%)	0.558
DU	48 (25.0%)	28 (29.2%)	20 (20.8%)	0.243
Data of ECG				
IVS, mm	12.00 (3.000)	12.00 (2.000)	11.00 (3.000)	0.007
LVPW, mm	11.00 (3.000)	11.00 (3.000)	11.00 (2.000)	0.004
LVD, mm	45.00 (7.000)	45.00 (7.000)	44.00 (7.000)	0.184
LA, mm	30.00 (5.00)	31.00 (7.000)	29.00 (5.000)	0.001
LVEF, %	67.00 (7.00)	67.00 (8.000)	67.00 (6.000)	0.133
E peak	73.5 (29.000)	79.00 (28.000)	66.00 (27.000)	0.000
A peak	83.84 ± 20.305	83.52 ± 20.479	84.21 ± 20.211	0.815
e peak	6.00 (4.000)	5.00 (2.000)	8.00 (3.000)	0.000
a peak	11.00 (4.000)	11.00 (5.000)	11.00 (3.000)	0.812
E/A ratio	0.85 (0.517)	0.89 (0.548)	0.77 (0.466)	0.000
E/e ratio	15.08 (7.591)	16.25 (2.100)	8.67 (3.191)	0.000
Galectin-3, ng/ml	16.33 ± 3.504	17.90 ± 3.458	14.51 ± 2.569	0.000

Data are presented as number (%) for categorical variables, and as mean ± SD for continuous variables that conformed to a normal distribution. Other data that did not conform to a normal distribution are presented as median (IQR). Groups were compared using Chi-square, ANOVA, or Kruskal –Wallis tests. ECG, echocardiography; CHD, coronary heart disease; HBP, hypertension; NYHA, New York Heart Association; ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; CCB, Calcium channel blocker; B, Beta-adrenergic receptor blocker; DU, Diuretic; IVS, interventricular septal thickness; LVPW, left ventricular posterior wall thickness; LVD, Left ventricular diastolic diameter; LA, Left atrial diameter; LVEF, Left ventricular ejection fraction; E peak, Early diastolic mitral inflow peak velocity; A peak, late diastolic mitral inflow peak velocity; e peak, early diastolic Doppler spectrum of mitral valve; a peak, late diastolic Doppler spectrum of mitral valve.

TABLE 2 | Logistic regression analysis.

	B value	Wald	*P* value	OR value	95% C.I. of OR value	
					Lower limit	Upper limit
LVEF	−0.041	1.132	0.287	0.960	0.891	1.035
Galectin-3	0.454	40.096	<0.01**	1.574	1.368	1.812
LA	0.086	3.057	0.080	1.090	0.990	1.200
IVS	0.452	14.697	<0.01**	1.571	1.247	1.979
E/A value	1.597	8.014	0.005**	4.938	1.634	14.918

*IVS, interventricular septal thickness; LA, left atrial diameter; LVEF, left ventricular ejection fraction. **The difference was statistically significant.*

history of drug therapy. All patients signed a written consent form and the Ethics Investigation Committee approved the study.

Serum Concentration of Galectin-3 and Echocardiography

Blood samples were collected on the day subjects underwent echocardiography. Collected supernatants were centrifuged at 3,000 rpm for 15 min at 4°C. Serum concentration of galectin-3 was measured using an enzyme-linked immunosorbent assay protocol without cross-reactivity with collagens or other galectins. Detailed echocardiography was performed to evaluate parameters of diastolic function in accordance with published recommendations and guidelines (39).

The objective of this analysis was to compare the diagnostic value of galectin-3 in HFPEF with the relatively common echocardiographic criteria of HFPEF.

Statistical Analysis

Baseline features were compared between the two groups (HF group and control group). Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. Results are presented as mean (standard deviation, SD) for continuous variables, and as number (%) for categorical variables. Receiver operating characteristic (ROC) curves were established, and the area under the ROC curves (AUC) was calculated. AUCs were compared using the DeLong test. Sensitivity and specificity above the third and highest point of the Youlden index were used as indicators. We supplemented the analyses of diagnostic capacity by adjusting for age, sex, renal function, diabetes, hypertension, and atrial fibrillation. All statistical analyses were performed using SPSS software (version 25.0, Chicago, IL, USA). A two-sided P value < 0.05 was considered statistically significant.

RESULTS

Baseline Features

In accordance with the 2016 ESC guidelines for heart failure, 192 patients were enrolled. Among them, 96 met the criteria of HFPEF and were included in the HF group, while the remaining 96 were included in the control group. Baseline features are shown in **Table 1**. There were no significant differences in baseline features between the two groups. Overall, mean age was 66 years (interquartile range, 15.00), and 47.9% were female. Comorbidities included hypertension (81.8%), coronary heart disease (33.9%), diabetes (29.7%), and atrial fibrillation (8.3%). Mean concentration of serum galectin-3 was 16.33 ng/mL (SD, 3.504). Serum concentration of galectin-3 was significantly higher in the HF group compared with the control group ($P < 0.001$). Regarding echocardiogram data, the interventricular septal thickness, left ventricular posterior wall thickness, left atrial diameter, E peak, E/A ratio, and E/e ratio were higher in patients in the HF group, whereas left ventricular ejection fraction and e peak were lower in this group.

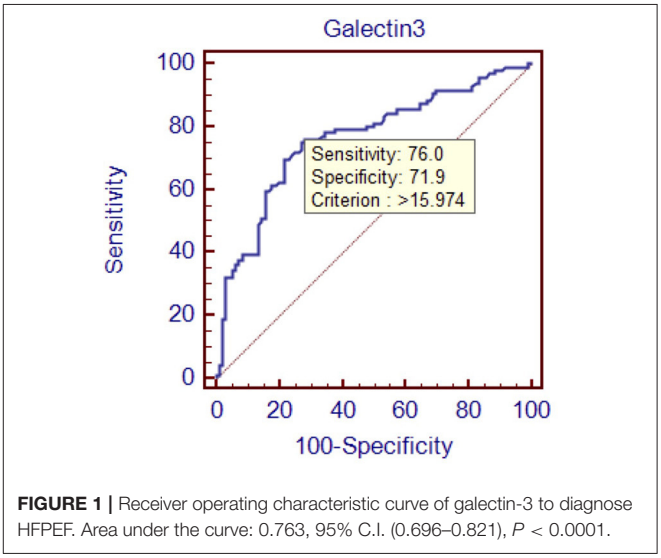

FIGURE 1 | Receiver operating characteristic curve of galectin-3 to diagnose HFPEF. Area under the curve: 0.763, 95% C.I. (0.696–0.821), $P < 0.0001$.

Binary Logistic Regression Analysis

To identify risk factors for HFPEF, we analyzed variables in which differences were observed between the HF and control groups but had no correlation between each other in regression analysis. The results showed that increased galectin-3 concentration increased the risk of HFPEF by approximately 57.4% [odds ratio (OR) 1.574, 95%CI: 1.368, 1.812, $P < 0.01$]. Interventricular septal thickness and E/A ratio also significantly increased the risk of HFPEF, OR and 95%CI were 1.571, (1.247, 1.979); 4.938, (1.634, 14.918), respectively, p values were all < 0.01 (see **Table 2**).

ROC Curve and AUC Analysis

To evaluate the diagnostic value of galectin-3 level for HFPEF, an ROC curve was constructed using MedCal software

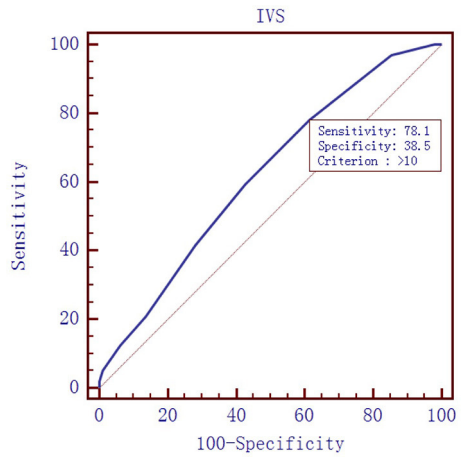

FIGURE 2 | Receiver operating characteristic curve of interventricular septal (IVS) thickness to diagnose HFPEF. Area under the curve: 0.619, 95% C.I. (0.546–0.688), $P = 0.0028$.

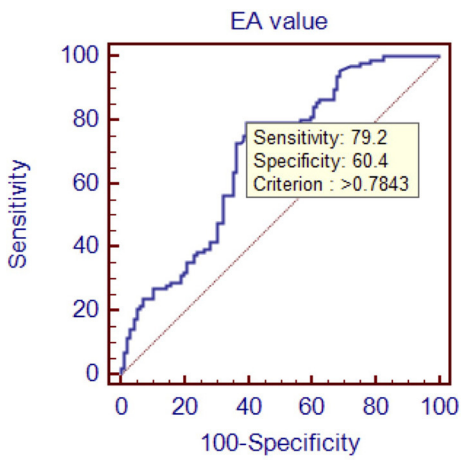

FIGURE 3 | Receiver operating characteristic curve of E/A value to diagnose HFPEF. Area under the curve: 0.688, 95% C.I. (0.618–0.753), $P < 0.0001$.

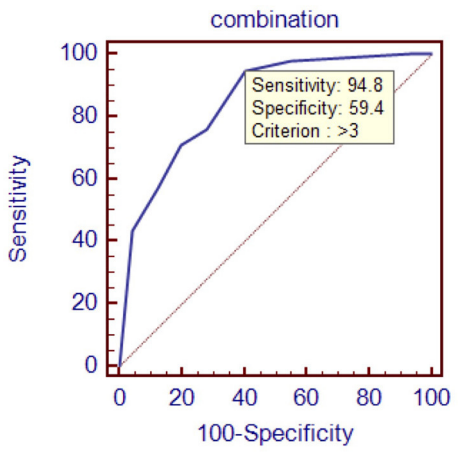

FIGURE 4 | Receiver operating characteristic curve of galectin-3 combined with interventricular septal thickness and E/A value. Area under the curve: 0.850, 95% C.I. (0.792–0.898), $P < 0.0001$.

based on galectin-3 concentration. The AUC was 0.763 (95% confidence interval (C.I.), 0.696–0.821, $P < 0.01$), and galectin-3 >15.974 ng/mL identified HFPEF with 76.0% sensitivity and 71.9% specificity. The AUC rose to 0.850 when galectin-3 was combined with interventricular septal thickness and E/A value, while the sensitivity rose to 94.8%. ROC analyses are shown in **Figures 1–4**, and data pertaining to the ROCs are shown in **Table 3**.

DISCUSSION

In the present study, we found that galectin-3 secretion was significantly increased in patients with HFPEF. This observation is consistent with recent findings (15–17, 40). In a study of 119 subjects, Gopal et al. demonstrated that galectin-3 level was increased in patients with heart failure, regardless of type (41). One study found that for each 1-ng/mL increase in galectin-3 concentration, the rate of heart failure readmission increased by 18% (35). Another study found that the risk of heart failure increased by 28% for each SD increase in galectin-3 concentration (26). Recent studies suggest that the targets of galectin-3 in myocardial fibroblasts and extracellular matrix, together with activated myocardial macrophages, can induce fibroblast activation and proliferation, stimulate infiltration of macrophages and mast cells, increase myocardial interstitial deposition of molecules such as type I collagen around the heart and blood vessels, and cause myocardial hypertrophy and decreased myocardial compliance, which ultimately lead to heart failure (42). Therefore, galectin-3 concentration in patients with HFPEF is higher than that in patients with heart failure without preserved ejection fraction, which confirms the microscopic mechanism from a macro perspective.

Binary logistic regression analysis showed that higher galectin-3 concentration was associated with the occurrence of HFPEF. Therefore, galectin-3 is an independent risk factor for HFPEF and can predict its occurrence. In this study, binary logistic regression analysis of galectin-3 concentration and HFPEF was consistent with previous studies and confirmed the value of using galectin-3 concentration for predicting HFPEF. Other studies made similar observations (20, 21, 23–26, 35, 40, 43–46), and galectin-3 has been approved for prognostic use in heart failure in the United States (29).

In fact, galectin-3 has proven to be predictive of morbidity and poor prognosis in many other diseases, not just heart failure. In diabetes, galectin-3 may mediate b-cell fibrosis through an inflammatory pathway, leading to impaired insulin secretion (47). In patients with cirrhosis, hepatocytes were induced to secrete Galectin-3, while normal hepatocytes had a decreased scavenging effect on galectin-3, which ultimately

TABLE 3 | ROC data.

variables	Sensitivity (%)	Specificity (%)	Cutoff point	AUC
Galectin-3	76	71.9	15.974 ng/ml	0.763
IVS	78.1	38.5	10 mm	0.619
E/A	79.2	60.4	0.7843	0.688
Combination	94.8	59.4	/	0.850

IVS, interventricular septal thickness; E peak, Early diastolic mitral inflow peak velocity; A peak, late diastolic mitral inflow peak velocity; AUC, Area under curve.

leaded to an increase in serum galectin-3 concentration, while the latter promoted the deterioration of liver cirrhosis by inducing activation of hepatic stellate cells and fiber synthesis (48). High levels of galectin-3 was thought to be associated with renal interstitial fibrosis, renal tubule atrophy, and endovascular fibrosis, possibly through immune reaction-related pathways (49). Elevated galectin-3 level was associated with the development of heart failure in hypertension patients (19). In galectin-3 knockout mice, a high-fat diet did not cause fat cell hypertrophy, suggesting that galectin-3 was involved in the pathogenesis of obesity (50). Galectin-3 was also demonstrated to be an independent predictor of all-cause and cardiovascular death in patients with systemic sclerosis (51). There were no significant differences in baseline data in our study, and renal function, BMI and other data were not matched. However, a high-quality, large-sample study showed that galectin-3 was an independent predictor of mortality, even after adjusting for factors such as blood pressure, lipids, kidney function, and BNP (14). Therefore, our results remain highly reliable.

To determine the diagnostic value of galectin-3 for HFPEF, an ROC curve was constructed and the AUC was calculated. The AUC was 0.763, indicating that galectin-3 has moderate diagnostic value for HFPEF. At the cutoff point of 15.974 ng/mL, the diagnostic sensitivity and specificity of galectin-3 for HFPEF was 76.0 and 71.9%, respectively, and were significantly higher than those of the other two risk factors (interventricular septal thickness and E/A value). There are prior reports on the diagnostic capacity of galectin-3 for heart failure, although most of these involved comparisons with BNP and other indicators. Javier Carrasco-Sánchez et al. obtained an AUC of 0.630 for galectin-3, and although this result was not ideal, it was superior to that of NT-proBNP (33). In our study, the diagnostic value of galectin-3 was compared with the current "gold standard" for heart function diagnosis in accordance with the latest heart failure diagnostic guidelines. Additionally, we found that galectin-3 had a higher diagnostic value than interventricular septal thickness and E/A ratio, two indicators that are clearly associated with E/E, which further demonstrated the high value of galectin-3 for diagnosing HFPEF. There were differences in cutoff points between our study and others. In the study by Chen et al., the cutoff point was 7.52 ng/mL (44), whereas Trippel et al. selected 17.8 ng/mL as the cutoff point (35). The large differences in cutoff points may be related to the study populations, sampling times, and testing methods. For example, in the study by Chen et al. the participants had chronic heart failure, while ours had HFPEF, and the ratio of NYHA III–IV was much higher than in our study (44).

A long-term follow-up study showed a significant increase in the rate of new-set heart failure with increased galectin-3 concentrations (21), Another spanning 10 years study also found that dynamically elevated galectin-3 level was more closely associated with new-set heart failure and mortality (52). This phenomenon can be explained by cellular mechanisms. Cardiac failure with fractional ejection retention was characterized by increased myocardial stiffness and myocardial interstitial fibers (53). An *in vitro* cell experiment showed increased secretion of galectin-3 after stretching cardiac muscle cells (18), Galectin-3 can increase infiltration of macrophages and mast cells in myocardial cells, leading to myocardial fibrosis, myocardial stiffness and left ventricular dysfunction (15, 19). A series of previous studies have confirmed a causal relationship between galectin-3 and cardiac remodeling (21). This explained that why there was diagnostic value of Galectin-3 in HFpEF.

The early diagnosis of HFpEF was the shortcoming of heart failure diagnosis at present (13), the diagnostic significance of this stage was to early manage and reduce the incidence of subsequent acute heart failure or other symptomatic heart failure (such as heart failure in stage C or D), and to reduce the depletion of medical resources. Studies had concluded that in the diagnosis of heart failure, because BNP is more sensitive to volume overload, galectin-3 is more sensitive to fibrosis (37), a combination of the two was recommended to increase diagnostic accuracy (36, 37). Such advice had some merit, but was bound to increase healthcare costs. Echocardiography for the diagnosis of heart failure with retained ejection fraction has been the basis of current diagnosis, but the examination process of echocardiography was time-consuming, relatively expensive, and subject to subjective influence by personnel. One report suggests that galectin-3 may be an alternative to ultrasound in diagnosing diastolic dysfunction (54). Galectin-3 showed considerable sensitivity and specificity, with low economic cost, time cost and labor cost. Therefore, galectin-3 may be considered for the diagnosis of HFpEF alone.

This study had some limitations. First, the sample size was relatively small. Future studies in larger populations are necessary to further clarify the diagnostic value of galectin-3. Second, we used the cardiac ultrasound E/e ratio as the gold standard reference for diagnosis, and although the values were measured by experienced echocardiographers, they were not performed by the same individual. Therefore, there may have been errors in the measured values because of the subjectivity of ultrasound diagnosis.

CONCLUSIONS

In this study, increased galectin-3 level was observed in patients with HFPEF. Galectin-3 level was demonstrated to be a risk factor for HFPEF (AUC: 0.763, 95% CI: 0.696–0.821, $P < 0.01$, and the sensitivity is 76.0% while the specificity is 71.9% at the threshold 15.974 ng/mL). Galectin-3 has moderate diagnostic

value for HFPEF. Owing to the overall lack of evidence in this area, more studies are necessary to verify our conclusions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of First Affiliated Hospital of Shantou University Medical College. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Segmental Tissue Speckle Tracking Predicts the Stenosis Severity in Patients With Coronary Artery Disease

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Objective: Two-dimensional speckle tracking echocardiography (2D-STE) has been used as a diagnostic tool for coronary artery disease (CAD). However, whether vessel supplied myocardial strain and strain rate (SR) predict the severity of coronary artery stenosis in patients with CAD is unknown. This study aimed to investigate correlation of cardiac mechanical parameters in tissue speckle tracking measurements with coronary artery stenosis diagnosed by cardiac catheterization in patients with clinically diagnosed CAD.

Methods and Results: Among 59 patients analyzed, 170 vessels were evaluated by coronary angiography and the corresponding echocardiography to quantify left ventricular myocardial strain and SR. The average longitudinal strain and SR of the segmental myocardium supplied by each coronary artery were calculated to achieve vessel myocardium strain (VMS) and strain rate (VMSR). The VMS and VMSR at each of four severity levels of stenosis showed significant differences among groups ($p = 0.016$, and $p < 0.001$, respectively). The strain and SR in vessels with very severe stenosis (≥75%, group IV; $n = 29$), 13.9 ± 4.3, and 0.9 ± 0.3, respectively, were significantly smaller than those of vessels with mild stenosis ≤25%, group I; $n = 88$, 16.9 ± 4.9, $p = 0.023$, and 1.2 ± 0.3, $p = 0.001$, respectively. The SR in vessels with moderate stenosis (26–49%, group II; $n = 37$), 1.0 ± 0.2, was significantly smaller than that in vessels with mild stenosis vessels ($p = 0.021$). The lower VMS and VMSR, the higher possibility of severe coronary stenosis is. The VMS and VMSR lower than 13.9 ± 4.3 and 0.9 ± 0.3, respectively predicted the severe coronary stenosis. The VMS and VMSR higher than 16.9 ± 4.9 and 1.2 ± 0.3, respectively predicted mild or no coronary artery stenosis.

Conclusions: The actual stenosis rate in catheterization demonstrates that this technique was able to assess coronary artery condition. Thus, the application of a non-invasive method of 2D-STE to evaluate and simplify diagnosis of CAD is feasible.

Keywords: coronary angiography, stenosis rate, tissue speckle tracking, echocardiography, coronary artery disease

INTRODUCTION

It is widely known that cardiovascular disease (CVD) is a leading cause of mortality, and CVD has affected the economy worldwide. According to a report from the American Heart Association in Heart Disease and Stroke 2021 Statistics Update, ∼18.6 million people died from CVD in 2019. In the US, the estimated direct and indirect economic cost of heart disease from 2016 to 2017 was $219.6 billion (1). Coronary artery disease (CAD), a major adverse cardiac event, is the underlying cause of angina, myocardial infarction, and sudden cardiac death. Despite various advances in technology, early diagnosis of CAD remains challenging. Moreover, tissue level cardiac mechanics are not understood systematically. Although coronary angiography is the gold standard method for identification of coronary artery stenosis, catheterization is invasive compared to other diagnostic tools (2). Echocardiography is the most accessible and cost-effective technique routinely used for these patients. This non-invasive imaging model has been utilized visually across the spectrum of CAD (3). Emerging ultrasound procedures, such as tissue Doppler imaging and the speckle tracking method, are gradually becoming required for first-line clinical evaluation. However, the disease process of myocardial mechanics occurs much earlier before the structural changes of the myocardium are expressed and visualized *via* traditional echocardiography (4). In terms of technical aspects, with improvement of echocardiographic processing, traditional Doppler imaging has evolved to the tissue level. To measure myocardial tissue velocity in the Doppler ultrasound system, a high-pass filter is implemented to exclude the low-frequency components from the vessel wall and the blood flow signal. However, this technique could lead to a potential loss of information from the low-velocity flow (5, 6). Speckle tracking echocardiography (STE) is a novel extension of the Doppler technique that focuses on left ventricular (LV) wall motion. LV wall motions represent the major cardiac events that occur in all individuals. Three main coronary arteries have their major distribution in this area. Two-dimensional speckle tracking echocardiography (2D-STE) has been determined to be a promising tool for LV functional assessment and can detect subclinical myocardial dysfunction early in the disease process (7, 8). Computer algorithms evaluate the fractional or percent change of "speckle" observed from the original dimension of the myocardium to compute the strain, deformation, dimensionless quantity, and strain rate (SR), which is the change in strain over time (9). Strain and SR are superior to the velocity measurement of tissue Doppler, which is inherently angle dependent (10). In 2D-STE, SR is a good representation of myocardial contractility and rate of change in pressure (dP/dt). Experimental studies have demonstrated that the degree of post-systolic thickening and SR are suitable parameters for ischemia detection (11, 12).

Here, we hypothesized that the regional strain and SR of vessels, specifically in segmental lesions, can be used to predict the stenosis condition in each coronary artery of patients with CAD. Thus, this study aimed to investigate potential correlations among strain, SR and coronary artery stenosis diagnosed by cardiac catheterization.

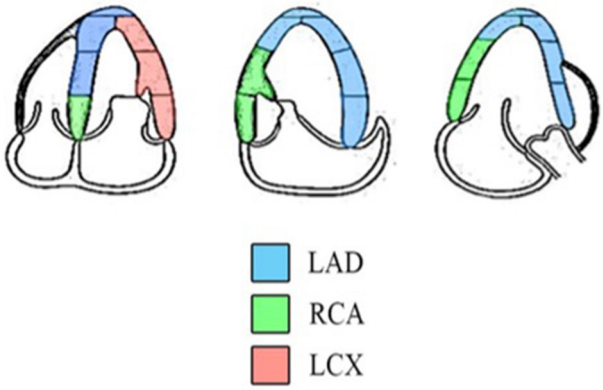

FIGURE 1 | Diagram indicating the distributions of coronary artery perfusion. The myocardium is supplied by the LAD, RCA, and LCX (18).

METHODS

Patient Selection

The cross-sectional study was conducted. We recruited 59 patients with suspected CAD in Taipei City Hospital Yangming Branch as selection criteria by clinical diagnosis from August 2020 to May 2021. Patients with clinically diagnosed CAD assessed by transthoracic echocardiography (TTE) were included. Individuals aged <20 years and >75 years were excluded. Patients with terminal major organ disease, cancer, hemodialysis, significant valvular disease or a prosthetic valve, any rhythm other than sinus (including atrial and ventricular arrhythmias and pacemaker rhythm), an unstable hemodynamic condition, obesity with BMI ≥30 kg/m² (13–15), and inadequate quality ultrasound images were excluded. Patients with a left ventricular ejection fraction (LVEF) <55% and regional wall motion abnormality (RWMA) were also excluded.

Echocardiographic Examination

All patients underwent comprehensive TTE by experienced sonographers, within 2–3 weeks before coronary angiography. The machine used for evaluation was a commercially available system (Vivid E95, GE Healthcare, Horten, Norway) equipped with M5S, a 1.4–4.6 MHz phased array probe. In all subjects, standard 2D images, the apical 4-, 3-, and 2-chamber views (A4C, A3C, and A2C, respectively), consisting of three cardiac cycles actuated to the QRS complex, were captured and analyzed. Conventional 2-D parameters were analyzed and recorded (16). LVEF was calculated by Simpson's biplane method. Preserved and normal LVEF were indicated as 50–60% and >60%, respectively. LV diastolic function was also assessed according to the guideline (17). Peak velocities of early (E) and late (A) diastolic flow, and the E/A ratio were measured using pulsed-wave interrogation of the mitral valve inflow. Tissue Doppler imaging was performed to assess septal mitral annular motion. Early septal diastolic annular velocity (e') based on tissue Doppler imaging was measured. The E/e' ratio was calculated (18).

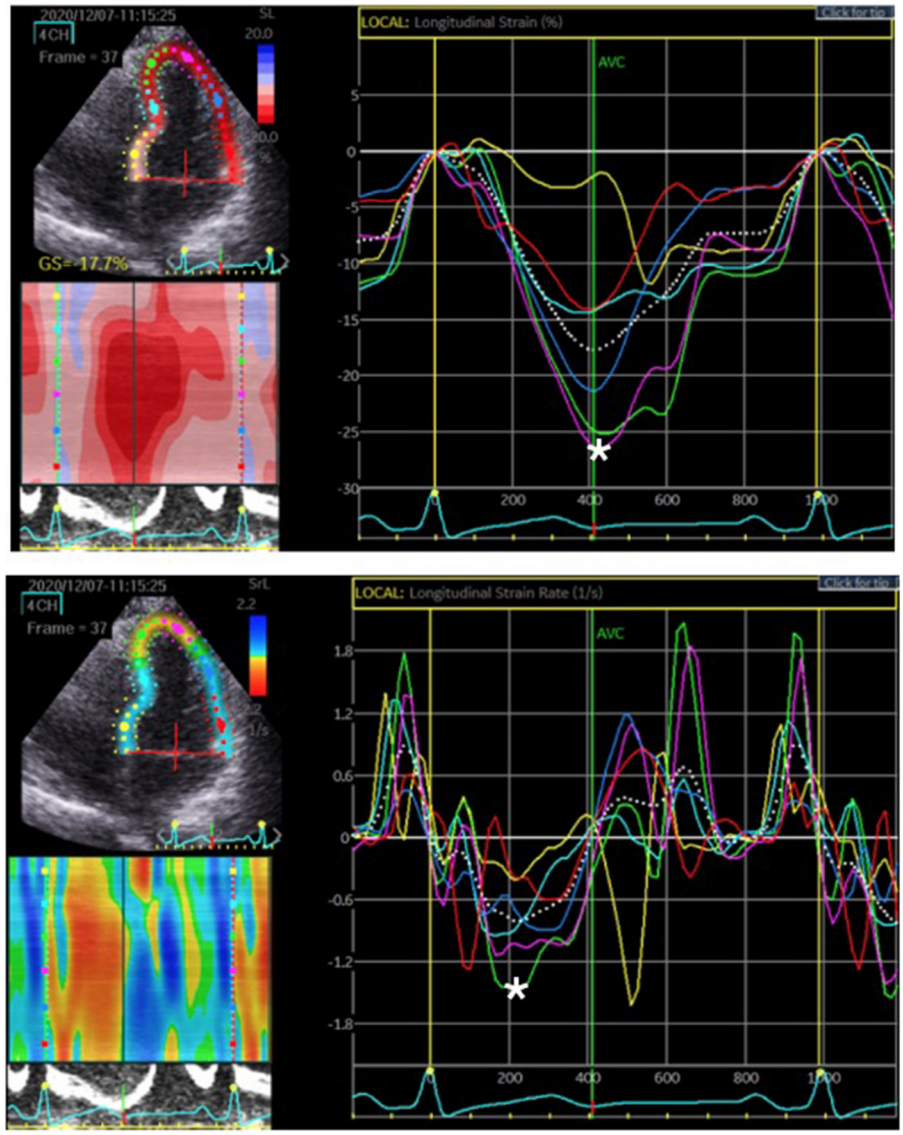

FIGURE 2 | The region of interest, LV myocardium, was tracked. The longitudinal strain and SR were quantified as the peak systolic value in each myocardial segment. The upper figure represents the peak systolic strain. The most negative value, which is denoted by the white asterisk, was measured before aortic valve closure (AVC). The lower figure represents the peak systolic SR. The most negative value is denoted by the white asterisk on the rate/time curve during systole.

2D Speckle Tracking

The standard echocardiographic views in A4C, A3C, and A2C on three consecutive beats were used to obtain longitudinal strain and SR analysis of the LV using 2D speckle tracking software (EchoPAC, GE Healthcare, Horten, Norway). Adequate TTE examinations, defined as good image quality and an optimum frame rate of 50–70 *frames per second, were used for* feature myocardial tracking. The myocardium was divided into six segments in each view. The recorded images were analyzed offline. A region of interest was defined at end-diastole by manual outline. Individual regions of the border were adjusted until the whole myocardium was correctly tracked. The wall thickness was adjusted manually if necessary for complete analysis (19). Myocardial strain is a measure of the deformation when two neighboring points of myocardium move at different velocities resulting in myocardium changing its shape (deforming). Strain can be presented as percentage (%), which includes lengthening (positive strains) and shortening (negative strains). Myocardial SR is the rate of deformation in the unit of 1/s. Cardiac strain and SR were assessed to evaluate myocardial deformation and displayed in an 18-segment LV model. Three main arteries, the right coronary artery (RCA), the left circumflex artery (LCX), and the left anterior descending artery (LAD), supply the myocardium. The regional wall segments in a series of longitudinal views were composed of basal septal, mid septal, apical septal, apical lateral, mid lateral, and basal

lateral segments of the LV. According to the American Heart Association recommendations for use of echocardiography (20), the distributions of coronary artery perfusion are described in **Figure 1**. The basal septal LV segment in A4C, basal and mid septal LV segments in A3C, and basal and mid septal LV segments in A2C are supplied by the RCA. The apical, mid, and basal lateral LV segments in A4C are supplied by the LCX. The mid and apical septal LV segments in A4C, apical septal and apical, mid, and basal lateral LV segments in A3C, and apical septal and apical, mid, and basal lateral LV segments in A2C are supplied by the LAD (20). The myocardium of the 2D-STE images of each of the three coronary arteries was quantified to obtain the longitudinal strain and SR of each wall, as shown in **Figure 2**. During systole and diastole, the myocardium shortens and lengthens the wall muscles in the longitudinal planes. The average longitudinal strain and SR of the segmental myocardium supplied by each coronary artery were calculated to achieve vessel myocardium strain (VMS) and strain rate (VMSR). Inter-observer reproducibility was also examined.

Coronary artery disease was diagnosed by clinical symptoms, electrocardiography, treadmill exercise stress test, thallium scan and cardiac CT. Common medications used in patients with CAD, such as nitrates, β-blockers and statins, were reported.

Cardiac Catheterization

The study population was categorized by the severity of coronary artery stenosis diagnosed by coronary angiography. Stenosis was considered significant if there was ≥70% diameter stenosis according to the indication for percutaneous coronary intervention (PCI) (21). The luminal stenosis of the three main arteries, RCA, LCX and LAD, was quantified for further evaluation of CAD. The stenosis condition was categorized into four severity levels, ranging from mild to very severe. Cases with ≤25% stenosis were classified as mild (group I); cases with 26–49% stenosis were classified as moderate (group II); cases with 50–74% stenosis were classified as severe (group III); cases with ≥75% stenosis were classified as very severe (group IV) following criteria modified from Arbab-Zadeh and Fuster (22, 23).

Among the patients analyzed, 170 vessels were evaluated by coronary angiography and 2D-STE. The results of vessel-supplied tissue tracking and coronary angiography were compared.

Statistical Analysis

All continuous variables are presented as mean ± standard deviation, whereas categorical variables are presented as proportions or percentages. Comparison of continuous variables within two groups was performed using an independent *t*-test. Comparison of continuous variables between coronary artery stenosis severity groups was performed using one-way ANOVA with Tukey *post-hoc* adjustments performed when significant differences were detected. Categorical variables were compared using the X^2 test, as indicated. Correlation between variables was analyzed by linear regression analysis for continuous variables and by logistic regression analysis for categorical variables. A p-value < 0.05 was considered statistically significant. The statistical analysis was done using SPSS software, version 21.0 (IBM Corporation, NY, USA).

TABLE 1 | Comparison of patient characteristics data in the insignificant and significant CAD groups.

	Insignificant CAD ($n = 33$)	Significant CAD ($n = 26$)	p-value
Gender (men/women), *n*	16/17	16/10	0.982
Age (years)	66.4 ± 10.7	62.7 ± 10.6	0.186
Weight (kg)	65 ± 13.1	73.1 ± 15.3	0.091
Height (m)	1.6 ± 0.1	1.7 ± 0.1	0.498
BMI (kg/m²)	24.4 ± 3.6	26.5 ± 5	0.162
Smoking, *n* (%)	7(21)	4 (15)	0.142
Family history, *n* (%)	19 (58)	14 (54)	0.763
Diabetes, *n* (%)	12 (36)	13 (50)	0.361
Hypercholesterolemia, *n* (%)	8 (24)	2 (8)	0.063
Hypertension, *n* (%)	20 (61)	16 (62)	0.658
Total cholesterol (mg/dL)	169.8 ± 40.6	158.2 ± 37.4	0.878
LDL cholesterol (mg/dL)	106.3 ± 36.7	99.7 ± 33.5	0.575
HDL cholesterol (mg/dL)	52.2 ± 14.6	42.6 ± 11.1	0.720
Triglycerides (mg/dL)	120.8 ± 71.7	150.1 ± 71.6	0.422
BUN (mg/dL)	19.6 ± 8.2	21.6 ± 10.6	0.372
Creatinine (mg/dL)	0.9 ± 0.5	1.1 ± 0.5	0.657
eGFR (mg/dL)	79.4 ± 31.5	58.8 ± 30.4	0.091
Glucose (mg/dL)	118 ± 40.8	143.3 ± 96.8	0.133
HbA1c (%)	7.4 ± 3	8.0 ± 2.5	0.630
Medications			
Anticoagulant, *n* (%)	19 (58)	26 (100)	0.375
Nitrate, *n* (%)	6 (18)	7 (27)	0.789
β-blocker, *n* (%)	10 (30)	9 (35)	0.973
ARB, *n* (%)	7 (21)	3 (12)	0.595
CCB, *n* (%)	13 (39)	15 (58)	0.234
Statins, *n* (%)	9 (27)	15 (58)	0.649
Diuretics, *n* (%)	9 (27)	4 (15)	0.308

LDL, low-density lipoprotein; HDL, high-density lipoprotein; BUN, blood urine nitrogen; eGFR, estimated glomerular filtration rate; HbA1c, glycohemoglobin; ARB, aldosterone receptor blockers; and CCB, calcium-channel blocker.
Data are presented as mean ± SD or number (percentage).

RESULTS

Clinical Characteristics

Patients ($n = 59$; mean age, 65.5 ± 9.2 years) who met the baseline inclusion criteria and from whom adequate image quality with optimal rational tracking of any myocardial segments was obtained were evaluated in this study. Patients were divided into two groups, those with insignificant CAD ($n = 33$; <70% diameter stenosis) according to angiography and those with significant CAD ($n = 26$; ≥70% diameter stenosis; mean age, 62.7 ± 10.6 years). Cardiac catheterizations were performed within 2–3 weeks following echocardiography. There were no significant differences in baseline parameters and clinical data between the insignificant and significant CAD groups, as presented in **Table 1**.

Baseline Echocardiographic Findings

Conventional echocardiographic data are shown in **Table 2**. No patient had evidence of RWMA, and all patients had

TABLE 2 | Comparison of conventional echocardiographic measurements in the insignificant CAD and significant CAD groups.

	Insignificant CAD ($n = 33$)	Significant CAD ($n = 26$)	*p*-value
IVSd (cm)	0.9 ± 0.2	1.1 ± 0.3	**0.024**
LVIDd (cm)	3.8 ± 0.4	4.0 ± 0.6	0.196
LVPWd (cm)	1.1 ± 0.3	1.2 ± 0.3	0.355
LVIDs (cm)	2.6 ± 0.3	2.7 ± 0.3	0.404
LVEF (%)	65.3 ± 4.8	67.2 ± 4.9	0.138
E vel (m/s)	0.7 ± 0.2	0.7 ± 0.2	0.914
A vel (m/s)	0.9 ± 0.2	0.8 ± 0.3	0.070
E/A ratio	0.8 ± 0.3	1.2 ± 0.9	0.061
e' (cm/s)	7.1 ± 2.4	6.8 ± 2.0	0.621
E/e'	11.0 ± 4.0	11.7 ± 4.4	0.572
GLS (%)	−16.7 ± 4.7	−15.1 ± 5.0	0.140
GLSR (1/s)	1.0 ± 0.4	0.9 ± 0.3	0.294

IVSd, intraventricular septal width in diastole; LVIDd, left ventricular Internal dimension in diastole; LVPWd, left ventricular posterior wall width in diastole; LVIDs, left ventricular Internal dimension in systole; LVEF, left ventricular ejection fraction; E vel, early mitral flow velocity; A vel, late mitral flow velocity; E/A, ratio of mitral peak velocity of early filling (E) to peak velocity of late filling (A); E/e', ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e'); GLS, global longitudinal strain; and GLSR, global longitudinal SR.

Data are presented as mean ± SD or number (percentage).

The bold value indicate statistically significant analysis, p-value < 0.05.

globally preserved and normal LVEF at admission, both in the insignificant (65.3 ± 4.8) and significant CAD groups (67.2 ± 4.9). There were no significant differences in echocardiographic parameters between patients with insignificant and significant CAD except interventricular septal width (IVSd). Patients with significant CAD had thicker IVSd than patients with insignificant CAD (1.1±0.3 vs. 0.9±0.2, respectively; $p = 0.024$).

2D-STE Analysis

We examined 177 vessels in 59 patients. Among these vessels, seven had hypoplasia. When a vessel had hypoplasia, the myocardium segments supplied by the nearby coronary artery were combined with the adjacent myocardial strain and SR of the adjacent coronary arteries. Therefore, the VMS and VMSR areas were adjusted accordingly. The representative cases of longitudinal strain and SR (**Figure 2**) with quantification using EchoPac software are presented. The global longitudinal strain (GLS) and SR (GLSR) were initially quantified. However, the GLS and GLSR in the insignificant CAD group were not significantly different from those in the significant CAD group, $p = 0.140$ and $p = 0.294$, respectively. The longitudinal strain and SR of the vessel supplied areas in each stenosis severity group showed significant differences between groups, as determined by one-way ANOVA [$F_{(3,169)} = 3.53$, $p = 0.016$] and [$F_{(3,169)} = 6.86$, $p < 0.001$], respectively (**Figure 3**). The VMSs and VMSRs in each group were compared. A Tukey's HSD *post-hoc* test revealed that the longitudinal strain in vessels with very severe stenosis (group IV; $n = 29$), 13.9 ± 4.3, was significantly smaller than that in vessels with mild stenosis (group I; $n = 88$), 16.9 ± 4.9, $p = 0.023$. For the longitudinal SR, vessels with very severe stenosis (group IV; $n = 29$), 0.9 ± 0.3, and moderate stenosis (group II; $n = 37$), 1.0 ± 0.2, showed significantly smaller values than that of vessels with mild stenosis (group I; $n = 88$), 1.2 ± 0.3, $p < 0.001$ and $p = 0.021$, respectively (**Table 3**). The results implied that vessels with more severe stenosis have lower SR values. Furthermore, the results demonstrated that VMSR is superior to VMS as a sensitive predictor of coronary artery condition. The inter-observer variabilities for the measurements of GLS and GLSR were 95.8 and 96.4%, respectively, and those for segmental strain and SR were 97.3 and 95.2%, respectively.

DISCUSSION

This cross-sectional study prospectively recruited patients diagnosed with CAD. According to previous studies, longitudinal myocardial strain is the most clinically relevant and reproducible index among all cardiac dimensional deformation (24, 25). We focused on the correlation between regional myocardial deformation and coronary artery stenosis to determine the potential of 2D-STE as an early diagnostic tool for CAD. Here, the VMS and VMSR were evaluated. The identification of CAD is accomplished by the aforementioned clinical protocols. No one tool is perfect for diagnosis. Thus, a combination of various methods is required to identify CAD precisely. The ideal utility is approachable, non-invasive, cost-effective, none/less radiative with high sensitivity and specificity. 2D-STE fulfills all these requirements. To the extent of accurate CAD diagnosis, presentation of the clinical symptoms, checking the laboratory data, baseline electrocardiogram test (ECG), exercise stress tests (treadmill exam) and echocardiography are routinely examined. On condition that using the combination of baseline evaluations could not verify CAD, computed tomography angiography and nuclear medicine procedures are required. Stefanini et al. described that the sensitivity and specificity of CT angiography to detect coronary diameter stenosis >50% are ∼81–99%, and 64–93%, respectively. However, CT angiography has more clinical role in patients with low to intermediate CAD risk, compared to catheterization exam. The specificity and negative predictive value decrease once patient risk increases (26). For nuclear thallium stress tests, the accuracy for detecting CAD was reported that the sensitivity varies from 70 to 92%, whereas the specificity is around 70% (27). Various analysts described that sensitivity of the diagnostic power of treadmill stress testing ranges from 61 to 73%, while specificity is around 59–81% (28, 29). For global longitudinal strain, the sensitivity of CAD diagnostic rate is 74.4%, and specificity is 72.1% (30). Given all the above data, the role of STE in CAD diagnosis is superior to treadmill stress testing, equivalent to nuclear thallium stress tests, and inferior to CT angiography. Nonetheless, CT angiography has limited roles in general practice. Echocardiography could be easily accessible and routinely performed in patients with suspected CAD. From all of the above factors, STE becomes a promising tool for diagnosis of CAD. Although these alternative methods have relatively higher sensitivity and specificity, the arrangements are time-consuming, costly, require radiologists, technicians

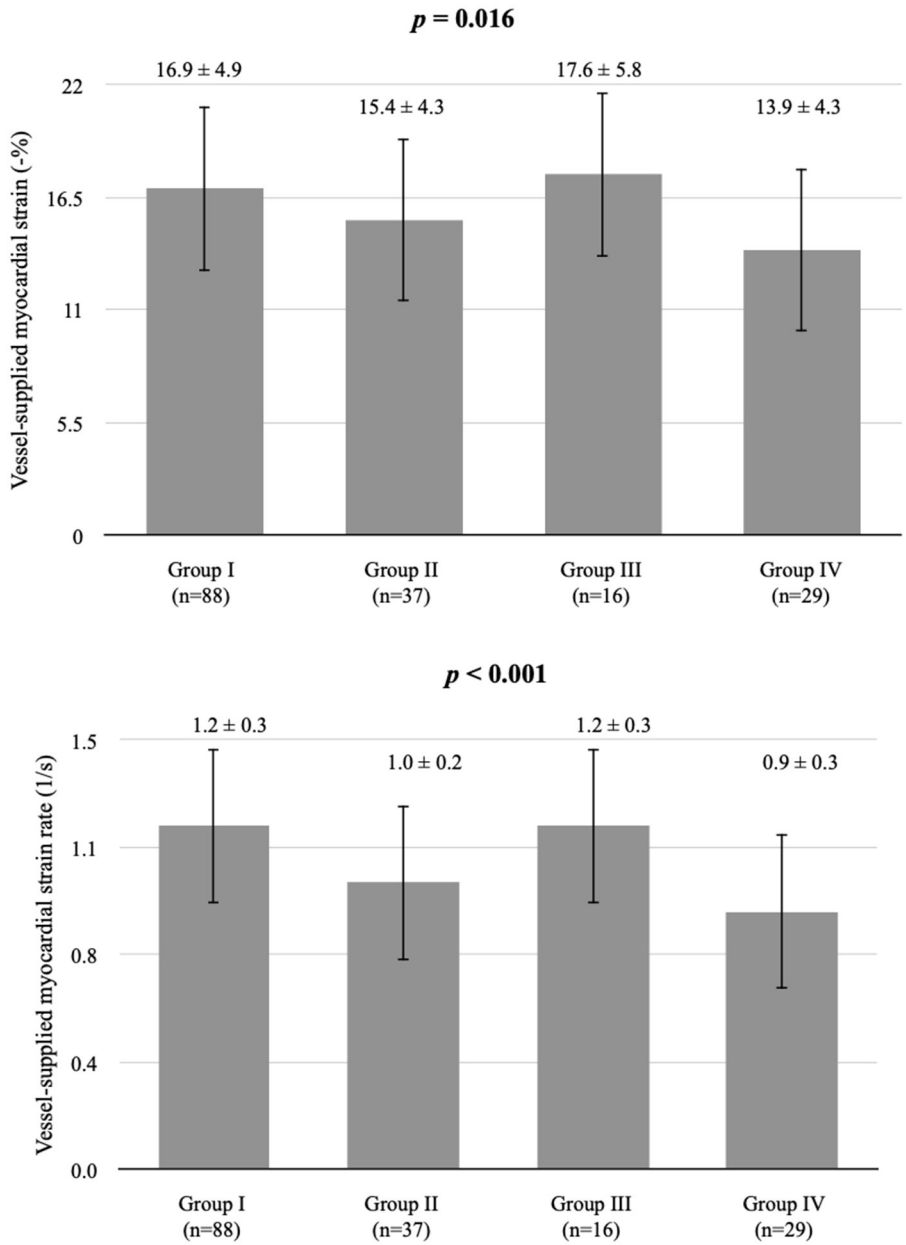

FIGURE 3 | Comparison of longitudinal strain and SR in vessel-supplied myocardium according to coronary artery stenosis severity. *Group I, mild, stenosis ≤25%; group II, moderate, stenosis 26–49%; group III, severe, stenosis 50–74%, and group IV, very severe, stenosis ≥75% following criteria modified from Arbab-Zadeh and Fuster (22, 23). Vessel-supplied myocardial strain is presented as a percentage. Vessel-supplied myocardial SR is in the unit of 1/s.

of nuclear medicine involvement, more health insurance reimbursement and delayed diagnosis. Besides, computed tomography angiography and nuclear medicine procedures have been concerned to be relative risk due to radiation exposure from cumulative imaging examinations. The application of 2D-STE demonstrated that early identification of CAD by echocardiography was a primarily credible diagnostic procedure non-invasively and less costly. The establishment of 2D-STE status contributes the "assisted technologies in diagnostic decision making" to be possible in CAD identification. STE data could be immediately proceeded following echocardiography by software, which reveals the possibility of vessel stenosis. Accordingly, the treatment plan is made. STE technique could early differentiate vessels with non or mild stenosis from the vessels with high possibility of severe stenosis which require further evaluation by angiography or angioplasty. Our modality of diagnostic technology proposed that the STE technique could be used to screen the condition of vessel stenosis in CAD

TABLE 3 | Longitudinal strain and SR according to coronary artery stenosis severity.

	Stenosis (I)	Stenosis (J)	Mean difference (I-J)	*p*-value
	I	II	1.4 ± 0.9	0.415
		III	0.7 ± 1.3	0.944
		IV	2.9 ± 1.0	**0.023**
Longitudinal strain				
	II	III	2.1 ± 1.4	0.430
		IV	1.5 ± 1.1	0.587
	III	IV	3.6 ± 1.4	0.069
	I	II	0.18 ± 0.06	**0.021**
		III	0.02 ± 0.09	0.997
		IV	0.28 ± 0.07	**<0.001**
Longitudinal SR	II	III	0.17 ± 0.09	0.320
		IV	0.09 ± 0.08	0.645
	III	IV	0.26 ± 0.10	0.052

The bold values indicate statistically significant analysis, p-value < 0.05.

time-efficiently and primarily in an economic way without performing unnecessary CT or nuclear medicine. Even though 2D-STE implementation requires investment in the technology including ultrasound and STE software, CT and nuclear medicine machines are much more costly. Since quality image acquisition is significant for analysis, capacity building of the human resource is important. The technique trainings and experience exchanges are needed to provide to physicians and sonographers for STE implementation and measurement. Our study elucidated the segmental tissue speckle tracking could predict stenosis severity of specific coronary arteries in patients with CAD, which provide clinical impression for early intervention and efficient treatment to prevent acute illness condition and more complex treatment thereafter.

GLS can be used early to identify patients with CAD based on findings of a previous study (31). However, we found that in patients without RWMA, GLS and GLSR were not able to differentiate significant from insignificant CAD. Classification of patient groups by significant (>70% stenosis) and insignificant (<70% stenosis) CAD in this study aimed to elucidate and decrease the confounding factors such as hypertension and diabetes mellitus, which impact on strain and SR. These factors were similar ($p > 0.05$) in both groups. Thus, these confounding factors will not affect our analysis of VMS and VMSR. This is the first study that reveals that VMS and VMSR serve as better indicators for the evaluation of CAD than global myocardium tissue speckle tracking. The deformation of the myocardium supplied by the three main arteries, as mentioned earlier, was comprehensively quantified. Our analysis demonstrated that segmental longitudinal strain and SR values of the particular vessel-supplied myocardium significantly decreased corresponding to the severity of vessel stenosis. In general, the longitudinal strain and SR of the vessel supplied areas in vessels with mild and very severe stenosis have demonstrated significant differences. This implies that VMS and VMSR are feasible as early diagnostic parameters of CAD at high risk of myocardial ischemia. The lower VMS and VMSR, the higher possibility of severe coronary stenosis is. The VMS and VMSR lower than 13.9 ± 4.3 and 0.9 ± 0.3, respectively predicted the severe coronary stenosis. The VMS and VMSR higher than 16.9 ± 4.9 and 1.2 ± 0.3, respectively predicted mild or no coronary artery stenosis. In our finding, VMSR correlated even more with coronary artery stenosis severity. This elucidates that VMSR is a sensitive predictor of coronary artery condition. It will have a promising role in the evolution of diagnostic parameters. Our results indicated that VMSR was generally superior to VMS. Previous studies in patients with CAD reported that the impairment of myocardium deformation, specifically strain evaluated by 2D-STE, initially occurs from the endocardial layer. The endocardial layer of the myocardium is more vulnerable to ischemia (32). Compared to strain, which is load-dependent, SR is less related to pre-load and after-load (33). Moreover, SR imaging with elastance has shown a strong correlation with peak and mean SRs, higher than conventional tissue velocity or strain (34). However, one pitfall of SR measurement was noise sensitivity. The SR calculation influences the signal-to-noise ratio (35). Tissue tracking techniques have been evolved for two decades. There are technical challenges in STE that will have to be overcome (36). For instance, LV global transitional motion is the cause of baseline drift. The measurement of displacement may not be zero at the end of the cardiac cycle (i.e., from breathing, which is not synchronized with the cardiac cycle). To correct the unwanted calculation error, vendors have suggested that users apply drift compensation (37, 38). Despite that, our study showed good inter-observer reproducibility, as mentioned above. This is due to the improvement of the machinery and software for speckle tracking algorithms that influence the reduction of this variation. As another example, calculations for all three myocardial layers contribute to the strain and SR being more reliable and reproducible. Imaging system validation could facilitate good quality images. In terms of resolution, the number of beams per image sector, pixel size (spatial) and acquisition frame rate (temporal) setting considerably improve image quality (39). We optimized the frame rate for the best tracking and circumspectly decreased the spatial resolution to elevate the accuracy of the tracking technique. To evaluate the VMS and VMSR precisely, our study minimized the risk of comorbidity effects by excluding confounding factors of heart wall motions, diabetes, and hypertension, which may influence cardiac function. In addition, patients with conditions of systolic dysfunction and RWMA were also excluded, because VMS and VMSR can be affected as well, especially in chronic patients.

LIMITATIONS

This was a small-scale, single-center study and the first of its kind. A multicenter study with a larger number of patients should be pursued to investigate this issue further. In addition, we excluded patients with RWMA. Therefore, our method can be applied only to patients without RWMA. However, we demonstrated the efficacy of VMS and VMSR. Finally, different machine vendors could be assessed, and their results compared

among. Standardization among different vendors and software applications is required to improve the technical pitfalls for more efficient clinical meaning and application for all 2D-STE.

CONCLUSION

Our findings revealed that strain and SR of the myocardium supplied by LAD, LCX, and RCA could be used to predict the stenosis condition in each coronary artery. The actual stenosis rate in catheterization proved that this technique is a potentially valuable clinical tool to assess coronary artery condition and implied the application of this non-invasive method of tissue speckle tracking for early evaluation and diagnosis of CAD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Taipei City Hospital (TCHIRB-1020802-E). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SC contributed to investigation, data curation, formal analysis, and writing original draft. S-JC contributed to conceptualization, methodology, resources, review, editing, and supervision. MD provided resources, validation, supervision, data curation, review, editing, and funding acquisition. S-CC contributed to validation and investigation. C-LC and C-YH contributed to investigation and resources. H-HC and C-LT provided supervision. All authors contributed to the article and approved the submitted version.

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Preclinical Study of Biphasic Asymmetric Pulsed Field Ablation

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Pulsed field ablation (PFA) is a novel method of pulmonary venous isolation in atrial fibrillation ablation and is featured by tissue-selective ablation. Isolation is achieved via the application of high-voltage microsecond pulses that create irreversible perforations in cell membranes (i.e., electroporation). We proposed a new biphasic asymmetric pulse mode and verified the lesion persistence and safety of this mode for pulmonary vein ostia ablation in preclinical studies. We found that biphasic asymmetric pulses can effectively reduce muscle contractions and drop ablation threshold. In the electroanatomic mapping, the ablation site showed a continuous low potential area, and the atrium was not captured after 30 days of pacing. Pathological staining showed that cardiomyocytes in the ablation area were replaced by fibroblasts and there was no damage outside the ablation zone. Our results show that pulmonary venous isolation using the biphasic asymmetric discharge mode is safe, durable, effective, and causes no damage to other tissues.

Keywords: pulsed field ablation, pulmonary venous isolation, atrial fibrillation, tissue-selective ablation, biphasic asymmetric pulse

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INTRODUCTION

Pulsed field ablation (PFA), also known as irreversible electroporation, has been applied to cardiac ablation in recent years (1–3). PFA is a non-thermal ablative modality. It is used to treat atrial fibrillation and does not cause damage to other tissues such as the esophagus and nerves, because the threshold for cardiomyocytes is the lowest of any other tissue (4–9).

Due to these potential advantages of PFA, the technique has attracted more attention in the field of ablation treatment of atrial fibrillation (10). Although the safety and effectiveness of PFA have been proved in many experimental studies (11, 12), PFA is still in the preliminary research stage and the optimal pulse modes and ablation dose remain unclear.

The ablation effect of PFA is greatly influenced by the pulse amplitude (y-axis) and pulse width (x-axis). Lavee et al. (13) were the first to perform cardiac PFA with a monophasic direct current pulse sequence of 1,500–2,000 V, 100 μs (microsecond) per pulse, and frequency of five pulses/second. However, an electrical pulse creates local and systemic muscle contractions that make it difficult to accurately perform ablation; to solve this problem, substantial doses of chemical paralytics need to be administered to patients. Arena et al. (14) proposed a new type of high-frequency biphasic pulse to reduce muscle contraction during ablation, but the high frequency is often accompanied by heat generation. Moreover, biphasic pulses require higher voltage to achieve a similar effect compared with monophasic pulses, because the cancellation effect means that the effect of the first pulse is reduced by

the second pulse of opposite polarity (15, 16). For example, Sano et al. (17) found that the lethal threshold of a biphasic symmetric pulse was 1,316 V/cm, which was significantly higher than that of a biphasic asymmetric pulse (536 V/cm). Our previous study on smooth muscle cells and cardiomyocytes found that asymmetric pulse width was superior to biphasic symmetric pulse ablation under equal amplitudes (18).

Based on our previous cell experiment, PFA with biphasic asymmetric pulses was carried out in 12 Bama miniature pigs. Gross examination and histological investigation were used to evaluate the lesion persistence and safety of PFA at the 7th and 30th day after pig PFA operation. Moreover, PFA with biphasic asymmetric pulses was carried out in 2 dogs, and electroanatomic mapping was used to display the lesion area. Our results would be used to help to make a treatment plan for clinical trials in the future.

MATERIALS AND METHODS

Materials

Experimental Animals

Twelve healthy 12-month-old Bama miniature pigs (weight 45 ± 5 kg; of either sex) were provided by Tianjin TEDA Cardiovascular Hospital-Animal Experiment Center (SYXK (JinBin) 2020-0004). Two healthy Labrador retrievers (weight 24 and 25.1 kg; of either sex) were provided by Beijing Tonghe Litai Biotechnology Co., Ltd. (SCXK (Jing) 2019-0005). All our experiments were approved by the Ethics Committee (approval number:2021021).

Reagents and Instruments

The medicine used in the present study were Sumianxin II injection (compound preparation of Jingsongling, edetic acid, Dihydroetorphine hydrochloride (DHE), and haloperidol) (Jilin Dunhua Shengda Animal Pharmaceutical Co., Ltd.), 1% propofol injection (AstraZeneca, Italy), and enoxaparin sodium injection (Sanofi, France). Other medicines and instruments were conventional equipment found in laboratories and catheterization laboratories.

Experimental Method

Preoperative Treatment

The animals were fasted for 12 h before operation, and water was withheld for 6 h. Aspirin (5 mg/kg) was administered once daily for the first 3 days. Before operation, blood was collected from the precaval vein for preoperative routine blood testing. Conventional doses of xylazine and midazolam were used for the induction of anesthesia. After the peripheral venous access was established, 30–50 mg of propofol was intravenously infused as appropriate to obtain stable anesthesia. After being weighed, the animals were placed in a *U*-shaped groove in supine position on the digital subtraction angiography operating bed, and tracheal intubation was performed. A ventilator was used to support mechanical ventilation. The skin on the front of the chest and the bilateral inguinal regions was prepared for operation. The bilateral femoral veins were punctured by Seldinger's method and a 6F vascular sheath was placed. Propofol was infused at a rate of 3–5 mg/kg/h throughout the operation to maintain anesthesia. The vital signs were routinely monitored intraoperatively.

Pulsed Field Catheter Ablation

After the atrial septal puncture sheath was guided into the left atrium under endoluminal sonography and X-ray fluoroscopy, 6,000 units of heparin were injected, and 1,000 units of heparin were added every hour during the operation. The position of the sheath was adjusted, and pulmonary venography was performed to show the shape and branching of the pulmonary veins. A circular mapping catheter was placed in the left superior pulmonary vein to evaluate the effect of electrical isolation.

The PFA system was composed of a pulse instrument (PFA instrument) (Tianjin Intelligent Health Co., Ltd., Tianjin, CHN) and a PFA catheter (Tianjin Intelligent Health Co., Ltd., Tianjin, CHN) (**Figure 1A**). The pulse instrument was used to set the parameters, including the number of pulses, number of pulse groups, and pulse amplitude. The 10.5 F PFA catheter had four frames; each frame contained two electrodes, one of which was a positioning electrode (**Figure 1B**). When fully expanded, the diameter of the most distal electrode was 28 mm.

The PFA catheter was half-opened in the left atrium through a flexible sheath, and then with the guidance of guidewires, the ablation electrode was pushed to a position close to the pulmonary vein ostium. The adherence condition was reflected by angiography and signal feedback of the PFA instrument (**Figure 1E**). The catheter electrode was optimized, and the pulse mode was modified. As shown in **Figure 1F**, based on the existing two pulse modes a and b, the pulse mode was improved to type c (**Figure 1F**, c), so that the negative narrow pulse depolarized the positive wide pulse and reduced the muscle contractions caused by the pulses, which enhanced the safety and maneuverability. The pulse width of all positive pulses was 5 μs and the pulse width of negative pulses was 3 μs. The pulse voltage, pulse width, frequency, and electrode spacing of the PFA system used in the present study were able to be adjusted to ensure the ablation effect. The pulse released 1,000 V microsecond pulses through the ECG synchronization signals.

The experiment included two groups. Group A and B comprised six pigs each. PFA was carried out in all pigs. Animals in Group A were euthanized at 7th day after ablation and in Groups B at 30th day after ablation. The ablation tissue (left superior pulmonary vein) was regarded as the experimental group and non-ablation tissue (left inferior pulmonary vein) was the control group. After electric discharge, pacing was performed by a pacemaker (Medtronic 5388, MN, USA) in groups A and B. The pacing voltage was 10 mv, and the pacing frequency was about 15% higher than the heart rate before ablation (**Figure 1D**). As the biphasic asymmetric pulse method greatly reduced the impact on the skeletal muscles, no intervention was performed for the skeletal muscles.

Besides, in order to further verify the effectiveness of PFA, two dogs were selected as dog group and electroanatomic voltage mapping of the left atrium was constructed after ablation.

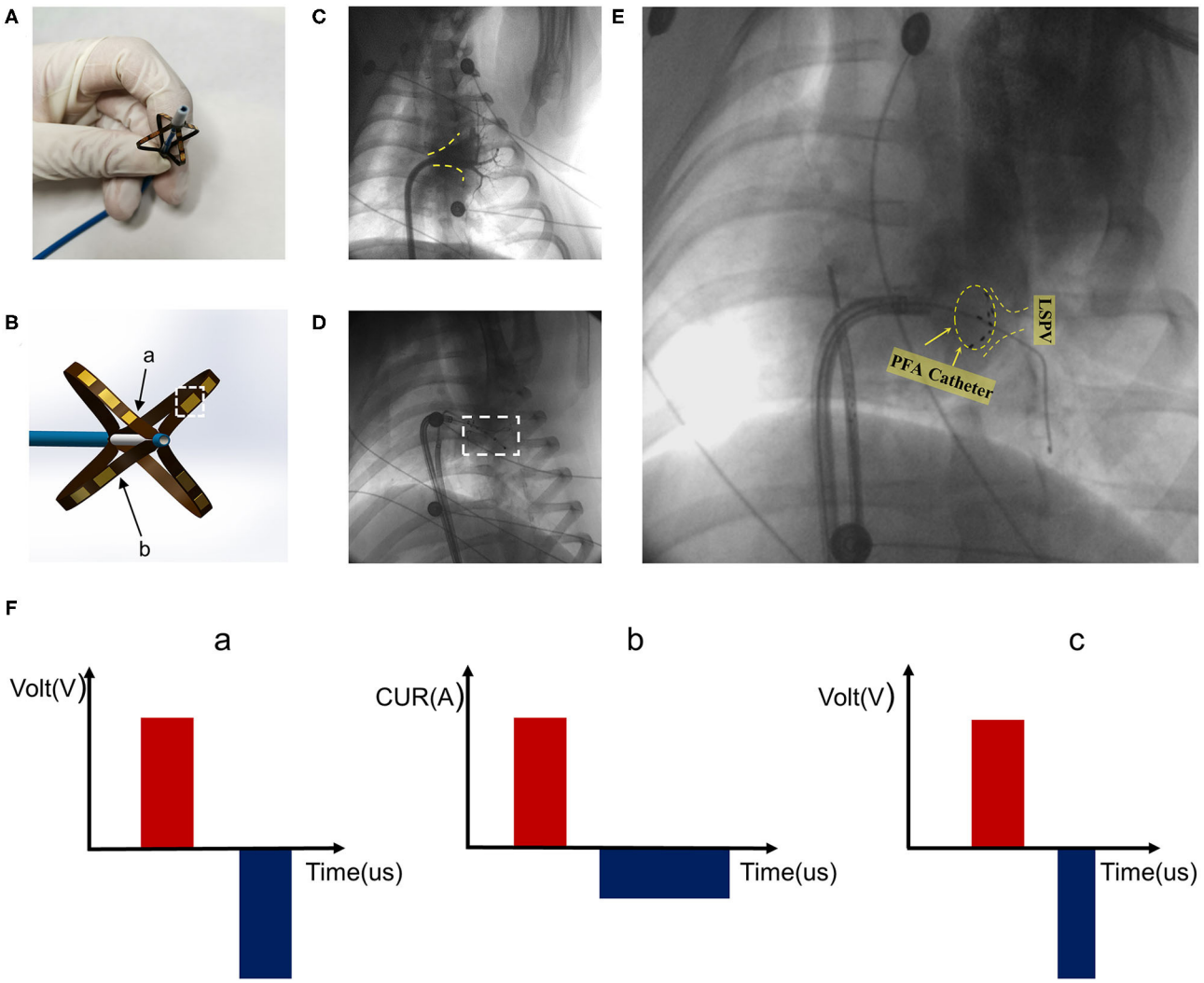

FIGURE 1 | Pulsed field ablation system. **(A)** Biphasic asymmetric pulsed field ablation catheter in open state. **(B)** Illustration of the front end of the ablation catheter. Arrow a is the positioning electrode. Arrow b refers to the catheter frame. The white dotted box represents the electrode. **(C)** Left superior pulmonary angiography. Yellow dotted line marking the contour. **(D)** Pacing after ablation. **(E)** PFA catheter for ablation at the left superior pulmonary vein ostia. PFA catheter shape shown in yellow dotted circle. **(F)** Pulsed field ablation mode. Mode c is biphasic asymmetric pulsed field ablation.

After Care

All animals underwent Computed Tomography (CT) to check for adverse conditions such as air emboli, thrombi, vascular access tears, and cardiac tamponade. After the catheter was withdrawn, the condition of the puncture points was observed. The vital signs, mental behavior, and activity status of the animals were observed after they awoke from anesthesia.

Animals were injected with 20 IU/kg of intramuscular penicillin sodium + 0.9% normal saline twice daily for 3 days after operation to prevent infection. Intensive care was performed after operation, and the clinical changes were recorded. Daily wound cleaning was implemented to prevent infection. On post-op days 7 and 30, twelve pigs were euthanized and dissected for gross observation and pathological analysis. The dogs were followed up for 30 days, and circular mapping electrodes were used to create electroanatomic maps on each animal.

Gross Examination of Specimens

The surviving pigs were euthanized on post-op days 7 (n = 6) and 30 (n = 6). The heart, lungs, and adjacent trachea and esophagus were removed as a whole. The hearts were dissected, the ablation sites were identified, and the pathological changes of the ablation sites and adjacent tissues were observed. The continuity of the ablation area and the presence of local thrombosis were evaluated.

Histological Investigation

The specimens were fixed in formalin and stained with Masson trichrome and HE to evaluate the presence

of lesions in the pulmonary vein ostia, transmural ability, neurological activity in the lesions, presence of thrombi and edema, degree of damage to adjacent tissues, and other related findings. Other assessed variables included fibrosis, inflammation, hemorrhage, and nerve damage.

Statistical Analyses

Origin8.5 software was used for data analysis. The data were presented by Average ± SD or Median (25th, 75th percentiles). The Mann-Whitney U test was used for continuous parameters in different experimental and/or control groups due to the non-normal distribution and the small sample size. $p < 0.05$ was defined as statistically significant.

TABLE 1 | Procedural characteristics of biphasic asymmetric PFA.

Group	A&B	Dog group
PFA Times, median (sec)	81.6 (73.7, 94.3)	71.9 (71.0, 72.8)
Peak current, average (Amp) ±SD	7.83 ± 1.90	7.10 ± 0.42
Therapy dose (V, Voltage)	1,000 V	1,000 V
Procedure time, median (minutes)	95 (88, 104.5)	81.5 (80.75, 82.25)

PFA Times data are presented as median (25th, 75th percentiles).
Procedure time data are presented as median (25th, 75th percentiles).
PFA, pulsed field ablation; sec, second; Amp, ampere; SD, Standard Deviation.

RESULTS

Clinical Observation and Survival Rate

The first day after operation, the behavioral activities, mental status, appetite, and food intake of the animals returned to normal. The animals had no hollow back, piloerection, loose stools, or perinasal bleeding throughout the experiment. No animals died, and the blood test results were normal on the 7th and 30th day after ablation.

Acute Experiments

The ablation zone was the left superior pulmonary vein in all pigs, with an ablation success rate of 100% (12/12). In the pigs (Group A&B), the average ablation times were 84.06 ± 13.09 s, and the average operation time was 92.3 min. The average peak current of ablation in the pig experiment was 7.83 ± 1.90 A (Ampere). The ablation zone was the right superior pulmonary vein in all dogs, with an ablation success rate of 100% (2/2). In the dog group, the average ablation time for 1,000 pulses was 71.90 ± 2.48 s. The average peak current of ablation in the dog experiment was 7.10 ± 0.42 A (**Table 1**). None of the animals showed obvious arrhythmia during the experiments.

When the pigs were given pacing stimulation after the ablation, the pacing signal was detected by ECG monitoring, but the heart rate did not increase. In the dog group, electroanatomic mapping showed that the right superior pulmonary vein potential disappeared immediately after

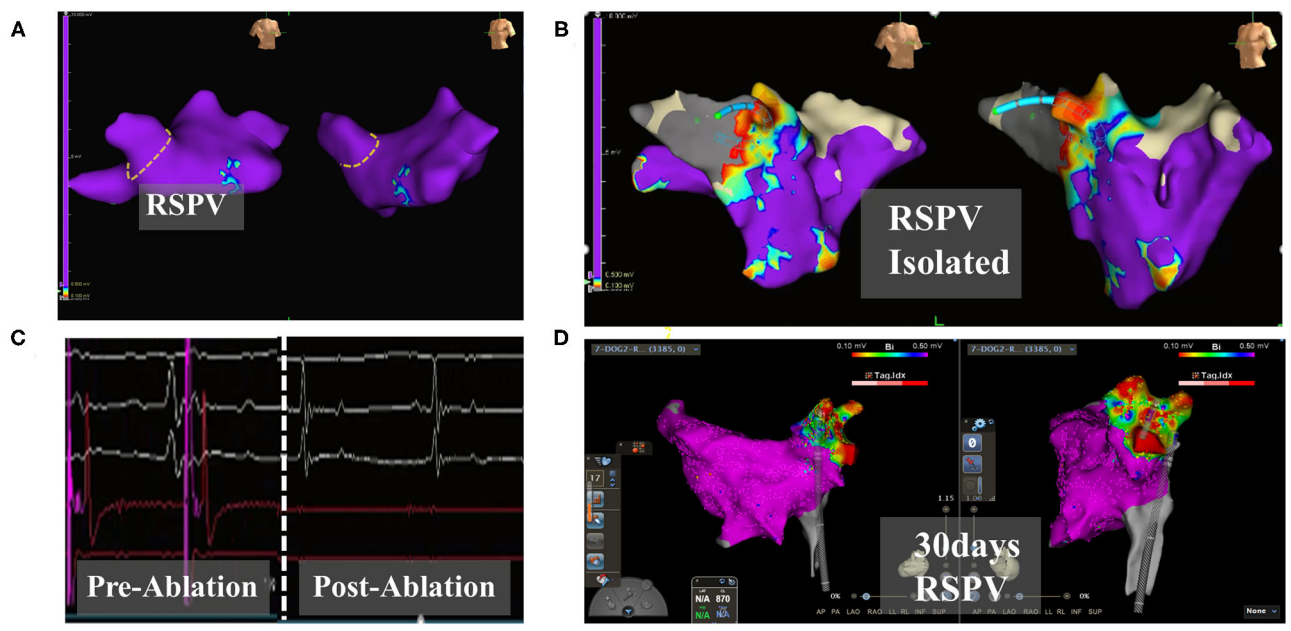

FIGURE 2 | Electroanatomic modeling of the right superior pulmonary vein. **(A)** Baseline potentials in right superior pulmonary were assessed. The yellow dotted line draws the right superior pulmonary vein ostia. **(B)** Post-operative ablation site shows a low potential area. **(C)** Pulmonary vein electrograms from PFA catheter ablation. Left: Pre-ablation. Right: Post-ablation. **(D)** Right superior pulmonary vein potential after 30 days. Continuous low potential in the ablation zone. The color of the mapping from red to purple indicates the potential from low to high. EnSite, Abbott: **(A–C)**. Carto3, Johnson & Johnson: **(D)**.

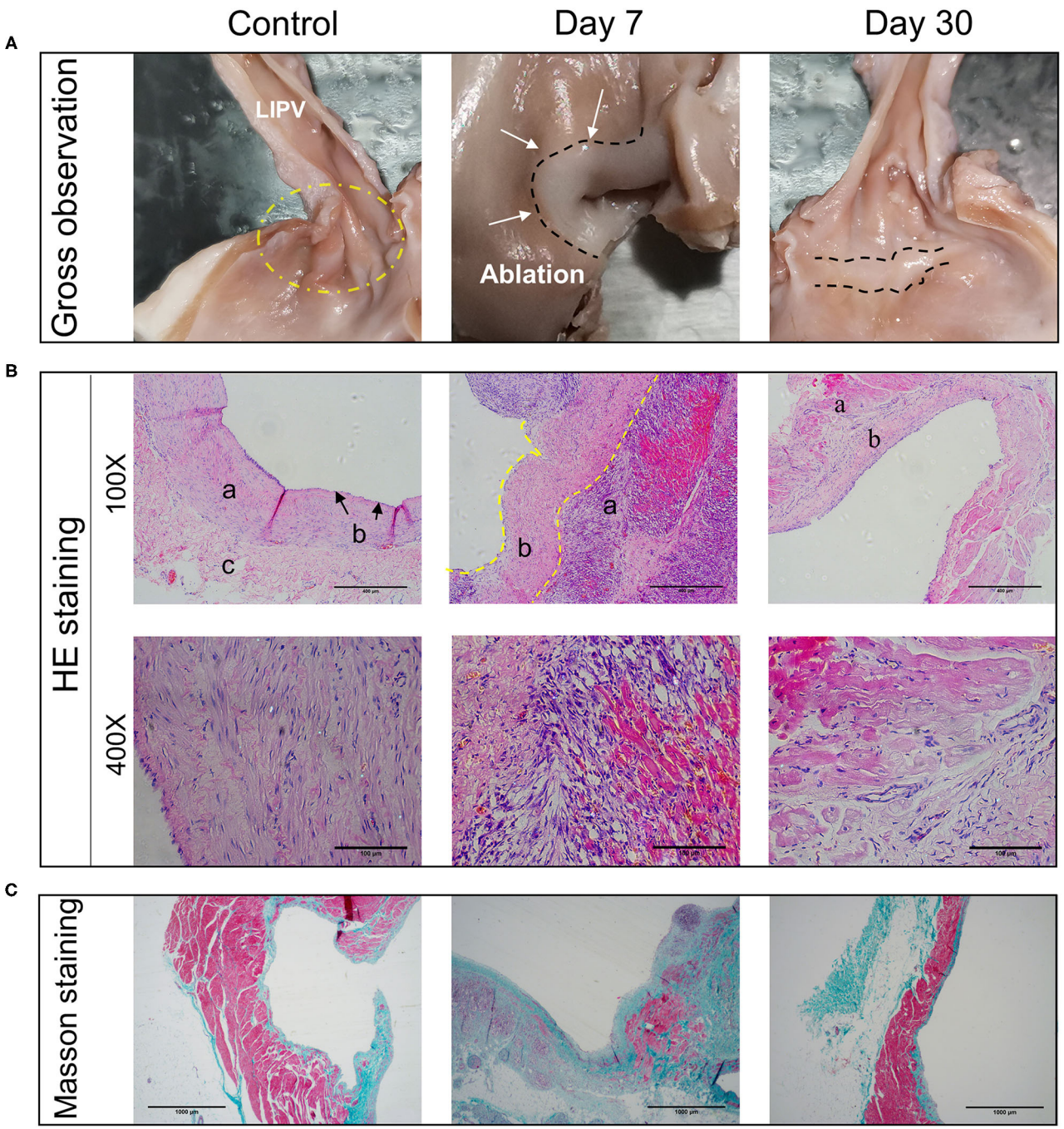

FIGURE 3 | Pathological changes of myocardial tissues after PFA ablation. **(A)** Gross observation of the left superior pulmonary vein ablation site. In the control group, lesion areas were not seen. The 7- and 30-day groups (group A and B) show a clear ablation zone. **(B)** HE staining of ablation sites at 100X and 400X. a indicates myocardial tissue. b represents intimal layer (endothelium, fibroblasts and connective tissue). c is marked with adventitia. **(C)** Masson staining of ablation sites (40X). Control group, days 7 and 30 from left to right.

ablation (**Figures 2A,B**). The voltage mapping showed low voltage, indicating afferent block (**Figure 2C**). At the 30th day after operation, the right superior pulmonary vein pacing did not cause atrial capture, indicating afferent block (**Figure 2D**).

Gross Observation of the Pulmonary Vein Ostia and Adjacent Tissues

After all pigs were euthanized, gross observation was conducted to identify any esophageal or tracheal deformation and to evaluate the smoothness of the surface. The conditions of the

TABLE 2 | Pathology summary of Group A and B.

Group	A	B	*P*-value*
Number of ablated locations (*n*, total)	6	6	–
Targeted anatomical location	LSPV	LSPV	–
Euthanasia (d, days)	7 d	30 d	–
Transmurally achieved	6/6	6/6	–
Wall thickness of ablated tissue, average (mm) ± SD	0.68 ± 0.24	0.60 ± 0.27	0.589
Thickness of Cf, average (mm) ± SD	0.68 ± 0.24	0.096 ± 0.03	0.002
Depth of Cf (median, %)	100.00%	18.30%	0.002
Other lesions	0/6	0/6	–

**P-values were shown for the Mann-Whitney U-test.*
LSPV, left superior pulmonary vein; RSPV, right superior pulmonary vein; Cf, collagen fibers.
The total wall thickness in the control group was 0.88 ± 0.02 (average ± SD).
The collagen fiber thickness in the control group was 0.11 ± 0.04 (average ± SD).

TABLE 3 | Comparisons for percentages of the collagen fiber depth over total thickness.

Groups	Depth percentage*	*P*-value
7 d after the operation		
Group A (*N* = 6)	100% (100%, 100%)	0.002
Control A (*N* = 6)	13.27% (11.28%, 14.95%)	
30 d after the operation		
Group B (*N* = 6)	18.30% (13.68%, 20.14%)	0.699
Control B (*N* = 6)	16.01% (11.30%, 19.04%)	

**Depth Percentage means the percentages of the collagen fiber depth over total thickness, and they are presented as median (the 25th percentile, the 75th percentile).*

adventitia and epithelium of the esophagus and the conditions of the tunica adventitia of trachea were observed with the naked eye and found there was no damage. The lung specimens were soft, light, smooth, moist, elastic, spongy, and free of scarring. The vagus nerves were intact and the upper and lower connections were normal under observation with the naked eye (**Figure 1**).

On the 7th day after operation, the ablation zones had a pale circular pulmonary vein appearance with a clear boundary (**Figure 3A**, Day 7). On the 30th day after the operation, there was an obvious white circular ablation zone in the pulmonary vein ostia, with similar morphology as on the 7th day after operation (**Figure 3A**, Day 30). There was no obvious damage outside the ablation zone. The boundary was clear, the transmural ability was obvious, and there was no pulmonary vein stenosis or thrombosis (**Table 2**).

Histological Investigation

At 7 days after the operation, there was a clear circumferential ablation zone at the ablation site. Under 100× magnification, HE (hematoxylin-eosin) staining showed a clear boundary between the ablation and non-ablation zones and a large amount of layer-by-layer deposition of collagen and fibrotic tissue proliferation under the intima of the ablation zone; the myocardial cells had irregular morphology and were arranged in a disorderly fashion (**Figure 3B**, 100X, Day 7). Under 200× magnification, there was increased infiltration of monocytes, a certain amount of cell infiltration and proliferation of epithelioid cells, and hyperemia in the middle layer of the myocardial tissue. Under 400× magnification, the nuclei of infiltrating cells were as oblong as those of smooth muscle cells (**Figure 3B**, 400X, Day 7).

At 30 days after the operation, the infiltration of the middle cardiac muscle layer had disappeared, and there was no congestion, inflammatory cells, or signs of thrombosis. The middle layer of cardiomyocytes had shrunk in shape, the nuclei had fragmented or disappeared, cardiomyocytes showed a large amount of necrosis, myocardial endothelial cells had formed, and a large number of fibroblasts had replaced cardiomyocytes and were growing under the endothelium. There were no obvious effects on arterioles and venules (**Figure 3B**).

Masson staining of specimens collected on the 7th post-operation (post-op) showed a thickened intimal layer of the pulmonary vein, a large number of collagen fibers. The average thickness of collagen fibers is 0.68 ± 0.21 (±SD). And a large amount of collagen in the intimal medial layer (**Figure 3C**, Day 7). At 30 days, the number of collagen fibers in the intimal layer had basically returned to normal (**Figure 3C**, Day 30), 0.096 ± 0.03 (±SD) (**Table 2**). Using the Mann-Whitney *U*-test, there is significant differences in the variable of transmural ability indicated by percentages of the collagen fiber depth at the 7th day after operation ($P = 0.002$), compared with the control (**Table 3**). However, the measurement of transmural ability appeared similar to the control on the 30th day after operation ($P = 0.699$).

DISCUSSION

The usual atrial fibrillation catheter ablation is performed using the RF technique, which applies a high-frequency alternating current to heat and damage the myocardial tissues (19). However, the disadvantages of the RF technique are the difficulty in controlling the size of the treatment zone and the high risk of adverse effects due to excessive damage. Subsequently, the cryoballoon ablation technique emerges. The cryoballoon technique is the use of cryogenic energy, which leads cells to necrosis by freezing. However, it damages blood vessels and other tissues (20). PFA technology is derived from the principle of electroporation, which exposes cells to electrical pulses to increase the permeability of cell membranes (21). Previous studies have shown that cardiomyocytes have lower electroporation thresholds than cell types related to collateral

damage, such as the cells of nerves, arteries, and the esophagus. For example, Kaminska et al. (22) found that a pulse intensity higher than 375 V/cm had an ablation effect on cardiac muscle in a MTT assay on rat cardiomyocytes. Koruth et al. (23) found no lesions in the lumen and outer surface of the esophagus after ablation with a peak electric field intensity of 900 V/cm during PFA of the esophagus. Maor et al. (7) found that the ablation of smooth muscle cells was ineffective when the electric field intensity of the pulse field was lower than 875 V/cm. Due to differences between cell types in electroporation thresholds, the unique tissue selectivity of PFA in the treatment of atrial fibrillation has the great advantage of reducing complications compared with ablation via traditional energy sources, such as RF, which indiscriminately damage all tissues in the hot zone. In clinical operation, isolation using the RF method is performed in a point-by-point mode. The mode needs further mapping and ablation. In contrast, PFA creates a closed-loop isolation region, which avoids the problem of RF ablation and greatly shortens the ablation time.

Preclinical studies have evaluated parameters that affect the effectiveness and safety of PFA, such as the electric field intensity and pulse field direction (24). And Reddy et al. had already demonstrated that PFA preferentially affected myocardial tissue with excellent durability and chronic safety in human trials (11). The mode of ablation in (11) was biphasic and symmetric. The difference between our experiment and previous PFA studies is the introduction of a new biphasic asymmetric pulse ablation mode, which narrows the width of the negative pulse and reduces the contractions of the muscle caused by the positive pulse (18). So before the clinical experiments, pigs were used to evaluate the safety and efficacy of biphasic asymmetric pulse ablation mode. As a result, there is no need to inject muscle relaxant before operation. In the original biphasic symmetric pulse mode (**Figure 1F**, a) (14), there was a certain amount of cancellation, which required the provision of a higher pulse intensity during ablation (25). The biphasic asymmetric pulse can reduce muscle contraction compared to monophasic pulses, and has the advantage of lower cell ablation threshold compared to biphasic symmetric pulses. We also updated the catheter used in previous experiments (18), and added positioning electrodes to the new catheter to ensure that the current state of electrodes was displayed under X-ray to provide more reliable information to doctors. Furthermore, we reinforced the framework of electrodes to make them more rigid and increase the stability of the electrode structure.

In the present study, the ablation results were recorded at 1 and 4 weeks, and the lasting effectiveness and safety of the biphasic asymmetric PFA system in the treatment of atrial fibrillation were verified, ensuring the safety of future clinical trials using the same system. In the pig experiment (Group A&B), there was no ventricular arrhythmia at any time during the operation, and the behavioral activities, mental status, appetite, and feed intake of the pigs returned to normal after the operation. We examined the near-ablation zone, including the vagus nerve, lung, trachea, and esophagus. A pathological analysis of the ablation zone performed at 1 and 4 weeks showed that all targeted parts produced complete transmural lesions and maintained good safety. At 4 weeks after PFA, fibroblasts had replaced the original cardiomyocytes and PFA had not destroyed the intercellular connection, which was conducive to the maintenance of the tissue structure. There was no thromboembolism, intracardiac injury, or acute or chronic collateral tissue injury after ablation. Consistent with our previous *in vitro* experiments (18), the present results further proved that the biphasic asymmetric pulse mode and PFA system used in the present study had good safety and produced effective lesions. In dog group, the immediately post-op ablation zones showed a low potential and a ring shape. The electrical signal level measured at 4 weeks after ablation showed that the potential remained low. Pacing did not capture atrium, and it confirmed the effectiveness of ablation and the safety of the experimental animals. More details in **Supplementary Figure 2**.

The number of pulses in the pulse sequence is an important parameter, and there is currently no clear consensus on the optimal number of pulses (26). Stewart et al. (27) set the number of pulses to a group of 60 (six pulses released per heartbeat), while Koruth et al. (23) proposed a pulse sequence with five pulses per group. We found that when the number of pulses was set to 20 (all pulses released after one R wave), from the 15th pulse, a current amplitude peak appeared which was much higher than the normal amplitude value. This phenomenon may be caused by an unstable heart rate. Alternatively, when the number of pulses is sufficient, a large amount of intracellular fluid may overflow from the tissue cells, increasing the conductivity and sharply increasing the current amplitude. When we reduced the number of pulses, the current returned to its normal value. We believe that this was due to the self-recovery function of tissue cells in a short period of time. The existence of this phenomenon allowed us to keep the number of pulses in each group to 10 (similar to the parameters used in previous studies). The length of the blank period between the positive and negative pulses is generally referred to as the pulse interval. There is no standard formula for determining the length of the pulse interval (16, 28). In subsequent studies, we plan to study the effect of the pulse width and the pulse interval on the ablation.

PFA is one kind of AF catheter ablation, so the drug treatment after the PFA can be referenced to the guideline of 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) (29). In the future clinical trials, we will investigate the interaction between the drug and PFA.

LIMITATIONS

In this experiment, the novel PFA catheter had high levels of safety and durability. However, the only parameter setting that was varied in this experiment was the number of pulses, while the other parameters of the PFA system were kept constant. The complex intracardiac environment and local dynamic electrical characteristics of tissues will have a certain

impact on the PFA zones. Considering the difference of heart between human and animal, the distance between electrodes should be adjustable. So the voltage amplitude and the number of pulses should be adjusted during the ablation process in order to achieve a high degree of durable pulmonary vein isolation.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The animal study was reviewed and approved by Tianjin TEDA Cardiovascular Hospital-Animal Experiment Center.

AUTHOR CONTRIBUTIONS

ZX and XX: conceptualization, writing—review and editing, and funding acquisition. SB, SS, and QH: methodology and investigation. QH: clinical operation. SB and FJ: data curation. SB and CL: writing—original draft preparation and visualization. All authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.859480/full#supplementary-material

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ORIGINAL RESEARCH
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Machine Learning Approaches for Predicting Hypertension and Its Associated Factors Using Population-Level Data From Three South Asian Countries

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Background: Hypertension is the most common modifiable risk factor for cardiovascular diseases in South Asia. Machine learning (ML) models have been shown to outperform clinical risk predictions compared to statistical methods, but studies using ML to predict hypertension at the population level are lacking. This study used ML approaches in a dataset of three South Asian countries to predict hypertension and its associated factors and compared the model's performances.

Methods: We conducted a retrospective study using ML analyses to detect hypertension using population-based surveys. We created a single dataset by harmonizing individual-level data from the most recent nationally representative Demographic and Health Survey in Bangladesh, Nepal, and India. The variables included blood pressure (BP), sociodemographic and economic factors, height, weight, hemoglobin, and random blood glucose. Hypertension was defined based on JNC-7 criteria. We applied six common ML-based classifiers: decision tree (DT), random forest (RF), gradient boosting machine (GBM), extreme gradient boosting (XGBoost), logistic regression (LR), and linear discriminant analysis (LDA) to predict hypertension and its risk factors.

Results: Of the 8,18,603 participants, 82,748 (10.11%) had hypertension. ML models showed that significant factors for hypertension were age and BMI. Ever measured BP, education, taking medicine to lower BP, and doctor's perception of high BP was also significant but comparatively lower than age and BMI. XGBoost, GBM, LR, and LDA showed the highest accuracy score of 90%, RF and DT achieved 89 and 83%,

respectively, to predict hypertension. DT achieved the precision value of 91%, and the rest performed with 90%. XGBoost, GBM, LR, and LDA achieved a recall value of 100%, RF scored 99%, and DT scored 90%. In F1-score, XGBoost, GBM, LR, and LDA scored 95%, while RF scored 94%, and DT scored 90%. All the algorithms performed with good and small log loss values <6%.

Conclusion: ML models performed well to predict hypertension and its associated factors in South Asians. When employed on an open-source platform, these models are scalable to millions of people and might help individuals self-screen for hypertension at an early stage. Future studies incorporating biochemical markers are needed to improve the ML algorithms and evaluate them in real life.

Keywords: Demographic and Health Survey, blood pressure, algorithms, risk factors, South Asia, artificial intelligence, cardiovascular diseases

INTRODUCTION

Hypertension is the leading cause of cardiovascular disease attributing to 8.5 million deaths globally, with 88% deaths in low-income and middle-income countries (1, 2). In South Asia, the prevalence of hypertension has been increasing primarily due to increased access to unhealthy foods, sedentary lifestyles, and rural-urban migration (3, 4). South Asia also has the lowest rates of hypertension detection, treatment, and control, with little improvement in these outcomes over the past three decades (2). Many people with hypertension remain largely undetected in South Asia due to decreased screening awareness among the general population (5). Hypertension can lead to coronary artery disease, stroke, heart failure, kidney failure, and premature mortality (6), which are mostly preventable through low-cost medications and timely interventions.

Several factors contribute to this higher prevalence of hypertension in South Asia, including physical inactivity, decreased awareness, smoking, unhealthy diet, access to healthcare, cost of medications (5, 7–9). However, most of the studies lacked population representativeness, had a small sample size, and used a wide range of tools to measure risk factors. Several risk prediction models have been successfully used to identify and stratify patients according to their risk factors and initiate preventative therapies, for example, Framingham Risk Score for predicting coronary heart disease (10) and American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations Risk Calculator (11). However, these models have several limitations, including non-representative populations, inadequate ethnic diversity, selected endpoints, and poor reliability (11). There is a need to develop population-specific risk prediction models for people in South Asia.

In recent years, machine learning (ML) techniques have been shown to outperform traditional statistical approaches in developing risk stratification tools for diagnosing cardiovascular diseases (12–15). ML is a branch of computer science that broadly enables computers to "learn" without being directly programmed (13) and process large data with complex interactions. Although ML algorithms are not based on causal inference compared to traditional statistical methods, it is still a critical approach to estimating causal effects in observational studies. ML often shows superior performance compared to traditional ststistical techniques for reducing bias, automatic managing of missing variables with less manipulation of original data, controlling for confounding and data balancing- a key factor that leads to improved results (13). ML provides accuracy values, for example, 85% accuracy for a model suggest that the algorithm correctly identified 85 out of 100 participants which can aid in decision making. In addition, ML techniques excel in analyzing "big data" problems where commonly used statistical approaches struggle. Thus, ML methodologies can help develop automated tools for disease prediction, decision-aids, and identifying likely rates of hypertension in a population (13).

A recent review identified and examined ML techniques in hypertension detection and reported a a lack of studies combining sociodemographic and clinical data with signal processing which could increase model performance (16). A previous study used ML algorithms for automatic classification of hypertension using personal features but failed to include sociodemographic data (17). Another study in India developed ML risk stratification algorithms for diabetes and hypertension using data from 2,278 patients collected by community health workers (18). Two studies in China used ML to detect hypertension using electronic health records (19, 20). Despite the advancement in ML models for individual risk prediction for different diseases, no studies have used ML models to predict hypertension at a population level and validated the models using large datasets in South Asian countries. We, therefore, aimed to use ML approaches to identify factors associated with hypertension diagnosis and compared the model's performances to predict hypertension in three South Asian countries.

METHODS

Study Design

A retrospective study using ML analyses to detect hypertension using cross-sectional nationally representative population-based surveys.

Data Source and Variables

We obtained individual-level de-identified data from the most recent nationally representative and internationally comparable Demographic and Health Survey (DHS) in Bangladesh (2017–18), Nepal (2016), and India (2015–16). We created a single dataset by harmonizing data from each survey to a standard data specification. We included 818,603 respondents who provided consent for measurement of blood pressure, weight, height and had complete data for the analyses. Participants with incomplete data were excluded. The details on DHS survey design, data availability is available on the DHS website (https://www.dhsprogram.com) (21). In brief, the DHSs are periodic nationally representative household surveys that collect data for a wide range of variables on population, health, and nutrition. These surveys usually are conducted by a national implementing agency in collaboration with the Ministry of Health and technical assistance provided by ICF International USA and USAID. Participants in DHSs are generally selected using stratified two-stage cluster sampling. Firstly, sampling census enumeration areas are selected using probability proportional to size sampling technique through statistics provided by the respective national statistical bureaus. Secondly, the administrative wards at the community level are considered primary sampling units (PSUs). Following systematic random sampling, the households are selected from the sampled PSUs. Data are provided by the household head or a member who has detailed information about the household and family members. Subsamples of eligible participants are chosen for biomarker testing (e.g., height, weight, and blood pressure) (22). DHS surveys have a very high response rate, usually more than 90%. We used the household member record dataset, which has one record for every household member.

Blood Pressure Measurement and Hypertension

Blood pressure (BP) was measured for participants using the DHS standard protocol (23, 24). In brief, three measurements were taken by trained health workers, at seating position, at about 10 min intervals. The mean of the second and third measurements was used to record systolic BP and diastolic BP. We defined hypertension based on the cut-offs provided by the Seventh Report of Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) guideline (25) where an individual was categorized as hypertensive if they had systolic BP $\geq$ 140 mmHg or diastolic BP $\geq$ 90 mmHg or reported to use antihypertensive medication during the survey.

The Biomarker Questionnaire

The biomarker questionnaire collected details on height, weight, hemoglobin, BP, and random blood glucose for women aged 15–49 and men aged 15–54. The response rate for BP measurements was 97% among women and 92% among men. Furthermore, irrespective of their BP, all participants were asked, "Were you told on two or more different occasions by a doctor or other health professional that you had hypertension or high blood pressure?" If they responded in the affirmative, they were asked a follow-on question, "To lower your blood pressure, are you taking a prescribed medicine?".

Other Covariates

DHS collected information on a wide range of variables from the selected households and the respondents from those households using face-to-face interviews conducted by trained personnel. Data on sociodemographic and economic factors like age, sex, education, and household wealth index were included. The education categories are defined based on the number of years of education completed by an individual: 0 year as "no education"; 1–5 years as "primary education"; 6–12 years as "secondary education"; and more than 12 years of educational attainment categorized as "higher studies". For household wealth index, each national implementing agency constructed a country-specific index using principal components analysis from data on household assets including durable goods (i.e., bicycles, televisions, etc.,) and dwelling characteristics (i.e., sanitation, source of drinking water, and construction material of the house, etc.,) (14). This wealth index was then categorized into five groups (i.e., poorest, poorer, middle, richer, and richest) based on the quintile distribution of the sample.

Data Analysis

Data were presented as mean $\pm$ SD for continuous variables and frequency (%) for categorical variables. We performed the chi-square test to assess the difference between hypertension and non-hypertension individuals for each categorical variable. P-value < 0.05 was considered significant. The wealth index was converted into a dichotomous variable; the bottom 60%, is, "poorest", "poor" and "middle" were combined into one group (low SES). The remaining two categories were clubbed into the other category (high SES). The following risk factors of hypertension were included in all the ML models: age, BMI, education, wealth, systolic BP, diastolic BP, taking medicine for high BP, and ever told by a physician to take BP medications based on data availability. Data analyses were performed using SPSS version 24 and Matlab software.

We then experimented with the six most commonly used supervised ML models to measure their predictive effectiveness to diagnosis hypertension using a classification task. In this task, we included hypertension as a independent variable and the other factors as independent variables. After model training, we measured the accuracy, precision, recall f1 score, and log loss values. The higher accuracy, precision, recall, and f1-score suggested comparatively better models. On the other hand, lower log loss value represented a better model. All the evaluation matrices used were within the range 0–100. In addition, we included feature ranking (considering the coefficient values of the features) suggesting factors that were mostly contributed for hypertension.

Decision Tree (DT)

A DT algorithm can be used for both classification and regression on a given dataset. Each node of the tree represents a specific condition on one of the dataset attributes. The decision process starts from the tree root. Each node's condition is checked based on which node edges are chosen, and the decision process continues to the next tree level. This trend continues until a leaf node is reached based on which the final decision is presented (1). A high-information-gain parameter at a node can partition

the training data to increase classification accuracy. Entropy (E) and information-gain (IG) is calculated as

$$E(Y) = -\sum_k p_k \log_2(p_k), \quad (1)$$

$$IG(D, X) = E(D) - \sum_{v \in Values(X)} \frac{|D_v|}{|D|} .E(D_v), \quad (2)$$

where Y and X are variables, D is data, p_k is the probability of observing value k for variable Y.

Random Forest (RF)

RF employs multiple decision trees to improve classification and regression performance. RF creates bootstraps by random resampling from the training dataset, and in the end, it combines the results (2). Bootstrap aggregation is used during training in RF algorithms. After training, the model can predict output given an unseen sample x' by averaging the predictions performed by all decision trees:

$$-\bar{f} = \frac{1}{B} \sum_{b=1}^{B} f_b(x') \quad (3)$$

where B is the total number of decision trees of the random forest, $f_b(x')$ is the prediction of b-th decision tree give input x'.

Gradient Boosting Machine (GBM)

GBM is another fixed-size tree-based algorithm that also can be used for classification and regression. It uses boosting strategies for better performance (3).

Extreme Gradient Boosting (XGBoost)

XGBoost is another tree-based algorithm that uses a gradient boosting framework. This algorithm can solve large-scale real-world problems using comparatively fewer resources than GBM (4).

Logistic Regression (LR)

LR is one of the classification methods in ML which uses logistic functions for binary dependent variables (5). The generalized fundamental linear equation for LR is,

$$g(E(y)) = \alpha + \beta x_1 + \gamma x_2 \quad (4)$$

where the link function is denoted as g (.), the target variables expectation is denoted as E(.), and the right side of the equation is the linear prediction.

Linear Discriminant Analysis (LDA)

LDA is used in machine learning, statistics, and pattern recognition problems. LDA is similar to regression analysis and analysis of variance (ANOVA) (5).

Model Evaluation

We compared the performance of the ML-classifiers using accuracy, precision, recall, F-1 score, and log loss, respectively. Using 10-fold cross-validation, the whole dataset was split into 10 subsets. In each fold, one of the subsets was used for model testing and the remaining subsets for model training. The training/testing process is repeated 10 times, corresponding to 10 folds. The evaluation metrics are calculated using the following equations:

$$Precision = \frac{TP}{TP + FP}, \quad (5)$$

$$Recall = \frac{TP}{TP + FN}, \quad (6)$$

$$F_1 = 2 \times \frac{Precision \times Recall}{Precision + Recall} \quad (7)$$

$$H_p(q) = -\frac{1}{N} \sum_{i=1}^{N} y_i . \log(p(y_i)) \quad (8)$$

$$+ (1 - y_i) . \log(1 - p(y_i)) \quad (9)$$

where TP is true positive rate, FP is false positive rate, FN is false-negative rate, y is target variable level, p (y) is predicted probability and $H_p(q)$ is log-loss.

Ethics Approval

DHS surveys received ethical approval from the ICF Institutional Review Board and country-specific review boards. Informed consent was taken from each participant to participate in the study. The DHS program authorized researchers to use relevant datasets for analysis upon submission of a brief research proposal. The data used in this study were anonymized to protect privacy, anonymity, and confidentiality. Therefore, no ethics approval is required for this research. More details on survey design, ethical approval, data availability can be found on the DHS program website (https://dhsprogram.com/).

RESULTS

Of the 8,18,603 participants included in the analyses, 82,748 (overall 10.11%) had hypertension. The majority of the participants were from the 15–24 years age group (33.68%), followed by the 25–34 years age group (28.90%), 35–44 years age group (23.85%), and 45 + years age group (13.57%). The majority of the participants (58.60%) had normal BMI, while 21.78% were underweight, 14.95% were overweight, and 4.67% were obese. Nearly half of the study participants received secondary education (47.43%) and were from a low-income family (44.91%). More than 90% of the respondents were informed about their high BP by a doctor, and 96.82% reported taking prescribed medicine to lower BP. However, only 60.28% measured their BP regularly. Participants' characteristics and significant variables are listed in **Table 1**.

Participants in the higher age groups (>45 years) were more likely to be hypertensive, compared to the younger age groups (24 years) (23.33 vs. 2.94%). Participants with no education were more likely to be hypertensive (13.02%) than those with higher education (8.02%). Further, participants in the rich wealth index were more likely to be hypertensive compared to the poor wealth index (12.64 vs. 8.05%). All of these differences were statistically significant (p-value < 0.001). The prevalence of hypertension was 11.01% among respondents who ever measured BP and 13.46% among those who had high

TABLE 1 | Background characteristics of the participants ($N = 8,18,603$).

Variables	Total	Level of hypertension		*p*-value
		No-hypertension	Hypertensive	
	n (%)	*n* (%)	*n* (%)	
Age of the respondent				
15–24	2,75,719 (33.68)	2,67,605 (97.06)	8,114 (2.94)	$p < 0.001$
25–34	2,36,583 (28.90)	2,18,453 (92.34)	18,130 (7.66)	
35–44	1,95,200 (23.85)	1,64,615 (84.33)	30,585 (15.67)	
45+	1,11,102 (13.57)	85,183 (76.67)	25,919 (23.33)	
Total	8,18,604 (100.00)	7,35,856 (89.89)	82,748 (10.11)	
Level of BMI				
Thin	1,78,284 (21.78)	1,69,855 (95.27)	8,429 (4.73)	$p < 0.001$
Normal	4,79,687 (58.60)	4,37,626 (91.23)	42,061 (8.77)	
Overweight	1,22,414 (14.95)	99,659 (81.41)	22,755 (18.59)	
Obese	38,218 (4.67)	28,715 (75.13)	9,503 (24.86)	
Total	8,18,603 (100.00)	7,35,855 (89.89)	82,748 (10.11)	
Level of education				
No education	2,12,323 (25.94)	1,84,683 (86.98)	27,640 (13.02)	$p < 0.001$
Primary	1,12,656 (13.76)	99,095 (87.96)	13,561 (12.04)	
Secondary	3,88,283 (47.43)	3,55,180 (91.47)	33,103 (8.53)	
Higher	1,05,342 (12.87)	96,898 (91.98)	8,444 (8.02)	
Total	8,18,604 (100.00)	7,35,856 (89.89)	82,748 (10.11)	
Wealth status				
Poor	3,67,661 (44.91)	3,38,073 (91.95)	29,588 (8.05)	$p < 0.001$
Middle	1,62,088 (19.80)	1,45,454 (89.74)	16,634 (10.26)	
Rich	2,88,854 (35.29)	2,52,329 (87.36)	36,525 (12.64)	
Total	8,18,603 (100.00)	7,35,856 (89.89)	82,747 (10.11)	
Ever measured blood pressure				
No	3,14,579 (39.72)	2,88,775 (91.80)	25,804 (8.20)	$p < 0.001$
Yes	4,77,383 (60.28)	4,24,845 (88.99)	52,538 (11.01)	
Total	7,91,962 (100.00)	7,13,620 (90.11)	78,342 (9.89)	
Told by a doctor to have high blood pressure				
No	7,22,313 (91.21)	6,53,345 (90.45)	68,968 (9.55)	$p < 0.001$
Yes	69,648 (8.79)	60,275 (86.54)	9,373 (13.46)	
Total	7,91,961 (100.00)	7,13,620 (90.11)	78,341 (9.89)	
Taking prescribed medicine to lower blood pressure				
No	7,66,754 (96.82)	6,92,265 (90.29)	74,489 (9.71)	$p < 0.001$
Yes	25,208 (3.18)	21,356 (84.72)	3,852 (15.28)	
Total	7,91,962 (100.00)	7,13,621 (90.11)	78,341 (9.89)	

BP diagnosed by a doctor. 15.28% of the respondents taking medication for BP had hypertension. Results of the bivariate analysis show that all the sociodemographic variables had a statistically significant relationship with hypertension ($P < 0.05$) (**Table 1**).

According to performance metrics presented in **Table 2**, all the algorithms performed with a reasonable accuracy score (>80%). XGBoost, GBM, LR, and LDA achieved the highest accuracy of 90%, while RF and DT achieved 89 and 83%, respectively. DT reached the precision value of 91%, and the rest performed with 90%. XGBoost, GBM, LR, and LDA achieved the highest recall value, 100%, while RF scored 99% and DT scored 90%. Regarding the F1-score, XGBoost, GBM, LR, and LDA scored 95%, the highest, while RF scored 94%, and DT scored 90%. All the algorithms performed with good and small log loss values for the last evaluation criteria log loss values <6%. **Figure 1** shows that GBM provided the highest mean accuracy, followed by LR and XGBoost (XGB in **Figure 1**). Unlike the boxplot, the entire distribution of the 10-fold accuracy can be visualized in the violin plot (**Figure 1**). The significant features determined by the algorithms after training are shown in **Figure 2**. Most of the algorithms found that the significant factors for hypertension were age and BMI. Ever measured BP, education, taking medicine to lower BP, and doctor's perception

TABLE 2 | Performance indicators of all selected machine learning algorithms.

Algorithms	Accuracy	Precision	Recall	F1 score	Log loss
Random forest	0.89	0.90	0.99	0.94	3.63
Decision tree	0.83	0.91	0.90	0.90	5.92
XGB	0.90	0.90	1.00	0.95	3.52
GBM	0.90	0.90	1.00	0.95	3.33
LR	0.90	0.90	1.00	0.95	3.55
LDA	0.90	0.90	1.00	0.95	3.57

XGB, XGBoost; GBM, Gradient Boosting Machine; LR, Logistic Regression; LDA, Linear Discriminant Analysis.

of high BP was also significant but comparatively lower than age and BMI (**Figure 2**).

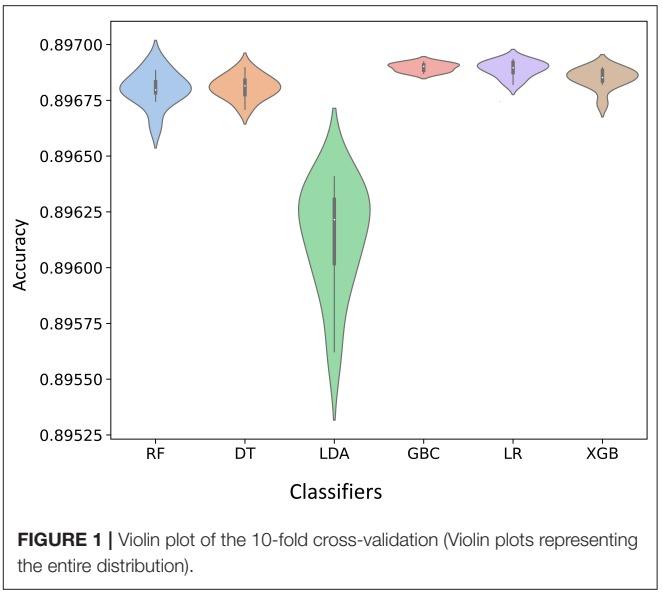

FIGURE 1 | Violin plot of the 10-fold cross-validation (Violin plots representing the entire distribution).

DISCUSSION

To our knowledge, this is the first study to apply ML approaches to predict hypertension and its associated factors using population-representative data in three South Asia countries. We identified seven risk factors associated with hypertension in the South Asian population: age, BMI, education, wealth status, ever measuring BP, being diagnosed by a doctor, and taking medication to lower BP. After applying ML algorithms, we observed that XGBoost, GBM, LR, and LDA had the highest accuracy and recall with a score of 90 and 100%, respectively. DT achieved the highest precision value of 91%. ML models are superior to traditional statistical techniques where complex relationships between variables may not be fully explained using standard statistics. Our work has implications for hypertension prevention by applying these ML models to population-level data for hypertension screening among the population and automating the tasks without substantial human labor.

Several recent studies have proposed ML models to predict hypertension using a variety of demographic, biomarker, fitness, and spirometry data in various combinations (26–28). Ture et al. used age, gender, smoking, lipoprotein, and triglyceride levels and evaluated the performance of three three decision trees, four statistical algorithms, and two neural networks on 694 participants (29). Radial Basis Function showed the best performance for sensitivity (95.24%), specificity (66.67%), and predictive rate (81.48%). Similarly, Heo and colleagues developed hypertension prediction ML models using obesity, biomarkers, and spirometry data. They identified that obesity indices were most closely related to the risk of developing hypertension where wrapper-based feature selection methods-LR model showed the best performance (sensitivity and specificity of 0.813 and 0.401, respectively (30). A study in Canada using medical records and demographics used a neural network model for predicting hypertension with about 82% accuracy (26).

Several recent studies have demonstrated that ML models might be feasible and valuable for predicting and managing hypertension (27, 31). However, despite the growing interest, ML-informed BP prediction is yet to be implemented in clinical practice due to limitations such as lack of ML algorithms, consistency, accuracy, and reliability (31). Recently, a study in Korea utilized three different classification methods, namely LG, LDA, and classification and regression tree for hypertension risk prediction using an extensive database. All three methods performed reasonably well, with LR only marginally better with 58% accuracy (32). A similar study applied ML algorithms on patients with hypertension using 12-year longitudinal data from a nationwide cohort with 55 variables, where RF showed the best performance (F1-score = 0.772) in terms of generalization to detect high-risk patients (33).

Our study found BMI to be a good predictor of hypertension. Previous studies have shown obesity is strongly related to the risk of developing hypertension (34–36). Studies in the United States, China, and India have shown that BMI is a risk factor for hypertension (37–39), whereas waist circumference is correlated with cardiovascular diseases (34, 38). Another study in China using ML identified high education, sedentary job, a positive family history, overweight, physical activity, and unhealthy diets as risk factors for hypertension (40). A prospective cohort of 33,000 people from India, Pakistan, and Bangladesh reported a significantly higher prevalence of hypertension among urban-dwelling, higher education, and higher wealth index participants (41). We found a significant association of hypertension with BMI, wealth status, and education in the South Asian population. These disparities might be due to lack of access to healthcare facilities, poor BP screening, recording, reporting, lack of awareness regarding risk factors, and inappropriate treatment (42, 43).

Several mathematical techniques and ML models have been used to develop risk prediction models in healthcare (44, 45). Ture and colleagues' used DTs, statistical algorithms, and neural networks and identified that neural networks have the best predictive ability for hypertension using risk

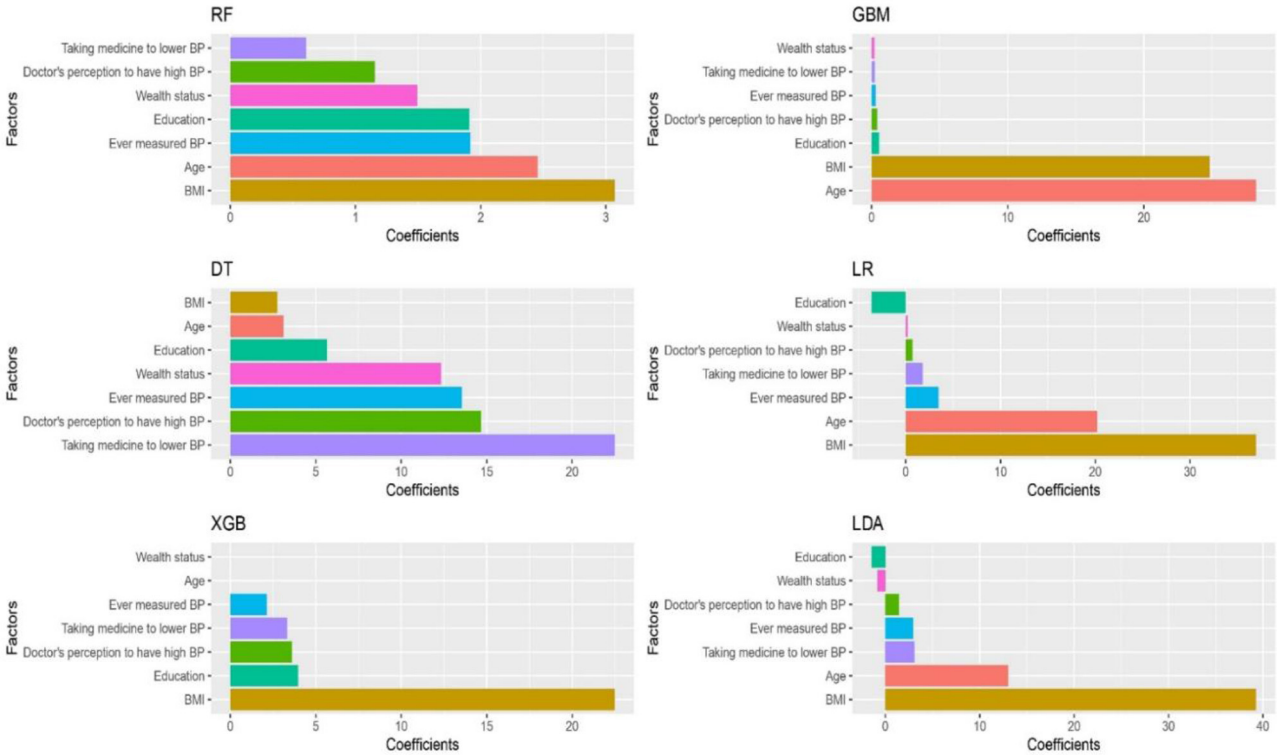

FIGURE 2 | Significant features for hypertension in three South Asian countries.

factors as inputs (30). However, a limitation to this study was the missing obesity data which is known to be associated with hypertension (29). Heo and colleagues also developed hypertension prediction models using DT, LR, and NB classifiers using obesity, biomarkers, and spirometry indices as variables in creating these models. An important limitation of this study is the lack of data on wealth index, education levels, smoking, alcohol use, and physical activity (30). We utilized non-invasive data to develop ML models to predict hypertension in the South Asian population. Previous studies in South Asia have shown the effectiveness and cost-effectiveness of mobile phones and digital technologies (46–50). However, there is a need for demographic representativeness in training data, model transparency and standardized frameworks for using these ML prediction models to improve representativeness and reproducibility (51).

The following limitations should be considered when interpreting the findings. First, a limited number of variables are included in the models. Data on risk factors such as family history, race, alcohol consumption, waist-hip ratio, physical activity levels, dietary intake, and biochemical parameters (e.g., blood glucose, lipid profile) were unavailable for all countries, which might have affected the measurement precision of our models. Second, the risk factors may have changed since some study data were from the 2016 survey. Third, ML models have an inherent weakness in making claims about causation. Finally, we could not externally validate our models using other data sources from these countries. Therefore, our results should be interpreted with caution. Despite these limitations, the primary strength of this study is the use of large-scale nationally representative survey data from 3 South Asian countries using ML approaches to predict hypertension.

Future research on developing country-specific risk assessment tools and validation are essential since risk factors, particularly demographics, education level, and wealth index, are not the same among different countries. These models can also be made available online or via mobile phone applications where individuals can check their risks of developing hypertension at home by answering simple questions such as their age, BMI, and sex. Models based on robust biochemical data, electronic health records (52) and external validation are recommended in the future A two-stage approach can be put into clinical practice, where ML model identifies individuals who are at risk of hypertension and in the second stage, at-risk individuals undergo evaluation by a physician for a confirmed diagnosis and appropriate treatment (53).

CONCLUSION

Our study suggests that using simple, non-invasive information, ML models can predict hypertension among the South Asian population with high accuracy. Age and BMI were the most significant risk factors associated with hypertension in our study

population. Further research is needed to include other risk factors and biomarkers associated with hypertension. ML models can then be trained and incorporated into the dataset to develop population-based hypertension risk assessment tools.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: data are available from DHS website upon registration and request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Boards (IRBs) of the ICF International, Rockville, Maryland, USA and Respective Country National Ethics Board approved the study. The permission for using the data was obtained in December 2019. All participants provided informed consent to participate into the survey. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SI: concept, study protocol development, drafting, and preparing the final manuscript for submission. AT, MMA, BA, and MAA: data analysis and drafting. All authors have contributed to intellectual inputs and review of the manuscript.

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Derivation and Validation of a Screening Model for Hypertrophic Cardiomyopathy Based on Electrocardiogram Features

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Background: Hypertrophic cardiomyopathy (HCM) is a widely distributed, but clinically heterogeneous genetic heart disease, affects approximately 20 million people worldwide. Nowadays, HCM is treatable with the advancement of medical interventions. However, due to occult clinical presentations and a lack of easy, inexpensive, and widely popularized screening approaches in the general population, 80–90% HCM patients are not clinically identifiable, which brings certain safety hazards could have been prevented. The majority HCM patients showed abnormal and diverse electrocardiogram (ECG) presentations, it is unclear which ECG parameters are the most efficient for HCM screening.

Objective: We aimed to develop a pragmatic prediction model based on the most common ECG features to screen for HCM.

Methods: Between April 1st and September 30th, 2020, 423 consecutive subjects from the International Cooperation Center for Hypertrophic Cardiomyopathy of Xijing Hospital [172 HCM patients, 251 participants without left ventricular hypertrophy (non-HCM)] were prospectively included in the training cohort. Between January 4th and February 30th, 2021, 163 participants from the same center were included in the temporal internal validation cohort (62 HCM patients, 101 non-HCM participants). External validation was performed using retrospectively collected ECG data from Xijing Hospital (3,232 HCM ECG samples from January 1st, 2000, to March 31st, 2020; 95,184 non-HCM ECG samples from January 1st to December 31st, 2020). The C-statistic was used to measure the discriminative ability of the model.

Results: Among 30 ECG features examined, all except abnormal Q wave significantly differed between the HCM patients and non-HCM comparators. After several independent feature selection approaches and model evaluation, we included only two ECG features, T wave inversion (TWI) and the amplitude of S wave in lead V1 (SV1), in the HCM prediction model. The model showed a clearly useful discriminative performance (C-statistic $>$ 0.75) in the training [C-statistic 0.857 (0.818–0.896)], and temporal

validation cohorts [C-statistic 0.871 (0.812–0.930)]. In the external validation cohort, the C-statistic of the model was 0.833 [0.825–0.841]. A browser-based calculator was generated accordingly.

Conclusion: The pragmatic model established using only TWI and SV1 may be helpful for predicting the probability of HCM and shows promise for use in population-based HCM screening.

Keywords: electrocardiogram (ECG), screening model, hypertrophic cardiomyopathy, left ventricular hypertrophy, C-statistic

HIGHLIGHTS

What Are the Novel Findings of This Work?

- Using multiple independent statistical approaches, the two easily acquired ECG parameters, TWI and SV1, were selected and showed satisfactory C-statistics of 0.871 and 0.833 validated by internal and external cohorts, respectively.
- We developed a pragmatic prediction model based on TWI and SV1, which can automatically be acquired by electrocardiography, to screen for HCM. The corresponding web-based calculator may be helpful for improving the detection rate of HCM in the general population.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM), one of the most common genetic cardiovascular diseases that is heterogeneous in its clinical profile and natural history including progressive heart failure (HF), atrial fibrillation (AF)/embolic stroke, and is frequently visible non–trauma-related sudden death in young asymptomatic student-athletes, which accounting for approximately one-third of these catastrophic events (1–5). It should also be recognized that approximately 60% of sudden deaths due to HCM occur in individuals during routine physical activity and not exclusively in athletes (6–8). The advancement of effective treatment interventions has significantly reduced the disease-related mortality rate to 0.5% (9–11). HCM is treatable and consistent with normal longevity; thus, the ability to diagnose HCM in a timely and convenient manner for detailed clinical assessment has increased substantially in importance. It is estimated that there are approximately 20 million HCM patients worldwide. However, 80–90% of HCM patients are still clinically unidentified, such a high rate of underdiagnosis may lead to an increased risk of HF, thromboembolic events attributable to AF, and sudden cardiac death (SCD) among these "hidden" patients, seriously endangering human health and social development (2, 5).

The current diagnostic criteria mainly rely on echocardiography (Echo) or cardiac magnetic resonance (CMR), combined with genetic testing, which contributed to substantial advancements in understanding this disease and facilitated patient management (12). However, these approaches are relatively unpopular and expensive, need expertized interpretation, and have high inter- and intrareader variability and lack defined conclusions of variant results, all of which have hampered the detection rate of HCM (13–15). Furthermore, since Asians have smaller left ventricular volumes than Caucasians, the diagnostic threshold of maximum wall thickness (MWT) for Asians should be reduced accordingly (recommended from 15 mm to 10–12 mm) (16). This will then further increase the prevalence and underdiagnosed rate of HCM in Asia, as well as the incidence of potential adverse events, including in China.

More than 90% of HCM patients have abnormalities on electrocardiogram (ECG), which may be the only early manifestation of HCM (17–19). Compared to imaging modalities such as echocardiography and cardiac magnetic resonance (CMR), ECG is more convenient, non-invasive, less expensive, and potentially more sensitive for detecting left ventricular hypertrophy (LVH) in the context of HCM screening. Current guidelines recommend 12-lead ECG for the initial clinical evaluation of patients with HCM (2, 20). With a vast array of ECG abnormalities, there are no simple, convenient and pragmatic models to use in screening for HCM. Furthermore, there is a lack of specialized ECG interpreters, especially in underdeveloped countries and regions.

In the current study, we aimed to develop a practical model based on the most common and easily acquired ECG features by electrocardiography as an initial screening tool for HCM to improve the detection rate of HCM in the population, prevent adverse cardiac events, and improve long-term prognosis.

MATERIALS AND METHODS

Study Population

Between April 1st and September 30th, 2020, 423 consecutive subjects from the International Cooperation Center for Hypertrophic Cardiomyopathy of Xijing Hospital [172 HCM patients, 251 participants without LVH (non-HCM)] were

Abbreviations: HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death; AF, atrial fibrillation; BBB, bundle branch block; ECG, electrocardiogram; Echo, echocardiography; LVEF, left ventricular ejection fraction; LA, left atrium; SAM, systolic anterior motion; MWT, maximum wall thickness; LVH, left ventricular hypertrophy; TWI, T wave inversion; SV1, the S wave amplitude of lead V1; LASSO, the least absolute shrinkage and selection operator; LR, logistic regression; AIC, Akaike Information Criterion; BIC, Bayesian information criterion; ROC, receiver operator characteristic; R^2, R square; CI, confidence interval.

prospectively included in the training cohort, and between January 4th and February 30th, 2021, 163 participants from the same center were included in the temporal internal validation cohort (62 HCM patients, 101 non-HCM participants). External validation was performed using retrospectively collected ECG data from Xijing Hospital (3,232 HCM ECG datasets from January 1st, 2000, to March 31st, 2020; 95,184 non-HCM ECG datasets from January 1st to Dec 31st 2020). The study flowchart is shown in **Figure 1**.

HCM was diagnosed according to the European Society of Cardiology (ESC) guidelines for HCM (2, 12), which is defined as a maximum wall thickness (MWT) $\geq$ 13 mm or $\geq$ 15 mm for individuals with and without a family history of HCM, respectively, with the absence of any abnormal secondary causes, such as uncontrolled hypertension or aortic stenosis (AS), capable of producing such a magnitude of hypertrophy. Otherwise, classified as non-HCM. Patients who had previously been treated with an interventricular reduction procedure, including septal myectomy, alcohol septal ablation, and percutaneous intramyocardial septal radiofrequency ablation (21), or had a pacemaker with ventricular pacing, atrial fibrillation (AF), bundle branch block (BBB) and missing ECG data were excluded.

All enrolled participants had data from at least one standard 12-lead ECG and transthoracic cardiac echocardiography examination. The research protocol was approved by the ethics committee of Xijing Hospital, and the requirement for written informed consent for this analysis was waived by the institutional review board. The study was performed in accordance with local law and the regulations of Xijing Hospital and complied with the Declaration of Helsinki.

Echocardiography Acquisition

Transthoracic standard two-dimensional and Doppler echocardiography measurements were obtained according to the recommendations of the American Society of Echocardiography and the European Association of Cardiac Imaging for cardiac chamber quantification by echocardiography in adults (22). The MWT was defined as the greatest thickness in any single segment (12, 23). The Doppler signals were collected from the mitral inflow, and the peak velocity of early E- and late A-waves was recorded at a speed of 100 mm/s (24).

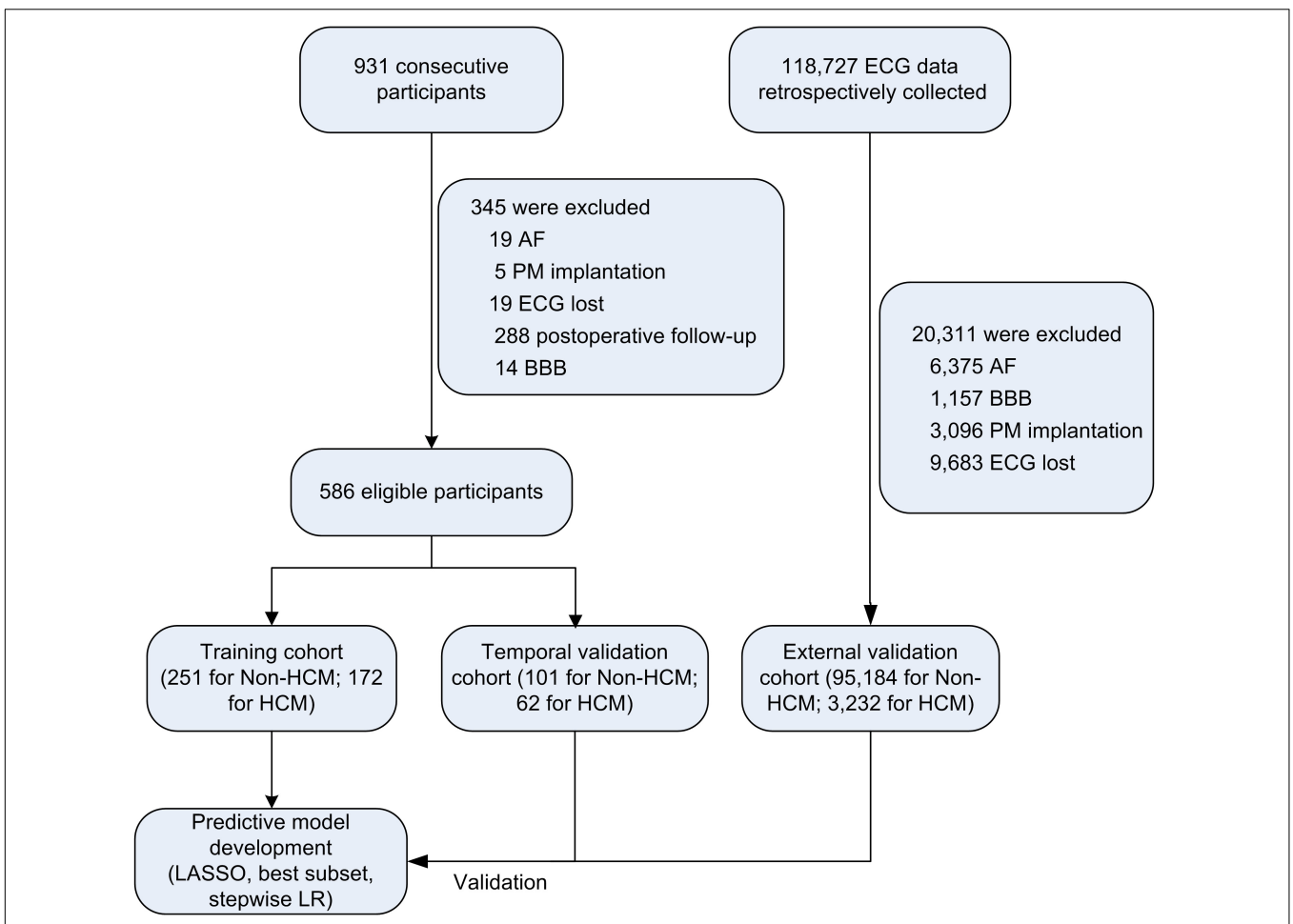

FIGURE 1 | Study flow chart. AF, atrial fibrillation; PM, pacemaker; BBB, bundle branch block; HCM, hypertrophic cardiomyopathy; LASSO, the least absolute shrinkage and selection operator; LR, logistic regression.

Electrocardiogram Evaluation

Routine 12-lead ECG for each eligible participant was acquired in the supine position at a sampling rate of 500 Hz, an amplitude of 10 mm/mv and a speed of 25 mm/s. The ECG features were measured automatically by the computer, and these data were checked independently by two experienced ECG reviewers blinded to clinical details. A total of 30 common ECG parameters were acquired. The mean heart rate (HR), P width, and PR and QT intervals were calculated by using three consecutive cycles. The QT interval was defined as the distance between the start of the QRS complex and the last point at which the T wave intersected the isoelectric line. The corrected QT (QTc) interval was calculated by using the Bazett formula. An abnormal Q wave was defined (25) as a Q wave with a width $\geq$ 3 mm or depth 1/4 of the ensuing R wave in two or more contiguous leads (except lead III and aVR). T wave inversion (TWI) (26) was diagnosed as an inverted T wave amplitude greater than 1 mm in two or more contiguous leads (excluding III, aVR, and V1). The amplitudes of the R and S waves were measured in all precordial leads and limb leads I, III and aVL. The presence of a pathologically high LV wall voltage was assessed by the amplitudes of RV5 + SV1 (RV5SV1, Sokolov–Lyon index), RaVL + SV3 (RaVLSV3, Cornell index), and RI + SIII (RISIII) (27). The amplitudes of the R and S waves in leads V1-4, reflecting interventricular septum (IVS) hypertrophy, were also included.

Statistical Analysis

The sample size was determined by acquiring all available data during the investigation period. Since there was no formal statistical hypothesis of the study, no power calculation was done in advance. However, the minimum acquire sample size was determined. The data used for model development and validation has no missing values. Categorical variables are presented as the frequency and percentage, while normally distributed continuous variables are expressed as the mean and standard deviation (*SD*); otherwise, are expressed as the median and interquartile range (IQR). The baseline characteristics and ECG parameters were compared with *t*-tests or non-parametric Mann–Whitney *U*-tests, as appropriate (for continuous variables), and Fisher's exact tests (for categorical variables).

Model development was performed according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidance (**Supplementary Table 1**) (28). Four different approaches were applied in JMP Pro 16.0 for feature selection and model development: (1) the adaptive least absolute shrinkage and selection operator (LASSO) analysis; (2) LASSO followed by multivariable logistic regression with backward stepwise selection; (3) LASSO followed by best subset selection; and (4) multivariable logistic regression with backward stepwise selection. The comparison of Receiver operating characteristic (ROC) curves for different models with distinct variables were performed using the DeLong test (R package "pROC") in the training and validation cohorts. The discriminative accuracy was quantified using the C-statistic. According to previous literature, a C-statistic less than 0.6 was considered to reflect poor discrimination; 0.60–0.75, possibly helpful discrimination; and greater than 0.75, clearly useful discrimination (29). The R packages "CalibrationCurves" and "ResourceSelection" were used to generate the calibration plots, and the Hosmer–Lemeshow test was used to assess the goodness-of-fit of the model. A browser-based calculator was generated accordingly.[1]

Statistical analyses were carried out using R software, version 4.1.1, JMP Pro 16.0 and SPSS 26.0. A two-tailed *P*-value < 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Baseline characteristics are presented in **Table 1**. The median age was 47 years, and there was no difference between the HCM and non-HCM groups ($P > 0.05$). In both the training and temporal internal validation cohorts, the male sex, hypertension and coronary artery disease were more common in HCM patients compared with non-HCM participants (all $P < 0.05$). Although there was no difference in the left ventricular ejection fraction (LVEF) between the HCM and non-HCM groups ($P > 0.05$), the average MWT (22 mm vs. 8 mm) and left atrial diameter (43 mm vs. 35 mm) were larger in the HCM group than in the non-HCM group, as was the incidence of LV diastolic dysfunction, reflected by E/A (all $P < 0.05$).

Electrocardiogram Characteristics

Except for abnormal Q wave, all remaining 29 ECG variables showed a significant difference between the HCM and non-HCM groups. HCM patients had a longer P wave, QRS interval, and QTc interval and higher R and S wave amplitudes in all precordial leads. HCM patients also had higher amplitudes in limb leads I and III (all $P < 0.05$). Parameters of hypertrophy, such as RISIII, RV5SV1, and RaVLSV3, other parameters reflecting interventricular hypertrophy, including the R or S wave amplitude in lead V1, V2, and V3, and combinations of RV1V2, SV1V2, RV2V3, SV2V3, RV3V4, and SV3V4, were higher in the HCM group than in the non-HCM group. In addition, TWI was more common in the HCM than in the non-HCM group, both in the training and temporal internal validation cohorts, respectively, all $P < 0.01$) (**Supplementary Table 2**).

Selection of Predictors and Construction of Prediction Model for Hypertrophic Cardiomyopathy

ECG variables, age, and sex were included for variable selection. Four different approaches were used for feature selection, including the adaptive LASSO analysis (**Supplementary Table 3**), multivariable logistic regression with backward stepwise selection (**Supplementary Table 4**), LASSO followed by multivariable logistic regression with backward stepwise selection (**Supplementary Table 5**), and LASSO followed by best subset selection (**Supplementary Table 6**). Several indexes

[1] http://121.36.159.143:9999/hcm.do

TABLE 1 | Baseline characteristics.

	Overall			Training cohort			Temporal validation cohort		
	non-HCM	HCM	*P*	non-HCM	HCM	*P*	non-HCM	HCM	*P*
	N = 352	*N* = 234		*N* = 251	*N* = 172		*N* = 101	*N* = 62	
Age, y (mean *SD*)	47 (16)	47 (15)	0.584	47 (16)	47 (15)	0.670	45 (15)	46 (15)	0.799
Male	191 (54.3)	163 (69.7)	<0.001	137 (54.6)	120 (69.8)	<0.001	54 (53.47)	43 (69.35)	0.045
Co-existing conditions									
Hypertension	65 (18.47)	91 (38.89)	<0.001	49 (19.52)	73 (42.44)	<0.001	16 (15.84)	18 (29.03)	0.044
CAD	34 (9.66)	40 (17.09)	0.008	29 (11.55)	38 (22.09)	0.004	5 (4.95)	2 (3.23)	0.710
CA	36 (10.23)	0 (0)	<0.001	22 (8.76)	0 (0)	0.008	14 (13.86)	0 (0)	0.001
AS	14 (3.98)	0 (0)	0.002	10 (3.98)	0 (0)	<0.001	4 (3.96)	0 (0)	0.299
Echocardiography parameters									
MWT, mm	9 (8, 11)	22 (18, 26)	<0.001	9 (8, 11)	22 (18, 26)	<0.001	10 (8, 12)	21 (18, 26)	<0.001
LA, mm	35 (33, 37)	43 (38, 46)	<0.001	35 (33, 37)	43 (38, 46)	<0.001	34 (32, 36)	43 (39, 46)	<0.001
LVEF,%	60 (56, 63)	59 (56, 62)	0.409	60 (57, 63)	59 (56, 62)	0.458	59 (56, 63)	59 (57, 61)	0.725
E/A < 1	119 (33.8)	193 (82.5)	<0.001	75 (29.9)	154 (89.53)	<0.001	44 (43.6)	39 (62.90)	0.016
SAM sign	0 (0)	122 (52.14)	<0.001	0 (0)	96 (55.81)	<0.001	0 (0)	26 (41.94)	<0.001

Data are expressed as n (%) or median (IQR), unless otherwise specified.
IQR, inter-quartile range; CAD, coronary artery disease; CA, cardiac amyloidosis; AS, aortic stenosis. MWT, maximum wall thickness; LA, left atrium; LVEF, left ventricular ejection fraction; E/A, E/A ratio, mitral peak E/A wave velocity ratio; SAM, systolic anterior motion.

were calculated, including the Akaike information criterion (AIC), Bayesian information criterion (BIC), R^2 and C-statistic of each model constructed by different combinations containing a distinct number of ECG variables.

To evaluate the performance of each model, we focused on the AIC, BIC, R^2, and C-statistic. In general, the model with the smallest AIC is preferred. However, we found that in the temporal internal validation cohort, models with 2 variables (TWI + SV1; TWI + RV5SV1) had C-statistics of 0.871 and 0.872, R^2 of 0.354 and 0.323, but with the biggest AIC (449.023 vs. 393.220) and BIC (461.108 vs. 405.305). Furthermore, the model constructed by TWI and SV1 had a smaller AIC and BIC compared with the one constituted by TWI and RV5SV1. When the number of variables ranged from 9 to 13, the C-statistics of the models ranged from 0.923 to 0.939, but with the relatively small AIC (ranging from 322.709 to 310.423) and BIC (374.435–350.363) values. Considering the moderate decrease in the C-statistics from the models with the smallest AIC values to the models with 2 variables (**Supplementary Figure 1**) and the credendum that models with fewer variables have greater clinical applicability, we selected the simplest model with 2 variables as having the best performance for HCM screening. The comparison using Delong test of 2 models with TWI + SV1 and TWI + RV5SV1 was shown in **Supplementary Table 7** and **Supplementary Figure 2**, indicating no significant difference between the two models, even the former showed slightly better performance in the external validation cohort. Finally, the TWI and SV1 was selected to construct the HCM model, the following formula shown as:

$$Y = -2.714 + 2.146 \times \mathrm{TWI} + 1.337 \times \mathrm{SV1}(\mathrm{TWI} = 1,\ \mathrm{No\ TWI} = 0).$$

Estimation of Discriminative Performance for Hypertrophic Cardiomyopathy Screening Model

The Hosmer–Lemeshow test showed χ^2 as 10.037 (P = 0.262) in the training and 7.714 (P = 0.462) in the temporal validation cohort, indicating good fitness of the model. Calibration plots showed a good imitative effect of the model, with slope (1.00 vs. 1.10) and intercept (0.00 vs. -0.03) in the training and temporal validation cohorts, respectively (**Figures 2A,B**). The C-statistics of the model were 0.857 (0.818–0.896) in the training cohort, and 0.871 (0.812–0.930) in the temporal internal validation cohort (**Figures 2C,D**).

Furthermore, receiver operating characteristic (ROC) curve analysis of retrospectively collected data from a large-population-based, external validation cohort (HCM = 3,232 vs. non-HCM = 95,184) yielded a C-statistic of 0.833 (0.825–0.841) (**Figure 3**). When the false-negative rate was 10%, the false-positive rate was 54%.

Examples Illustration

At last, the web-calculator was developed for clinical application (see text footnote 1). **Figure 4** showed two case scenarios. The case one was a 57-year-old male with no evident discomforts. During an accidental examination in clinic, the ECG showed sinus rhythm, with P interval 120 ms, SV1 1.55 mV, and TWI in precordial leads V2 to V4, and no indications of LVH (**Figure 4A**). The online calculator indicated that the patient had a high probability of HCM (**Figure 4B**), so he was recommended a referral to our HCM center, and diagnosed as HCM, with an MWT of 23 mm and LV outflow tract gradient (LVOTG) of 50 mmHg at rest by echocardiography. The Case Two was a 35-year-old female. Her ECG showed sinus rhythm with SV1 of 0.49 mV and no TWI (**Figure 4C**). She was classified as having a low probability of HCM by the

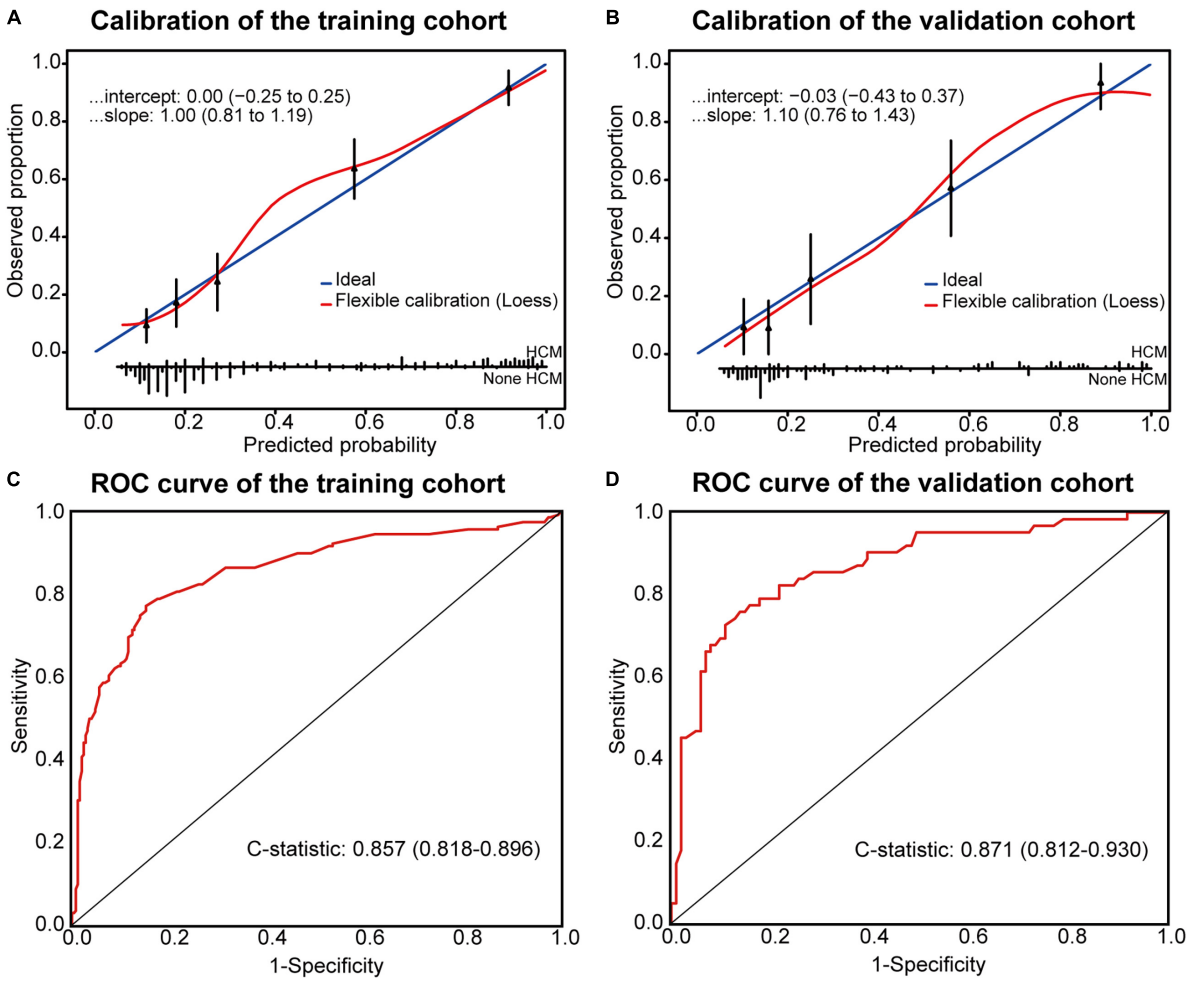

FIGURE 2 | Calibration plots and ROC curve for the Model. Calibration plots between predicted and observed HCM in the training **(A)** and temporal validation **(B)** cohorts. The 45° blue line represents a perfect prediction, and the red line represents the predictive performance of the model. ROC curve of the model in the training **(C)** and temporal validation **(D)** cohorts.

model (**Figure 4D**). Finally, she was diagnosed as systemic lupus erythematosus, and the echocardiography found no obvious abnormality, ruling out HCM.

DISCUSSION

In this study, we developed a screening model for HCM using the two most common and easily acquired ECG parameters and validated the model in a large-scale external validation cohort.

HCM is a major cause of SCD, HF and AF. Most HCM patients present with abnormalities on ECG. However, the abnormal ECG presentations in HCM are diverse, none are specific for HCM, and there are no standard and available models that can be used to quickly screen for HCM. Recently, an artificial intelligence (AI)-enabled ECG model using a convolutional neural network (CNN) also showed high sensitivity and accuracy for detecting HCM (30). Nevertheless, the precise features that the web sees are obscure and unexplainable through the AI process, and an advanced infrastructure may be required for its application. In the current study, TWI and SV1 were selected to identify HCM. These two variables can be automatically calculated and acquired by electrocardiography and might be more readily used to distinguish between HCM and non-HCM in a screening scenario.

Previous reports have suggested that repolarization abnormalities, such as TWI, are more indicative of HCM (31). TWI, especially in inferior and lateral leads, have been reported to account for nearly 70% of HCM cases (17). In the current study, we found TWI in nearly 60% of HCM cases and only 10% of non-HCM cases. It has been reported that among patients with giant TWI but a normal LV thickness on echocardiography, over 20% would exhibit progression and fulfill the criteria of HCM over a median follow-up period of 2 years (32). Therefore, TWI may be an early presentation of HCM. TWI has also been reported to be an indicator of the SCD risk in HCM. The ventricular repolarization dispersion due to ionic remodeling in coexisting regions of septal and apical hypertrophy may explain the normal QRS complex and TWI

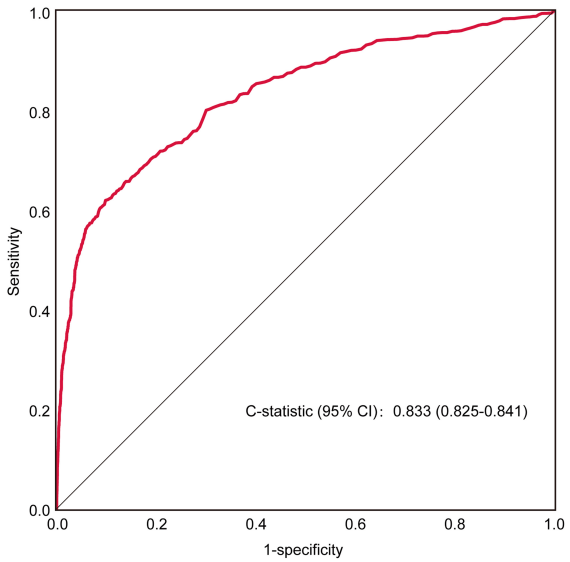

FIGURE 3 | ROC curve for the model in the external validation cohort.

observed in the phenotype associated with an increased SCD risk score (33, 34).

A recent study (35) found that while 96% of HCM patients had abnormalities on ECG, only a few of the QRS voltage elevations reached the standard for LVH (RV5SV1). Among several LVH indexes, the Cornell index (RaVLSV3) has shown the greatest net sensitivity and specificity for diagnosing LVH in young HCM patients (27, 36). In the present study, indexes reflecting LVH and IVS hypertrophy, including RV5SV1, RaVLSV3, RISIII, RV2V3, SV2V3, RV3V4, and SV3V4 were significantly increased in HCM patients. However, compared to TWI and SV1, these indexes are less able to discriminate HCM from non-HCM (**Supplementary Figure 3**). With increasing hypertrophy or enlargement of the left ventricle, the effects of LVH become more prominent, resulting in an increase in the R wave amplitude in leads facing the left ventricle (leads I, aVL, V5 and V6) and a deepening of the S wave in leads facing the right ventricle or deviating from the left ventricle (V1 and V2). IVS hypertrophy in HCM changes the direction of septal depolarization from right-to-left to left-to-right; thus, the vector turns to the right and forward. Therefore, compared with non-HCM, in HCM, the S wave increases in V1 and V2. The systolic anterior motion (SAM) sign of obstructive HCM makes this trend more obvious, with greater increases in SV1 than SV2. This explains why SV1 is given more weight in the model for HCM screening.

HCM has become a highly treatable condition with effective options that alter natural progression along specific adverse pathways at all ages. ECG, with the advantages of wide availability, low-cost and high reproducibility, remains a mainstay in HCM management. The prediction model based on ECG might be more practical than the screening approaches

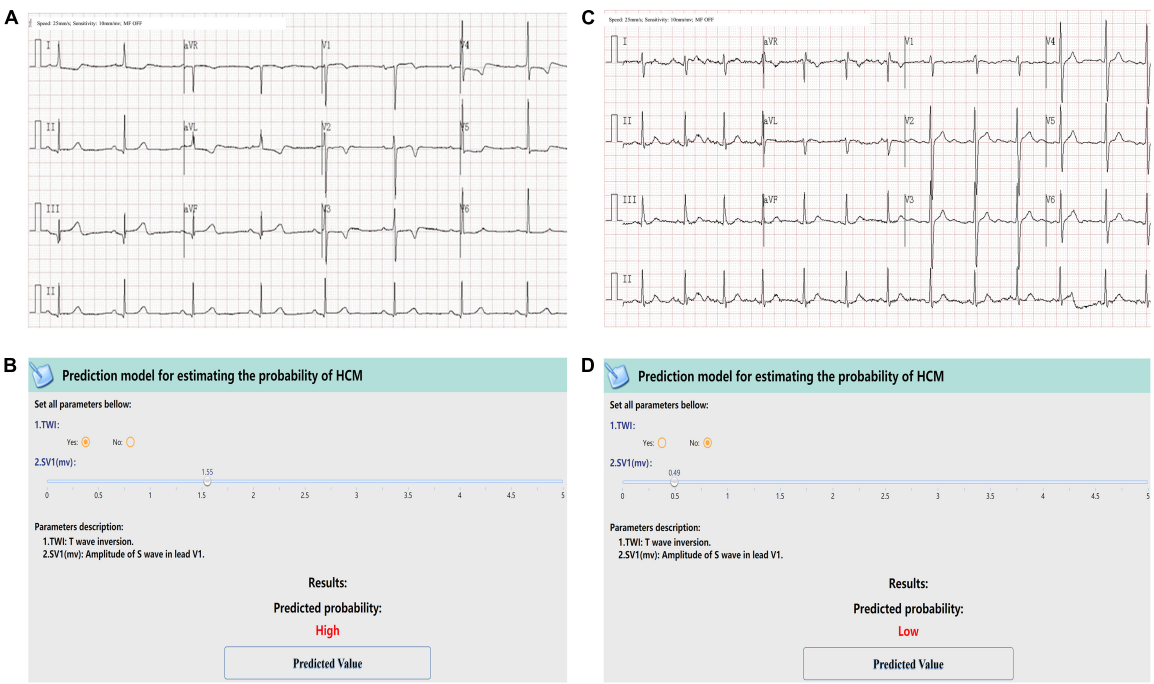

FIGURE 4 | Examples of the screen-shots of the web-based calculator. The first case was a 57-year-old male. ECG showed sinus rhythm, SV1 = 1.55 mV, and TWI in precordial leads V2 to V4. ECG showed no indications of LVH **(A)**. A screenshot of the web-based calculator indicated a high probability of HCM and recommended a referral to a dedicated HCM center. Then the patient was diagnosed as HCM, with an MWT of 23 mm and an LVOTG of 50 mmHg at rest by Echo **(B)**. The second case was a 35-year-female. Her ECG showed sinus rhythm with SV1 of 0.49 mV and no TWI **(C)**. She was classified as having a low probability of HCM by the model **(D)**. The echocardiography found no obvious abnormality, ruling out HCM.

such as Echo, CMR, or gene tests. Compared with the patent AI algorithm for HCM screening, the current formula and the online-calculator of the prediction model is open and free available. We believe that this prediction model may facilitate HCM screening in general population, especially in the undeveloped regions. Furthermore, the clinical significance of the screening model would be strengthened if the results of a cost-effectiveness analyses could be provided. We shall collect relative data and perform such analysis in our further study.

Limitations

First, all the ECG data in the current study were from a single hospital. Further external validation using participants from multiple centers and a population with more heterogeneity is needed. Second, the analysis of ECG variables in the current study focused only on those parameters that are easily assessed in clinical practice; thus, some important but less frequently used variables might have been omitted. Third, we did not consider the effects of genotype on the ECG results, but some researchers, using an ECG-AI model, have reported that the result was correlated with the HCM phenotype rather than the genotype (37). Finally, the model showed high sensitivity for HCM screening, at the cost of a high false-positive rate. Expectedly, once a high probability of HCM is identified by an initial assessment, further examinations should be suggested to exclude HCM, as well as other common cardiovascular diseases, such as coronary heart disease. Therefore, this model may have practical value for further clinical application.

CONCLUSION

This pragmatic model using only TWI and SV1 may be helpful to predict the probability of HCM and shows promise for use in population-based HCM screening.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the First Affiliated Hospital of the Air Force Medical University, and the requirement for written informed consent for this analysis was waived by the institutional review board.

AUTHOR CONTRIBUTIONS

LG, LL, FZ, and LT designed the study. LG, WY, ZM, MZ, HZ, GH, LZ, ZC, FS, and DS collected the data. LG, WY, ZM, JL, HS, BW, XG, and CH analyzed the data. LG and CG wrote the manuscript. LG, CG, FZ, LL, and LT revised the manuscript. LT provided fund assistance for the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.889523/full#supplementary-material

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Repostioning of Telemedicine in Cardiovascular World Post-COVID-19 Pandemic

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Background: During the COVID-19 pandemic, telemedicine is a quickest expanding service solution to provide improved access to sophisticated healthcare that is efficient, cost-effective, and time-consuming.

Methods: This analysis is evaluated on the basis of several studies that look at the history, benefits, various techniques, challenges, uses, and impact of telemedicine in the treatment of heart failure and cardiac rehabilitation as during COVID-19 outbreak.

Results: Patients avoided or refused medical treatment during COVID-19 pandemic despite the risk of illness and the threat of infections spreading. Telemedicine has become a non-traditional form of care delivery due to better access and high-end technologies such as virtual consultations, face-to-face video, smartphone visits, two-way text communication, distant patient history, and distal characteristic assessment. Remote monitoring can help manage cardiovascular disease risk factors and increase patient participation in blood pressure, heart failure data, and workout or other activity progress.

Conclusion: Based on the findings of past studies, we can infer that telemedicine is still an emerging subject in the treatment and management of cardiovascular disease. Telemedicine and similar technologies will also revolutionize healthcare services by expanding their reach and providing a big pool of database for better research and analysis.

Keywords: telemedicine, cardiovascular disease, COVID-19, advantages, challenges

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INTRODUCTION

Telemedicine is the evaluation and clinical care over long distances leveraging telecommunications technology, allowing low-income populations to access high-quality healthcare (1). Information and Communication Technology's (ICT) have the potential to resolve some of the obstacles that eventually created countries have in delivering appropriate, cost-effective, and enhanced health care services. Telemedicine is a type of information and communication technology (ICT) that is used to overcome geographical obstacles and improve access to health-care services. This is especially beneficial for developing nations' rural and underdeveloped communities, which have historically restricted access to health care (2).

"The shipment of quality healthcare, where proximity is a crucial factor, by all healthcare providers employing information and communication technologies for the interaction of valid information for diagnosis, treatment, and preventive care and injuries, research and evaluation, and professional development of healthcare professionals, all in the preferences of advancing the health of individuals and communities," according to the World Health Organization (WHO) (3). Telemedicine dates from the mid- to late-nineteenth century, with one of the first documented occurrences occurring in the early twentieth century, when electrocardiograph findings were sent *via* telephone wires (2).

High rates of cardiovascular disease (CVD) have been linked to difficulties in diagnosing and referring patients, particularly in rural areas and developing countries like India (4–6). According to various studies and statistics, the burden of CVDs is fast increasing, which usually reflects of coronary heart disease tripling in the last thirty years. In India, cardiovascular disease appears to have overtaken cancer as the major cause of mortality. According to a survey conducted in 45 localities in 2004, cardiovascular disease (CVD) was responsible for 32% of all deaths. Infectious diseases cost the lives of 13% of the population (7).

With 32 million diabetics, India will already be regarded as the world's diabetes hotspot. By 2025, this number is expected to climb to 69.8 million. Hypertensive persons are anticipated to increase from 118 million by 2020 to 214 million by 2025. A huge disparity in health-care distribution is exacerbating the problem. Despite the reality that more than 75% of Indians live in rural areas, more than 75% of Indian healthcare professionals work in urban settings (8).

There is an expanding market for telemedicine linked facilities around the country as the ICT platform improves. Specialists may now acquire clinical data of patients along with imaging information including such X-rays, echocardiography, as well as other photographs from many modalities thanks to the growing usage of desktops, smartphones, and tablet devices to access the internet (9).

Since the 1980s, telecardiology has been used to consult with cardiologists while also transmitting electrocardiograms (ECGs). The need for tele-echocardiography is being driven by the continued and significant growth of echocardiography as the primary cardiac imaging modality (40%), which includes the usage of portable ultrasound scanners. High-resolution echocardiographic images can now be displayed on tablet computer screens to provide diagnosis and treatment guidance, thanks to the diagnostic quality of these devices' screens. The purpose of this research is to look into the history, benefits, issues, applications, and influence of cardiac rehabilitation as during COVID-19 pandemic.

ADVANTAGES

Telemedicine was established with the primary objectives of enhancing chronic disease care, particularly in crises, in remote locations or in regions wherein access to health care services is limited. The employment of increasingly new digital technological tactics has spurred all use of telemedicine as during multiple phases of disease far more consistently, just like during the SARS outbreak in 2003 as, later, MERSCoV in 2013, and currently during the outbreak of COVID-19. This revolutionary innovation patient care system includes a number of conveniences for both the patient and the medical professional, in addition to the traditional mode of health care delivery.

EFFICIENCY IN TERMS OF COST

Brouwers et al. (10) observed that a Tele-rehab III clinical trial, which included the ongoing analysis of data from the SmartCare-CAD research, showed similar cardiac healthcare cost benefits over the intervention period but no differences in Quality adjusted Life Years (QALYs) between groups. When Cardiac telerehabilitation (CTR) was used in conjunction to center-based Cardiac Rehabilitation in the Tele-rehab III study, QALYs enhanced and health-care costs decreased well over course of 2 years [a cost savings of €878 ($1003) for the intervention group].

The economic benefits were attributed to a difference in cardiovascular hospital readmission (32 with in experimental group vs. 60 in the control group), which could have influenced participants' Quality Of Life. This discrepancy in rehospitalizations could be related to Tele-rehab III participants having a larger residual cardiovascular risk; as a result, participants in the intervention group may very well have benefited more from a longer CR program. Extended CR interactions may be useful and cost effectiveness in higher-risk people, according to the outcomes of the Tele-rehab III clinical study in high-risk individuals, it is both useful and cost-effective (10).

Wang et al. (11) revealed that neoplasms (19.4%), traumas (13.9%), and cardiovascular disorders (10.3%) were the 3 most prevalent diagnoses in a telemedicine deployment in China's Western province. 4,772 patients (39.8%) had their diagnoses changed as a result of teleconsultations, while 3,707 patients (77.7%) had respective evaluations severely amended. Moreover, 6,591 (55.0%) of individuals had their therapy modified, with 3,677 (55.8%) of those modifications unrelated to changes in diagnosis. The telemedicine network saved $2,364,525 (if patients traveled to the hub) or $3,759,014 (if patients did not extend to the hub) (if patients did not visit the hub, and specialists visited the spoke hospitals).

When surveying the entire community, including both use amongst, total medical costs reduced by roughly 15% between 2019 and 2020, according to Weiner et al. (12).

TIME SAVING

Telemedicine has now become a form of "advance triage," or triaging patients prior they enter an emergency room, during the COVID-19 outbreak. Despite the fact that it is self-quarantined, simple telemedicine, also known as on-desired telemedicine, seems to have become a handy way for individuals to be evaluated. This type of triage keeps patients and healthcare personnel safe while obtaining patient-centered therapy (13).

TABLE 1 | Comparison of different telemedicine cost effectiveness studies from Jiang et al. (21).

Technologies or devices for digital health intervention delivery	Country	Targeted disease	Time horizon	Intervention vs. comparator	Incremental cost-effectiveness ratio
Burn et al. (22) (Short message service)	Australia	Coronary heart disease	Lifetime	TEXT ME[a] program vs. UC[b]	TEXT ME program dominated UC
Grustam et al. (23) (Telephone support)	UnitedKingdom	HF[c]	0 years	TM[d] vs. UC	€12,479/QALY[e]
Grustam et al. (23) (Telephone support)	UnitedKingdom	HF	0 years	NTS[f] vs. UC	€8795/QALY
Grustam et al. (23) (Telephone support)	UnitedKingdom	HF	0 years	NTS vs. UC	NTS dominated TM
Martín et al. (24) (Mobile apps)	Spain	HF	Not declared	CardioManager vs. UC	€9.303/QALY
Thokala et al. (25) (Telemonitoring)	United Kingdom	HF	30 years	STS HM[g] vs. UC	UC dominated STS HM
Thokala et al. (25) (Telemonitoring)	United Kingdom	HF	30 years	TM vs. UC	£11,873/QALY
Thokala et al. (25) (Telemonitoring)	United Kingdom	HF	30 years	Structured telephone support with a human to human contact vs. TM	£228,035/QALY
Cowie et al. (26) (Telemonitoring)	United Kingdom	HF	10 years	CardioMEMS Vs. UC	£19,274/QALY
Sandhu et al. (27) (Telemonitoring)	United States	HF	Lifetime	CardioMEMS vs. UC	US $71,462/QALY
Schmier et al. (28) (Telemonitoring)	United States	HF	5 years	CardioMEMS vs. UC	US $44,832/QALY
Martinson et al. (29) (Telemonitoring)	United States	HF	5 years	CardioMEMS vs. UC	US $12,262/QALY
Healy et al. (30) (Wearable medical device)	United States	SCA[h]	5 years	WCD[i] vs. discharge home	US $26,436/QALY
Healy et al. (30) (Wearable medical device)	United States	SCA[h]	5 years	WCD vs. SNF[j]	WCD dominated SNF
Healy et al. (30) (Wearable medical device)	United States	SCAh	5 years	WCD vs. in-hospital stay	WCD dominated in-hospital stay

[a]TEXT ME, Tobacco, Exercise, and Diet Messages; [b]UC, usual care; [c]HF, heart failure; [d]TM, telemonitoring; [e]QALY, quality-adjusted life year; [f]NTS, nurse telephone support; [g]STS HM, structured telephone support with a human-to-machine interface; [h]SCA, sudden cardiac arrest; [i]WCD, wearable cardioverter-defibrillator; [j]SNF, skilled nursing facility.

When compared to the conventional method, the novel telemedicine service cut expenditures and transit time by 56 and 94%, respectively, according to a Bangladeshi study. According to the research, the percent of participants were delighted with the newly formed telemedicine service (14). **Table 1** shows the comparison of different telemedicine cost-effectiveness studies from Jiang et al. (21).

CHALLENGES OF TELEMEDICINE

The global outbreak of COVID-19 has resulted in significant morbidity and mortality. According to Chinese epidemiological statistics, people with concomitant cardiovascular illness are more likely to have substantial acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with potentially fatal results (15).

Concerns regarding access have stifled telehealth's enormous promise for a long time. Patients who've been elderly, live in distant places without dependable connectivity, or have a poor level of education are more likely to be denied telehealth services. One such factor appears to be age. Patients beyond the age of 65 battled with telemedicine technology, resulting in fewer video visits (16).

Low financing is wreaking havoc on all developing-country programs, including those that aren't directly related to health

care. Upkeep costs for keeping the system operating after preliminary tests and enthusiasm are substantially higher in poor countries when compared to comparable prices in developed countries. Most rural locations have inadequate fundamental ICT infrastructure, making any form of link with remote hubs and facilities impossible. One of the most obvious causes of telemedicine system crash is a scarcity of ICT infrastructure.

Telemedicine services, according to regulatory agencies, must be adequately controlled both within and across countries. Even the best telemedicine system may result in a less effective system if connectivity to the remote medical center(s) is poor. A restricted system with a good link, on the other hand, can produce high-quality results. The other potential challenges are as mentioned below:

- Methodology of payment
- Confidentiality and security of patient's data
- Access discrepancies
- Depersonalization
- Appropriate utilization and adoption of digital world

HOW TO OVERCOME THE CHALLENGES OF TELEMEDICINE

The ability to use the appropriate technology is an important aspect of the telehealth adoption process. To bring telehealth services online, facilities will need PCs, tablets, smartphones, and other technology. The advantages of employing current digital technology, such as speedier communication, automatic backups, and the capacity to communicate with patients on the road, should be widely understood by healthcare practitioners and personnel.

Digital Literacy is very important for the success of telemedicine. Patients and physicians should feel at ease with the technology; but, old age patients, may have difficulty using it. Providers can discuss this technology with their patients to determine whether they will use a telehealth program, which includes sending and receiving personal health information, responding to SMS, and setting up automatic reminders.

TELEMEDICINE SUCCESS DURING COVID-19 PANDEMIC

Throughout COVID-19, the primary goal of telemonitoring is to provide patients with a "health management strategy" that defines a personalized goal for each patient and changes attempts to keep the measured indicators as close to ideal as possible. Because of its novelty and wide range of potential applications, a clear demarcation of circumstances for how to employ telemedicine in short bursts has also proven difficult (17).

Telemedicine could be used to deal with patients who are isolated at home or at a hospital. In this case, telemedicine provides sufficient protection for both professionals and caregivers by limiting physical exposure to infectious patients to extremely non-deferrable crises (18).

Cardiovascular disorders, in particular, demand constant monitoring, putting both sufferers, and practitioners at risk of infection (19). With rapid developments in e-health technologies witnessed during epidemics and pandemics, remote monitoring has spread transcend emergency scenarios in this setting (20). The SARS-CoV-2 coronavirus pandemic has aided in the management of a variety of chronic disorders in this area.

Top five reasons to seriously consider TELEMEDICINE:

- Better accessibility
- Efficient care
- Millennial demand fulfillment
- Decreased absenteeism
- Improved patient satisfaction

Benefits for hospitals and healthcare professionals:

- Extend the reach and provide more healthcare services to people and connecting to underserved populations with boosting patient connections.
- Make better use of clinicians' outpatient slots.
- Monitor and manage protracted patient care with ease.
- Assist doctors in addressing more patients.
- Reduce patient access and manpower constraints challenges
- Preventing the delay in the diagnosis of certain fatal diseases
- Prevent the spread of airborne illnesses (for example, COVID-19 disease)—easily maintain social distancing practice.
- Expanding the pool of possible patients, resulting in additional revenue streams to clinicians and hospitals.
- Providing more preventive care.
- Providing more affordable health care services.
- Appointment no-shows are becoming less common.
- The gratification of providing superior patient care.
- Relationships with patients have been strengthened

Benefits for patients:

- Not having to travel a considerable distance for appointments.
- Not having to pay as much, especially when compared to emergency department or usual walk-in outpatient services.
- Not having to worry about a lack of local specialists for unusual disorders.
- No need to wait for assistance from a qualified healthcare professional.
- Specialized therapy for unique medical disorders is also easily accessible.
- Bedridden individuals can receive treatment swiftly and conveniently from the comfort of their own home.

CONCLUSION

According to the current research, the use of telemedicine has increased significantly during pandemic. As a result of recent research and technical breakthroughs, telemedicine seems to have become a critical asset in the treatment of chronic

illness', including both healthcare personnel and patients. Enhanced patient education, device accessibility, and improved connection are all key components in introducing telemedicine in impoverished nations.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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ORIGINAL RESEARCH
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Consensus on Recommended Functions of a Smart Home System to Improve Self-Management Behaviors in People With Heart Failure: A Modified Delphi Approach

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Background: Smart home systems could enhance clinical and self-management of chronic heart failure by supporting health monitoring and remote support, but evidence to guide the design of smart home system functionalities is lacking.

Objective: To identify consensus-based recommendations for functions of a smart home system that could augment clinical and self-management for people living with chronic heart failure in the community.

Methods: Healthcare professionals caring for people living with chronic heart failure participated in a two-round modified Delphi survey and a consensus workshop. Thirty survey items spanning eight chronic health failure categories were derived from international guidelines for the management of heart failure. In survey Round 1, participants rated the importance of all items using a 9-point Liket scale and suggested new functions to support people with chronic heart failure in their homes using a smart home system. The Likert scale scores ranged from 0 (not important) to 9 (very important) and scores were categorized into three groups: 1–3 = not important, 4–6 = important, and 7–9 = very important. Consensus agreement was defined a priori as ≥70% of respondents rating a score of ≥7 and ≤15% rating a score ≤ 3. In survey Round 2, panel members re-rated items where consensus was not reached, and rated the new items proposed in earlier round. Panel members were invited to an online consensus workshop to discuss items that had not reached consensus after Round 2 and agree on a set of recommendations for a smart home system.

Results: In Round 1, 15 experts agreed 24/30 items were "very important", and suggested six new items. In Round 2, experts agreed 2/6 original items and 6/6 new items were "very important". During the consensus workshop, experts endorsed 2/4 remaining items. Finally, the expert panel recommended 34 items as "very important" for a smart home system including, healthy eating, body weight and fluid intake, physical activity and sedentary behavior, heart failure symptoms, tobacco cessation and alcohol reduction, medication adherence, physiological monitoring, interaction with healthcare professionals, and mental health among others.

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Conclusion: A panel of healthcare professional experts recommended 34-item core functions in smart home systems designed to support people with chronic heart failure for self-management and clinical support. Results of this study will help researchers to co-design and protyping solutions with consumers and healthcare providers to achieve these core functions to improve self-management and clinical outcomes in people with chronic heart failure.

Keywords: Delphi survey, cardiovascular diseases, lifestyle behaviors, self care, health monitoring, information technology

KEY POINTS

- **Question:** What essential functions are recommended by healthcare professionals for a Smart Home system for people with heart failure?
- **Findings:** An expert panel of healthcare professionals agreed on 34 items as essential functions for a smart home system to support self-care for heart failure, including healthy eating, body weight and fluid intake, physical activity and sedentary behavior, monitoring of symptoms, tobacco cessation and alcohol reduction, medication adherence, physiological monitoring, interaction with healthcare professionals, and mental health.
- **Meaning:** The recommendations from the expert panel can guide the development of future smart home systems for people with heart failure.

INTRODUCTION

Chronic heart failure is an increasingly prevalent condition and is associated with a considerable health burden (1). Despite significant advances in medical treatment, approximately 44% of people with heart failure are re-hospitalized within 1 year of discharge (2), and 50% die within 5 years (3). This is primarily due to rapid health deterioration, severe comorbidities and lack of post-acute care monitoring. International guidelines recommend self-management as an essential strategy to improve care for people with chronic heart failure (4, 5). Self-management includes monitoring symptoms, adhering to prescribed medications, and adopting and maintaining lifestyle behaviors such as a healthy diet and physical activity (5, 6). A meta-analysis of patient-level data from 20 trials (n = 5,624 patients) demonstrated that self-management interventions reduced the risk of time to the combined endpoint of heart failure-related hospitalization or all-cause death (HR 0.80; 95% CI 0.71–0.89), and time to heart failure-related hospitalization (HR 0.80; 0.69–0.92) (7). However, sub-optimal symptom recognition, a lack of patient education, delayed symptom reporting, and medication non-adherence make optimal self-management challenging (8, 9). Innovative approaches that support people to better manage their heart failure are needed to improve individual's health and wellbeing, and ease burden on the healthcare system.

Previous trials involving implantable devices, mobile phone applications, text messaging, web-based programs and telemonitoring have shown to support self-management in people with heart failure (10–12). A systematic review and meta-analysis of randomized controlled trials, comparing whether people with heart failure received telemedicine or usual standard care, showed overall all-cause mortality (pooled OR = 0.80, 0.71 to 0.91, $p < 0.001$) and heart failure-related admission rate (pooled OR = 0.63, 0.53 to 0.76, $p < 0.001$) were significantly lower in the telemedicine group (13). Notwithstanding these findings, telemedicine has focussed predominantly on medical outcomes (such as symptoms) and has largely ignored the need to support people with heart failure to better self-manage their condition. Technology has the potential to address these limitations, by empowering people with heart failure to better manage their health, and to optimize communication with their clinicians when and if needed. Further, current approaches for designing technology interventions have typically failed to include patients and clinicians in the product design (14), which leads to lower levels of acceptance, dissatisfaction, stress and non-adherence (15–17).

In recent years, more smart technology solutions, which move beyond soley monitoring have emerged. Smart solutions incorporate network-connected sensors and communication platforms, have been used to monitor people's daily activities, communicate with care providers and support independent living (18–20). These smart systems have the potential to enable post-discharge monitoring, detect a worsening health status, allow healthcare professionals to tailor treatments remotely and support people to be proactive in seeking support (21). In collaboration with clinical, behavioral, and information technology experts, we are developing a smart home system for people living with chronic heart failure in the community. The smart home system connects different elements to support self-management of people living with chronic heart failure, thereby improving health ouctomes. Smart home systems incorporate network-connected sensors and communication platforms and have been used in recent years to monitor patients' daily activities, communicate with care providers, and support independent living (18, 19, 22, 23). For the purpose of this research, a smart home ecosystem carries out three key actions: sensing, processing, and communication (24). Specifically, the system will connect sensors (e.g., wearable and environmental) and medical devices (e.g., blood pressure monitor), send data from these devices to a cloud-based server for interpretation, and

provide feedback to the end-users (people with chronic heart failure and healthcare professionals) (**Figure 1**). The system will also facilitate communication between people living with chronic heart failure and healthcare professionals. One step in the development process is to identify necessary functions. To the best of our knowledge, no published studies have undertaken this work. Therefore, we aimed to develop a consensus-based set of core functions, based on international guidelines, that healthcare professionals recommend for inclusion in a smart home system to support people living with chronic heart failure in their homes.

METHODS

We used a modified Delphi survey methodology with two survey rounds and an online consensus workshop. The Delphi technique is a *well* -established approach to answering a research question through the identification of a consensus view across subject experts. This study is compliant with the "Recommendations for the Conducting and REporting of DElphi Studies" (CREDES) (25). Delphi consensus processes systematically aggregate expert input to identify areas of agreement and are commonly used to develop clinical guidelines, standards and quality measures(26). Consensus methods are appropriate where published information is inadequate or non-existent to provide a means of harnessing the insights of appropriate experts to enable decision making (27). Furthermore, the anonymous and iterative features of the Delphi method permit panel members to share their opinion without any individual dominance and peer pressure, which offers an advantage over other group research methods (28).

Participants and Panel Recruitment

Panel members with experience caring for people with chronic heart failure were sought from a range of healthcare professionals (e.g., general practitioners, cardiologists, nurses, pharmacists, and physiotherapists) from clinical and academic settings. A research team member (SMSI) established initial contact with potential panel members *via* email, phone, or an in-person meeting. Contacts were also asked whether they could recommend others who may add value to the project. The final selection of panel members aimed to ensure representation from multiple clinical fields. The identity of panel members was kept confidential throughout the survey process to ensure that each member felt free to agree or disagree with other members' responses.

Delphi Surveys

A limit of two survey rounds was chosen to reduce the panel members' burden and ensure a high response rate. Each survey was tested prior to distribution using people who were not participants in the Delphi rounds. They were asked to consider comprehension and the structure and readability of statements, and to identify any procedural problems when administering the surveys. Round 1 was tested by five clinical researchers, including a general practitioner, cardiologist, nurse, pharmacist, and physiotherapist with clinical experience in managing patients with heart failure for completeness, applicability and clarity.

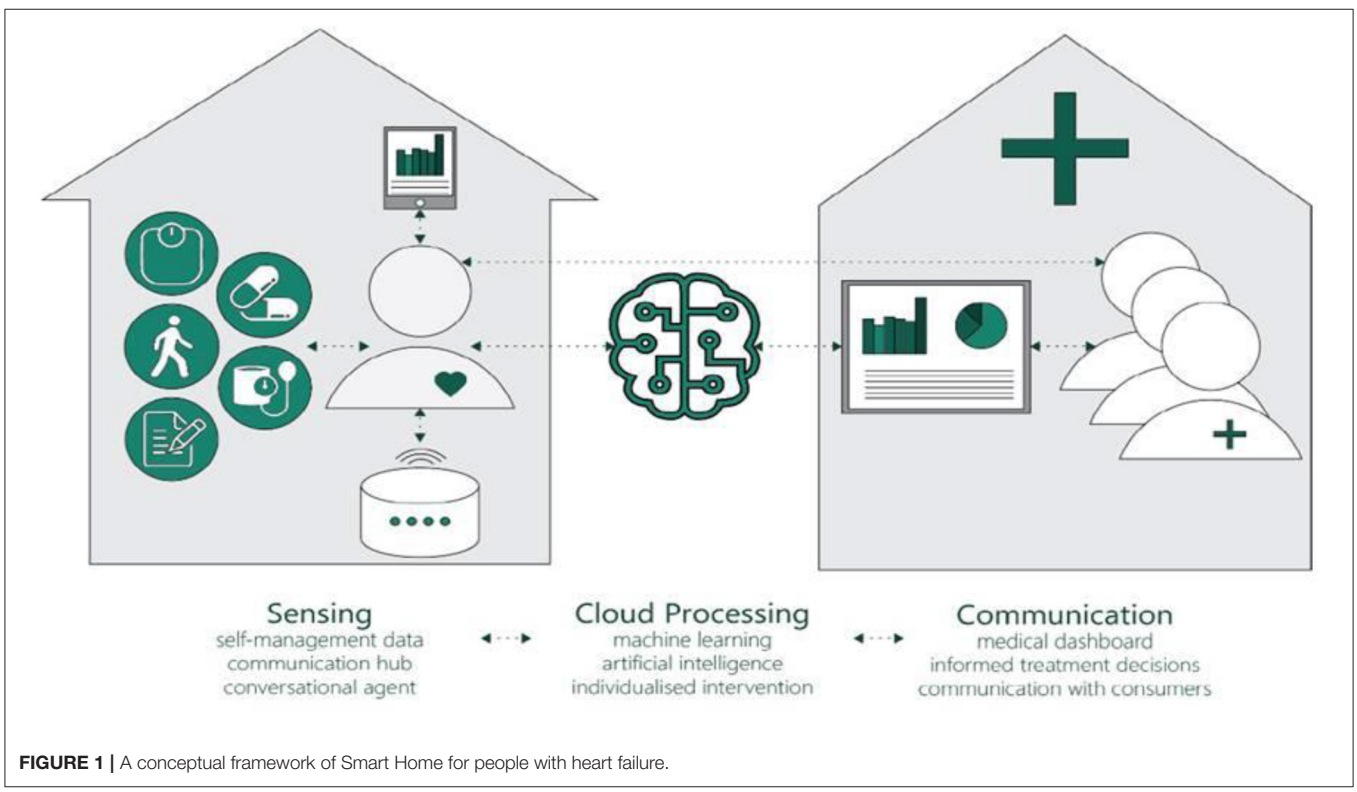

FIGURE 1 | A conceptual framework of Smart Home for people with heart failure.

Round 2 was tested by three clinician researchers. Panel members received links to electronic surveys (hosted on Qualtrics) via email, and were asked to complete each survey within 2 weeks, with reminders sent after 1 week. Panel members rated the importance on a 9-point Likert scale ranging from 0 (not important) to 9 (very important) and scores were categorized into three groups: not important (score 1 to 3), important (score 4 to 6), and very important (score 7 to 9). The scale and the scoring were based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which is used to rate the strength and quality of evidence (29). Instructions to panel members were to consider the importance of including each item in a smart home system for delivering information technology-supported care at home to a typical patient with chronic heart failure living in the community. Furthermore, panel members were instructed not to consider cost implications when making judgements to ensure ratings were not impacted by a lack of information about the technologies and costs needed to deliver each component. Participant anonymity was maintained by individualized communication for each round.

Survey Round 1

Survey items were derived from a review of the literature and relevent guidelines for people with chronic heart failure. Sources included international heart failure guidelines (4, 5, 30, 31) and previous systematic reviews (1, 8). Given the lack of published research on the topic, a free-text item asked panel members to suggest other items that they felt may warrant inclusion in a smart home system. The first survey consisted of 30 items grouped into eight categories (**Table 1**): (1) healthy eating, body weight and fluid intake; (2) physical activity and sedentary behavior; (3) heart failure symptoms; (4) tobacco cessation and alcohol reduction; (5) medication adherence; (6) physiological monitoring; (7) interaction with healthcare professionals; and (8) mental health.

Survey Round 2

Round 2 was developed based on Round 1 analysis. Panel members were invited to re-rate items where consensus agreement was not reached in the previous round and rate new items generated from free-text responses in Round 1.

Consensus Workshop

Panel members were invited to an online consensus workshop by email, and the research team followed up with panel members who did not respond to the initial email. The workshop began with a welcome and introduction by SMSI, followed by a review of the workshop objectives, an agenda, and information about the group activity and introductions of the research team and panel members. To provide additional context for the discussion, researchers with experience in digital health for chronic disease management presented their findings related to a scoping review of smart home-based systems for chronic disease management, a conceptual framework for a smart home ecosystem (**Figure 1**) and the preceding Delphi surveys. The workshop facilitator (RN) then encouraged the panel members to generate reasons to accept or reject survey items that did not reach consensus, promote discussion and guide panel members to reach a consensus agreement for each item.

Data Analysis

Participant characteristics and survey response rates are reported descriptively. For Likert scale items, the median rating, % rated ≥ 7 and % rated ≤ 3 were calculated. Consensus for both rounds was defined as follows; items were classified as important if $\geq$70% of respondents rated a score $\geq$7 and $\leq$ 15% of respondents rated a score $\leq$ 3 (32). During the workshop, items were categorized as either "endorsed" if participant responses were positive (i.e., use of words like "agree," "support," "good"). The final list of recommended functions included items that reached consensus agreement as "important" or were endorsed during the workshop.

Ethics Approval

The study was approved by Deakin University Human Research Ethics Committee (HEAG-H 151_2019). All participants provided informed consent.

RESULTS

In total, 21 experts were invited to participate in the study; 15 provided consent and formed the panel ($n = 9$ female, $n = 4$ general practitioner (GP), $n = 3$ cardiologist, $n = 3$ physiologist, $n = 2$ pharmacist, $n = 2$ nurse, and $n = 1$ dietician). All participants responded to both surveys. Only four panel members were able to attend the workshop ($n = 2$ GP, $n = 1$ cardiologist, and $n = 1$ nurse) therefore, a short report outlining the results was circulated by email to the panel with a request for feedback arising from any concerns; no panel members responded with disagreements.

Survey Round 1

Consensus was reached for 24 of 30 items (80%); all were rated as "very important" (**Table 1**). No items were considered "not important". Items that did not achieve consensus related to physiological monitoring (items 18, 19, 21, and 23) and mental health (items 29 and 30). Seven experts provided optional free-text responses, and six additional items were generated from these responses (items A1 to A6).

Survey Round 2

The second survey (**Table 2**) consisted of six items where no consensus was reached (18, 19, 21, 23, 29, 30) and six new items suggested by the panel during Round 1 (31–36). Items 18 and 21 reached consensus agreement as "very important". Items related to physiological monitoring (19 and 23) and mental health (29 and 30) (**Figure 2**). All new items suggested by the panel in Round 1 reached a consensus agreement as "very important".

Consensus Workshop

Four items where no consensus was reached during the survey rounds were discussed at the workshop. Discussion of item 23 ("monitoring diet") centered on feasibility, and the item was subsequently endorsed. Discussion of item 30 (provide

TABLE 1 | Delphi survey round 1 scoring and classification.

Item serial number/ Items	Median	% rated ≥7	% rated ≤3	Consensus	Classification
Healthy eating, body weight and fluid intake					
A Smart Home should provide education on…					
1. healthy dietary choices (e.g., fresh fruits/vegetables)	8	80	7	Yes	Very important
2. low sodium diet	8	80	0	Yes	Very important
3. weight monitoring	9	93	0	Yes	Very important
4. fluid monitoring	8	87	0	Yes	Very important
Physical activity and sedentary behavior					
A Smart Home should…					
5. provide individualized exercise prescription	8	80	0	Yes	Very important
6. monitor physical activity behaviors	8	87	0	Yes	Very important
7. monitor sedentary behaviors	8	73	0	Yes	Very important
Heart failure symptoms					
A Smart Home should…					
8. help participants to record heart failure symptoms (e.g., shortness of breath, swelling of legs, fatigue, and weakness)	8	87	0	Yes	Very important
9. remind participants about monitoring their heart failure symptoms	8	80	0	Yes	Very important
10. engage individuals to monitor their symptoms	8	73	0	Yes	Very important
Tobacco cessation and alcohol reduction					
A Smart Home should…					
11. provide support to reduce/quit tobacco	8	93	0	Yes	Very important
12. provide support to reduce/quit alcohol consumption	8	93	0	Yes	Very important
Medication adherence					
A Smart Home should…					
13. provide information on medication adherence	8	87	0	Yes	Very important
14. provide medication alerts (e.g., sensors on medication packs)	8	87	0	Yes	Very important
15. provide reminders to take prescribed medications	9	100	0	Yes	Very important
Physiological monitoring					
A Smart Home should…					
16. monitor blood pressure	9	100	0	Yes	Very important
17. monitor heart rate	9	93	0	Yes	Very important
18. monitor blood glucose	8	60	0	No	Round 2
19. monitor sleep duration	7	53	0	No	Round 2
20. monitor weight	9	93	0	Yes	Very important
21. monitor fluid intake	8	67	7	No	Round 2
22. monitor medication use	8	100	0	Yes	Very important
23. monitor diet	7	67	0	No	Round 2
Interaction with healthcare professionals					
A Smart Home should …					
24. support communication between users and healthcare providers	8	93	7	Yes	Very important
25. be linked with clinical management systems (e.g., electronic health records)	8	93	0	Yes	Very important
26. provide reminders for clinic appointments	8	87	0	Yes	Very important
27. provide alerts to healthcare providers about the patient's deteriorating condition	9	93	0	Yes	Very important
Mental health					
A Smart Home should…					
28. monitor individuals' mental health (e.g., depressive symptoms)	8	80	0	Yes	Very important
29. connect with a mental health support system (e.g., Beyond Blue)	8	67	0	No	Round 2
30. provide support for optimizing mental health in the form of messages delivered via a conversational agent (e.g., Google Home, Alexa)	7	53	0	No	Round 2

Consensus for an item was defined as: ≥ 70% of respondents rated a score ≥7 and ≤15% of respondents rated a score ≤ 3 [Likert scale: 1 (not important) to 9 (very important)].

TABLE 2 | Delphi survey round 2 scoring and classification.

Item serial number/ Items	Median	% rated ≥7	% rated ≤3	Consensus	Classification
Items from round 1					
A Smart Home should …					
18. monitor blood glucose	8	73	13	Yes	Very important
19. monitor sleep duration	7	**67**	7	**No**	Discuss
21. monitor fluid intake	8	80	0	Yes	Very important
23. monitor diet	7	**67**	0	**No**	Discuss
29. connect with a mental health support system (e.g., Beyond Blue)	7	**60**	7	**No**	Discuss
30. provide support for optimizing mental health in the form of messages delivered via a conversational agent (e.g., Google Home, Alexa)	6	**40**	0	**No**	Discuss
Additional items					
A Smart Home should…					
31. monitor ECG	7	73	7	Yes	Very important
32. be able to provide individualized care package (e.g., fluid monitoring in those with multiple fluid overload admission)	8	93	7	Yes	Very important
33. provide peer support (e.g., connect with family, friends)	8	80	0	Yes	Very important
34. use accelerometry for falls monitoring	8	73	0	Yes	Very important
35. remind participants for self-management of medication titration if symptomatic	9	100	7	Yes	Very important
36. have exercise charts and dietary plans	7	73	0	Yes	Very important

Consensus for an item was defined as: ≥ 70% of respondents rated a score ≥7and ≤15% of respondents rated a score ≤ 3 [Likert scale: 1 (not important) to 9 (very important)].

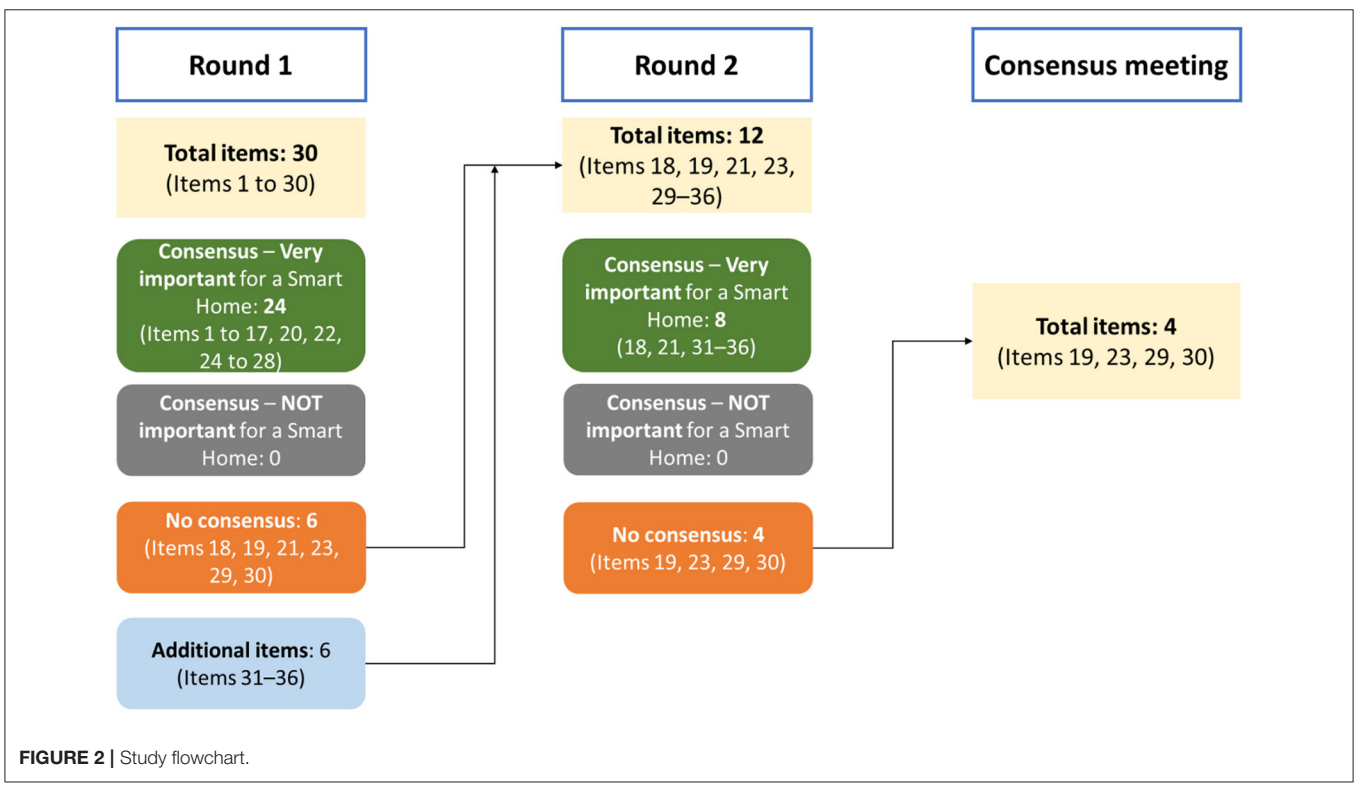

FIGURE 2 | Study flowchart.

support for optimizing mental health in the form of messages delivered via a conversational agent) highlighted a need to ensure messaging interventions to support mental health are personalized. The item was reworded as 'provide personalized mental health messages delivered *via* a conversational agent (e.g., Google Home, Alexa) before being endorsed. Item 19 ("monitor sleep duration" was not endorsed as the panel perceived technical challenges with sleep measurement, and cited a lack of evidence suggesting sleep monitoring affects the clinical presentation of heart failure. Finally, item 29 ("connect with a mental health

support system") was not endorsed as the panel perceived referral to mental health support services would not provide a personalized approach required by people with heart failure.

After two survey rounds and one workshop, 34 items were classified as very important or endorsed by the panel (**Box 1**).

DISCUSSION

To our knowledge, this is the first study to use the Delphi consensus process to identify recommended core functions for smart home systems designed to support people with chronic heart failure living in the community. An experienced multidisciplinary expert panel agreed on 34 core functions related to healthy eating, body weight and fluid intake; physical activity and sedentary behavior; heart failure symptoms monitoring; tobacco cessation and alcohol reduction; medication adherence; physiological monitoring; interaction with healthcare professionals; and mental health among others to be included in smart home systems.

Both survey rounds demonstrated high levels of agreement amongst panel members, with no apparent differences between disciplinary or clinical backgrounds. However, additional clarification was still required on four items in the categories of "physiological monitoring" and "mental health" after the two survey rounds. The workshop provided this clarification and panel members emphasized smart home system monitoring functions should be limited to health parameters that have been found to improve heart failure symptoms and self-management. While monitoring self-management behaviors (physical activity, sedentariness, diet, fluid intake, and medication use), vital signs

BOX 1 | Smart Home system functions recommended as "Very important" by the panel.

Healthy eating, body weight and fluid intake

1. Provide education on healthy dietary choices (e.g., fresh fruits/vegetables)
2. Provide education on low sodium diet
3. Provide education on weight monitoring
4. Provide education on fluid monitoring

Physical activity and sedentary behavior

5. Provide individualized exercise prescription
6. Monitor physical activity behaviors
7. Monitor sedentary behaviors

Heart failure symptoms

8. Help participants to record heart failure symptoms (e.g., shortness of breath, swelling of legs, fatigue, weakness)
9. Remind participants about monitoring their heart failure symptoms
10. Engage individuals to monitor their symptoms

Tobacco cessation and alcohol reduction

11. Provide support to reduce/quit tobacco
12. Provide support to reduce/quit alcohol consumption

Medication adherence

13. Provide information on medication adherence
14. Provide medication alerts (e.g. sensors on medication packs)
15. Provide reminders to take prescribed medications

Physiological monitoring

16. Monitor blood pressure
17. Monitor heart rate
18. Monitor blood glucose
20. Monitor weight
21. Monitor fluid intake
22. Monitor medication use
23. Monitor diet

Interaction with healthcare professionals

24. Support communication between users and healthcare providers
25. Be linked with clinical management systems (e.g. electronic health records)
26. Provide reminders for clinic appointments
27. Provide alerts to healthcare providers about the patient's deteriorating condition

Mental health

28. Monitor individuals' mental health (e.g. depressive symptoms)
30. Provide personalized mental health messages delivered via a conversational agent (e.g., Google Home, Alexa)

Additional items

31. Monitor ECG
32. Be able to provide individualized care package (e.g. fluid monitoring in those with multiple fluid overload admission)
33. Provide peer support (e.g. connect with family, friends)
34. Use accelerometry for falls monitoring
35. Remind participants for self-management of medication titration if symptomatic
36. Have exercise charts and dietary plans

(blood pressure, ECG/heart rate), and other health parameters (blood glucose concentration, body weight, mental health) were recommended, but monitoring sleep duration was not recommended as a perceived lack of evidence about clinical utility suggesting experts believed sleep data would not enhance clinical management.

Experts specified that messaging to support mental health should be personalized. A similar approach may be important for other smart home functions as personalized interventions have been shown to improve behavior change and maintenance (33). However, persaonlization was not explicitly raised by the panel in relation to other functions. Recommended monitoring functions could play key roles in personalizing smart home system functionality by enabling a better understanding of individuals' self-management behaviors and health status. These data could also be shared with clinicians to enable more personalized clinical management; however, consideration is needed on how to achieve this without overwhelming healthcare professionals. Smart home systems can provide personalization at different levels, for example functions can be easily added or in their entirety, or tailored in their execution by applying data analytics to sensed data. This is pertinent to people living with chronic heart failure who may have different needs (e.g., types of support at different stages of the disease trajectory) and preferences (e.g., willingness to use different types of digital technologies).

This study is an important contribution to the literature. Delphi processes for establishing expert consensus have been used to develop clinical guidelines, quality measures and identify important processes of care associated with heart failure (26, 34). We extended these methods to the realm of a smart home system for people with heart failure. The Delphi process allowed for data to be collected anonymously, systematically and iteratively which allowed for reasoned expert feedback with less bias from more forthright participants (35). Whilst we recruited a multidisciplinary panel of experts from a range of clinical backgrounds, it was not representative of all clinicians involved in caring for people with heart failure. Other clinicians may have arrived at different conclusions with more opposing views and debate resulting in a longer and more challenging process of achieving consensus. Therefore, our findings should be considered as an initial step in establishing the core functions of a smart home system for supporting self-management and clinical management in chronic heart failure (27).

While there was a high level of agreement between experts, the results should be interpreted with the following limitations: First, the homogenous scores across most items made it problematic to determine their importance relative to one another. Second, the small sample size (n=15) could be identified as a limitation. However, there is no standard method to calculate the number of experts required for a Delphi study, which can range from a few to hundreds of participants (36), depending on the study objectives, group heterogeneity, and available resources (36, 37). A heterogeneous group of 5–30 experts have been suggested to reduce bias in opinion, given that increasing the sample size does not result in improved outcomes and can reduce the response rate (36–38). Whilst all panel members responded to both survey rounds, only four attended the workshop which is lower than suggested previously (36–38). However, this smaller group size did allow for all voices to be heard in the workshop discussion, and different clinical backgrounds still represented a range of expertise. Third, the consensus workshop took place 12-months after the final survey due to the challenges associated with the COVID-19 pandemic (e.g., additional clinical load), this may have contributed to the low workshop participation and concerns that panel members would not remember details of the surveys. The workshop presentations aimed to resolve this, re-orienting the panel to the research topic and the survey items. Finally, as panel members were asked not to consider cost, these recommendations should be viewed as a guide for ideal functionality. If resource constraints prevent execution of all functions, additional work may be needed to inform an iterative development roadmap that prioritizes functions based anticipated benefits and costs.

This study contributes a significant element toward the development of a smart home system to support clinicial and self-management in people with chronic heart failure. A smart home system with these functions could contribute to evidence gaps outlined in international clinical guidelines, including the need for more data on the effects of fluid restriction, dietary salt restriction and nutrition; the role of remote monitoring; optimal models for follow-up of stable heart failure patients; better definition and classification of patient phenotypes to facilitate improved treatment; and development of better strategies for congestion relief, including monitoring of diuretic administration (5, 6). Smart homes can address these gaps by collecting these data directly from patients' home, using machine learning algorithms to create phenotypes, providing automated alerts, remote medication titrations and care (39–41). The findings may also have implications for technology-based programs for other chronic diseases in which self-management is important (e.g., chronic obstructive pulmonary disease). However, further work is necessary to determine the condition-specific functions, test specific items to determine the practical feasibility, usability and validity of this approach and frameworks (42–44). Combining the results of this study with findings from formative research that gathers user insights will guide the development of an innovative, intelligent smart home system for people with chronic heart failure. Furthermore, work to determine the most useful functions for different disease phenotypes and people at different points on the disease trajectory (e.g., acute or chronic decompensation, de novo or worsening patients, patients with preserved or reduced ejection fraction) is needed (45). Once functional prototypes have been developed, clinical trials will be needed to understand the effectiveness and cost-effectiveness of smart home systems in improving health outcomes in people with chronic heart failure.

CONCLUSION

A multidisciplinary panel of heart failure clinicians recommended 34 functions spanning healthy eating, body weight and fluid intake, physical activity and sedentary behavior, heart failure symptoms, tobacco cessation and alcohol reduction, medication adherence, physiological monitoring, interaction with healthcare professionals, and mental health among others for inclusion in smart home systems designed to enhance clinical

and self-management of chronic heart failure. Results of this study will help researchers to co-design and protyping solutions with consumers and healthcare providers to achieve these core functions to improve self-management and clinical outcomes in people with chronic heart failure.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Deakin University Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis: SMSI. Concept and design and study supervision: SMSI and RM. Acquisition, analysis, or interpretation of data: SMSI and RU. Drafting of the manuscript and administrative, technical, or material support: SMSI, RN, RU, JR, and RM. Statistical analysis: RU. Obtained funding: SMSI. Critical revision of the manuscript for important intellectual content: All authors. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CACHET-CADB: A Contextualized Ambulatory Electrocardiography Arrhythmia Dataset

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ECG is a non-invasive tool for arrhythmia detection. In recent years, wearable ECG-based ambulatory arrhythmia monitoring has gained increasing attention. However, arrhythmia detection algorithms trained on existing public arrhythmia databases show higher FPR when applied to such ambulatory ECG recordings. It is primarily because the existing public databases are relatively clean as they are recorded using clinical-grade ECG devices in controlled clinical environments. They may not represent the signal quality and artifacts present in ambulatory patient-operated ECG. To help build and evaluate arrhythmia detection algorithms that can work on wearable ECG from free-living conditions, we present the design and development of the CACHET-CADB, a multi-site contextualized ECG database from free-living conditions. The CACHET-CADB is subpart of the REAFEL study, which aims at reaching the frail elderly patient to optimize the diagnosis of atrial fibrillation. In contrast to the existing databases, along with the ECG, CACHET-CADB also provides the continuous recording of patients' contextual data such as activities, body positions, movement accelerations, symptoms, stress level, and sleep quality. These contextual data can aid in improving the machine/deep learning-based automated arrhythmia detection algorithms on patient-operated wearable ECG. Currently, CACHET-CADB has 259 days of contextualized ECG recordings from 24 patients and 1,602 manually annotated 10 s heart-rhythm samples. The length of the ECG records in the CACHET-CADB varies from 24 h to 3 weeks. The patient's ambulatory context information (activities, movement acceleration, body position, etc.) is extracted for every 10 s interval cumulatively. From the analysis, nearly 11% of the ECG data in the database is found to be noisy. A software toolkit for the use of the CACHET-CADB is also provided.

Keywords: arrhythmias, context-aware ECG, wearable ECG, atrial fibrillation, ambulatory ECG, arrhythmia dataset

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1. INTRODUCTION AND BACKGROUND

A heart arrhythmia like AF alone affects nearly 2% of the global adult population and is one of the major contributors to CVD related morbid conditions and mortality (1, 2). The management of AF includes anti-coagulation to prevent strokes and heart rhythm-modifier medications (3, 4). Also, therapies like electrophysiological pulmonary-vein isolation (PVI)

can also be offered to selected and suitable candidates with good curative results (5). However, for treatment to be effective in preventing further complications, early diagnosis and timely evaluation of AF plays a vital role. Analysis of electrocardiogram (ECG) signals is a non-invasive and cost-effective way of diagnosing AF. Due to their transient nature, paroxysmal AF remains under diagnosed in baseline ECGs and require long-term ECG monitoring. However, long-term preemptive monitoring is challenging as manual analysis of days/weeks-long ECG needed for detecting paroxysmal AF is resource and time-consuming.

Over the years, many computer-based algorithms have been developed for faster and accurate detection of AF and other types of arrhythmias (6). More recently, with the advent of ML and DL, the field of computer-aided AF analysis has experienced a huge breakthrough (6–8). As compared to traditional ML and other feature engineering-based approaches, DL-based models can achieve end-to-end classification, thus removing the dependence on domain experts in the classification and stratification process. Despite all these advancements, one of the major challenge of using DL in AF classification is the availability of training and validation datasets. Although the DL algorithms can directly learn features from raw ECG data, it requires large and diverse datasets. The training data diversity helps the models to incorporate all the variations in inter/intra-personal ECG morphologies.

To meet this demand, many Internet ECG datasets such as the AFDB (9), MITDB (10), PTB-LX (11), CinCDB (12), OA-ADB (13), and DeepQ (14) have been published. **Table 1** provides a summary of these publicly available arrhythmia databases. MITDB and AFDB are the earliest available ones and have been used extensively as a benchmark in training and evaluating ML/DL-based arrhythmia detection models (6, 7, 15).

Although the aforementioned databases have made a significant contribution for developing and evaluating arrhythmia detection models; generalization and comprehensive performance evaluation of such models under free-living conditions remain questionable and face a number of significant challenges (6, 15, 16):

Firstly, as mobile and wearable technology is advancing, wearable ECG devices have become available for longitudinal arrhythmia screening under free-living conditions. However, the majority of the current databases are either collected in controlled in-hospital settings or, in some cases, under the environments where patients are sitting without any motion. Therefore, the recordings are relatively clean and lack the ECG morphology changes and confounding artifacts that occur under free-living conditions. When the classification models trained on these datasets are applied to ambulatory wearable-based ECG recordings, they result in non-trivial false positives due to the degradation in the signal quality (18).

Secondly, the patient's context, such as physical activity and posture change, food intake (drinks or heavy meal), or mental stress, are known to introduce morphological changes in the ECG signal (19, 20). Existing databases only provide the raw ECG data, while information on the patient's context during the recording is missing. Recent systematic literature reviews of computer-aided arrhythmia analysis highlight that the arrhythmia detection in an ambulatory setting remains challenging and prone to mis-classification, without understanding the patient's context in which the ECG was undertaken (6, 21). Even during a manual ECG analysis, whenever a cardiologist finds 10 or 30 s of ECG segment inconclusive, they often look for the longer context of the patient's ECG and rely on their knowledge about arrhythmia epidemiology (22). Therefore, the patient's ambulatory context is essential for avoiding inappropriate classification due to "arrhythmia mimicking artifacts." Recent databases like DeepQ (14) have tried to address this problem by providing ECG recordings under the following three activity classes viz. sitting, walking, and lying down. These are, however, still a very limited set of activities and are recorded under circumstances that are very discordant from the real-world free-living ambulatory settings.

Thirdly, databases are usually generated from a single center for a short time period (minutes or hours) on a homogeneous group of participants. Due to large variations that exist in the morphologies of ECG waveforms and the lack of diversity in current datasets, models trained on such datasets result in a large number of false positives when applied to ECG from different user contexts, ethnic characteristics, anthropomorphic features, gender, age group, and time-periods (6, 23, 24). For instance, a multi-scale convolutional neural networks (23) showed a 98.18% accuracy when trained and validated on the AFDB, but its accuracy was reduced to 94.93% when applied on a Chinese

TABLE 1 | Technical specifications and ECG annotation statistics of publicly available ECG databases. Freq, sampling frequency (Hz); Ch, no. of ECG channels.

Database	Ch	Freq (Hz)	No. samples	Sample length	Rhythm classes	No. subjects	Context	Remark
AFDB (9)	2	250	23	10 h	4	25	✗	Continuous, controlled environment
MITDB (10)	2	360	48	30 min	15	47	✗	Continuous, controlled environment
NSRDB (17)	2	128	18	24 h	1	18	✗	Continuous, ambulatory
DeepQ (14)	1	250	897	5 min	8	299	✗	Intermittent, controlled environment
OA-ADB (13)	6	400	2,000	30 s	15	200	✗	Continuous, ambulatory, patient-operated
CinC2017 (12)	1	300	8,528	9–60 s	4	–	✗	Intermittent, patient-operated
CACHET-CADB	1	1,024	1602	10s	4	24	✓	Continuous, ambulatory, patient-operated

dataset collected under free-living conditions. Similarly, the model by Andersen et al. (25) trained on AFDB has an excellent performance in 5-fold cross-validation on AFDB; however, it resulted in 4.9% FPR on previously unseen NSR database from healthy individuals.

To complement the existing databases and to address some of the above-mentioned challenges, we present the CACHET-CADB. In contrast to the existing databases, CACHET-CADB provides the following unique features:

- It contains longitudinal wearable based ECG data from arrhythmia patients collected under *free-living conditions*, thus suitable for training and evaluating algorithms aimed at enabling real-time ambulatory ECG monitoring of the patients.
- Along with the ECG dataset, it also provides *contextual data* such as activities, body positions, movement accelerations, patient-reported events like symptoms experienced, sleep quality, stress level, and food intake. This contextualized ECG data can help make the end-to-end DL-based ECG classification models more explainable. Further, identifying the algorithm's source of errors in relation to the patient's ambulatory context can help in dynamically fine-tune it for those false-positives prone/inducing contexts under free-living conditions.
- Is multi-site and diverse (currently, Denmark and India but will be expanded further).

Currently, the CACHET-CADB contains 259 days long contextualized ECG data from 24 patients. It also comprises 1,602 annotations of 10 s long ECG-waveform, manually annotated by two independent qualified cardiologists into four different heart rhythm classes: AF, NSR, "noise," and "other." The CACHET-CADB is under continuous development, and annotations by cardiologists will be added to the database as they become available. The ECG annotation tool will be made public to increase the effort of crowd-sourcing the annotation process. Along with the dataset, a set of Python scripts and other software tools for data access, visualization, and data processing are available on the CACHET GitHub repository (26). The dataset is freely available at DTU Data (27) at DTU.

2. METHODS

This section explains the data acquisition process, including ethical considerations, the data collection methods and technology, the data specifications, and the annotation process.

2.1. Data Acquisition

2.1.1. Ethical Consideration

The data for the CACHET-CADB was collected in India and Denmark. In Denmark, the study was exempted for ethical approval by the Danish Research Ethical Committee because the ECG recordings were only collected for technical purposes, and not to be used in a clinical setting (File # H-19071015). In India, the data collection was done with Mahatma Gandhi University of Medical Sciences and Technology (MGUMST), Jaipur, and the process complies with MGUMST's human participant's guideline and regulation as stated by the MGUMST Institutional Review Board (IRB). The approvals were granted on the ground that data collection was purely for technology development, and that the data would not be used for clinical diagnosis or treatment of the patients.

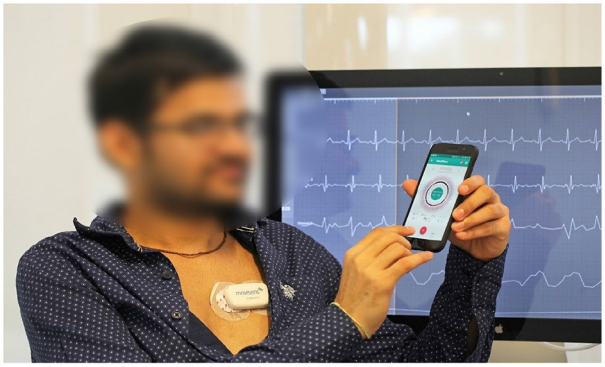

FIGURE 1 | Data collection setup: (i) a chest-mounted single channel wireless ECG monitor collecting ECG and inertial (movement) measurements, and (ii) the mCardia mobile application for collection of patient-reported data (28).

2.1.2. Recruitment

The participants were recruited during their out-patient arrhythmia clinic visits *via* a general announcement to participate in the data collection study. It was also made clear to participants that their participation was purely for research purposes, and the collected data would not be used in their ongoing clinical diagnosis or treatment. Preference was given to the participants with a known history of paroxysmal AF or high AF risk factors. All participants signed an informed consent form and allowed their data to be used and shared publicly after subject identity anonymization.

2.1.3. Data Collection Method

We used the mCardia system (28) for the data collection. It uses a single-channel chest-mounted wireless ECG Holter [the Movisens ECGMove4 (29)] and a mobile application for data collection (**Figure 1**). Participants wore the ECG device using two disposable adhesive wet Ag/AgCl electrodes. All data was forwarded to, and stored in the CARP (30), which is a secure and scalable cloud-based infrastructure for health data science hosted at DTU. Each participant installed the mCardia mobile application on his/her phone and continuously wore the ECG device for a minimum of 24 h and up to 3 weeks. Participants were instructed to change the ECG electrodes daily and fill in the patient-reported information (symptoms, stress levels, sleep quality, and food intake) in the mCardia app. They were also instructed to take off the ECG device only for charging or during bathing/shower. Further details on the mCardia system and CARP can be found at https://carp.cachet.dk/mcardia/.

2.1.4. Anonymization and Data Trimming

The initial recording length varied from 24 h to 3 weeks. For better manageability, analysis, and data handling, recordings

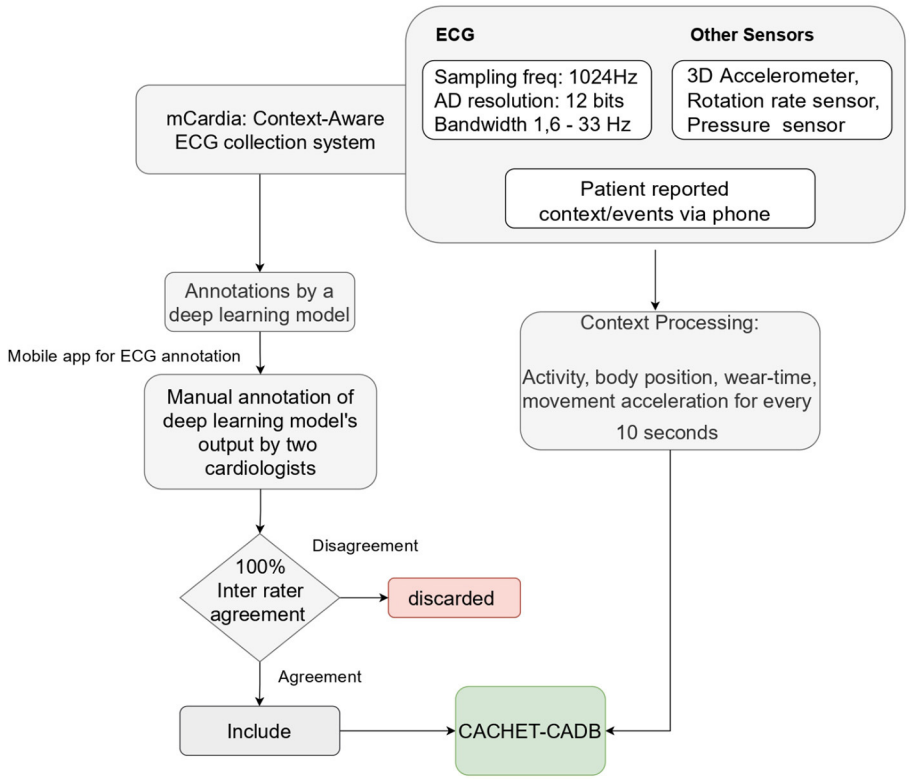

FIGURE 2 | Overview of data collection and annotation process.

were trimmed and assigned an anonymous ID (see **Figure 5**). In each record, the first (0th) and the last days are of variable lengths, whereas the rest are 24 h long, starting from midnight.

2.2. ECG Annotation Process

Figure 2 shows the process used for annotating the ECG samples in the CACHET-CADB. A DL based AF detection model (25) was used to process the raw ECG recording. The AF onset and offset timestamps marked by the DL model were stored in CSV files. Thereafter, the segments between the onset and the offset were chopped into 10 s interval recordings and sent to two independent cardiologists for manual annotation *via* a mobile ECG annotation app. **Figure 3** shows the user interface of the ECG annotation app used for the manual annotation. The annotation rules were discussed and agreed upon by the two cardiologists. A 10 s segment was assigned a label if it contained more than 50% of a particular rhythm type. If there were multiple rhythm classes in 10 s sample without having a majority ($\geq$50%) of a particular class, then it was annotated as "others." If artifacts in the 10 s signal precluded proper interpretation of the underlying rhythm, then the sample was annotated as "noise." The annotations of the two independent cardiologists were compared for inter-observer agreement. If there were disagreement between the two cardiologists, the annotations were discarded. Thus, the final database only includes samples where there is an agreement between the two cardiologist's annotations.

2.3. Processing Contextual Data

The collected contextual data is of two categories: (1) patient-reported data collected *via* the mCardia app, and (2) sensor-generated data which is passively collected from the sensors on the mobile phone and the ECG Movisens device. **Table 2** provides an overview of the types of collected data.

2.3.1. Patient-Reported Data

Patient-reported contextual data was collected when the patient manually enters data during the study period. We collected two types of patient-reported context information; (1) experienced events, and (2) daily health reports. The events were registered by patients when they experienced any unusual symptoms (e.g., palpitations, heartburn, etc.) during the ECG recording period. It includes details about the type of symptom, its duration, activity during the symptom, and a short note providing more context and experience. Health reports were provided daily and comprised of a three short survey on meals (timings and type of meal (light, heavy, moderate), self-perceived stress level, and sleep quality (on a scale of 1–5). It should be noted that we only collected food intake timings and quantity (as light, heavy, or moderate) and not the specific details of what patients ate in

FIGURE 3 | Mobile application used for ECG annotation.

TABLE 2 | Specifications of the collected data. S, sensed; PR, patient-reported; EB, event-based.

Collected data type	Type	Data source	Sampling rate
ECG	S	EcgMove4	1,024 Hz
3D acceleration	S	EcgMove4	64 Hz
Rotation rate sensor	S	EcgMove4	64 Hz
Pressure sensor	S	EcgMove4	8 Hz
Events	PR	EcgMove4 & Phone	EB
Sleep	PR & S	Phone	1/Day
Dietary	PR	Phone	1/Day

their meals. The description of the meal itself was optional in the freestyle text input. The freestyle comments added by patients for further describing the symptoms or events were either in English or in the local vernacular language.

2.3.2. Sensor-Generated Data

The sensed context is passively derived from the on-board sensors (3D acceleration sensor, gyroscope, and pressure sensor) of the chest-mounted Movisens ECG device and from the phone's sensors. **Table 2** lists the sensors' sampling rates. The DataAnalyzer Tool (31) was used for processing data from the Movisens sensors, and context data such as movement acceleration, body position, activity, step count, wear time, energy expenditure, and MET levels were derived for an interval of 10 s. The movement acceleration, also known as MAI, is a typical physical activity metric that depicts bodily movements' intensity. The MAI is measured in "g," which is multiples of Earth's gravity (1 g = 9.81 m/s^2). In the DataAnalyzer Tool, the body positions were classified based on the inclination obtained from the 3D accelerometer. Its activity recognition is based on a white-box decision tree on the features extracted from the accelerometer and the barometric air pressure data (32). The type of recognized activities include unknown, lying, sitting, standing, cycling, slope up, jogging, slope down, walking, and not-worn. Similarly, the body positions are classified based on the inclination obtained from the 3D accelerometer. The body position classes include unknown, lying supine, lying left, lying prone, lying right, upright, sitting/lying, standing, and not-worn.

3. DATA RECORDS

The CACHET-CADB includes over 259 days of single-channel contextualized ECG recording from 24 patients previously diagnosed with or suspected of the high risk of AF. Besides the patient's ambulatory contexts, it also contains 1,602, 10 s long annotation samples of 4 different ECG rhythm classes, namely, AF, NSR, noise, and others (anything excluding AF, NSR, and noise). A sample of each of these rhythm classes is shown in **Figure 4**. The CACHET-CADB is freely available on DTU Data figshare (27) under the name "CACHET-CADB."

Figure 5 describes the organization of the records in CACHET-CADB. For better manageability and incorporation of future updates, the dataset is split into two main parts: (i) the raw signals (i.e., ECG, 3D accelerometer, angular rate) and (ii) the annotations, while keeping the same folder structure inside each part. At the time of drafting this manuscript, the dataset has 24 records, spanning 259 days of recording from 24 patients of which, 7 were Danish and 17 were Indian. There were 15 males/9 females—with an average age of 59, and of which 11 patients had documented one or more AF episodes in past.

3.1. Raw Signals and Metadata

The raw sensor data is stored in Unisens (33) file format. It allows simultaneously multi-sensor data, with synchronous

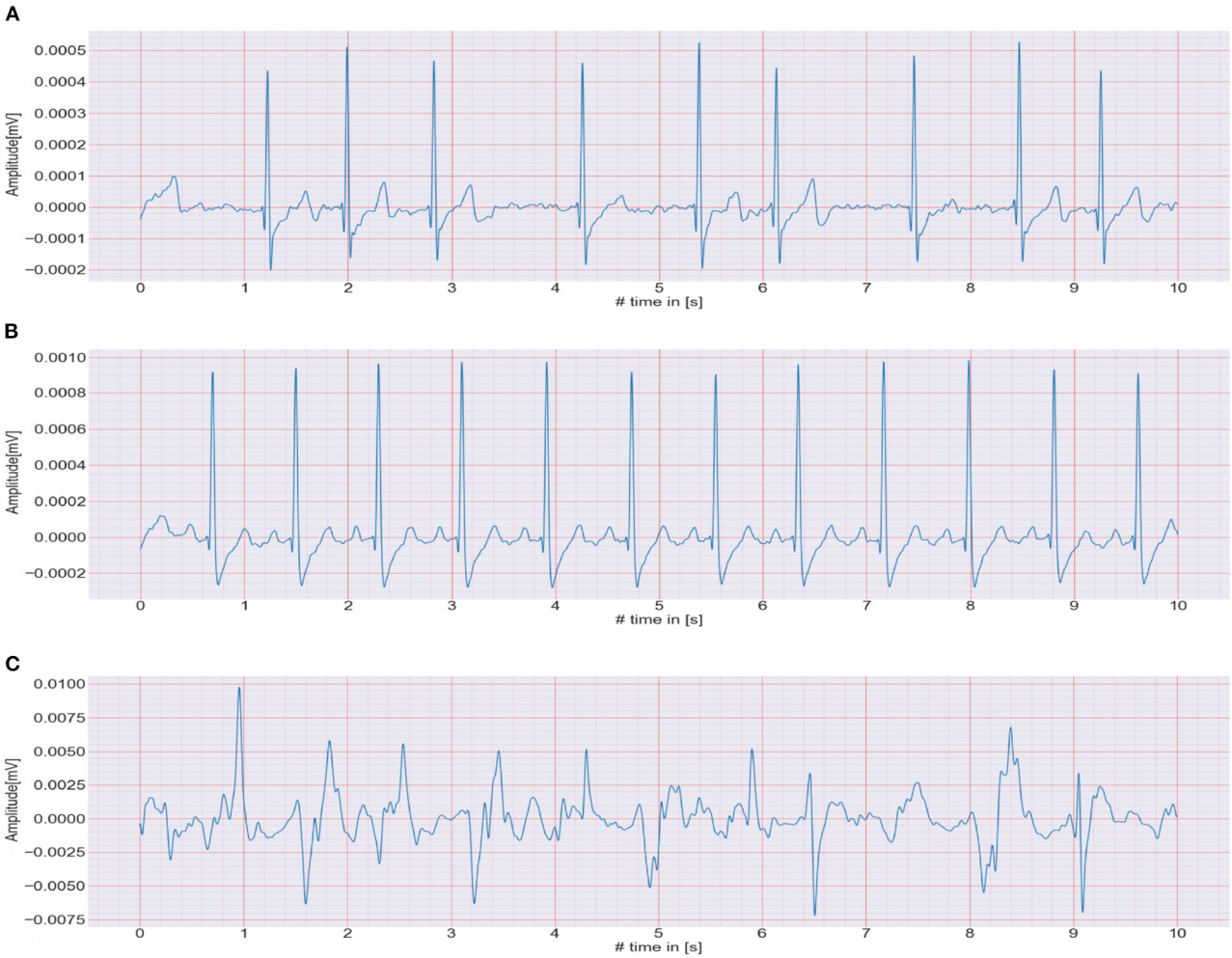

FIGURE 4 | (A–C) Show the 10 s ECG recordings of AF, NSR, and Noise classes, respectively.

storage at different sample rates, and comes with a human-readable meta-file in XML format. As illustrated in **Figure 5**, for each day the *unisens.xml* file contains the metadata for the raw signals. **Table 3** describes these metadata in detail. The general metadata information includes the start timestamp, the total recording time (in seconds), and the anonymous user id (same as the anonymous id for the entire recording). The patient metadata includes height, weight, gender, location of the ECG sensor, and age at the time of recording. The raw ECG, 3D accelerometer, angular rate, and pressure signals are in the *ecg.bin*, *acc.bin*, *angularrate.bin*, and *press.bin* files, respectively. To allow for any future processing and analysis of the recordings, the dataset contains the raw signal without any preprocessing or filtering.

However, given the recordings' ambulatory nature, any use of the data would probably need to implement baseline correction and removal of other artifacts beyond the normal ECG band [0.5–50 Hz].

3.2. Annotations and Metadata

As shown in **Figure 5**, the annotations follow the same folder structures as the raw signals. For each day, the *context.xlsx* and *annotation.csv* files contain the contextual and annotation data, respectively.

The *context.xlsx* file contains the patient's ambulatory context for every 10 s interval. These contextual data are derived from a 3D acceleration sensor, gyroscope, and pressure sensor, as described earlier. **Table 4** provides the metadata for these contextual data, where the attributes listed in the table are columns in the *context.xlsx* file. The "unit" column in **Table 4** represents the measurement unit of each attribute. The remark column provides the label of each subclass within the same column. For instance, *ActicityClass* has several sub-classes, such as lying, sitting/standing, cycling, slope up, or jogging. The corresponding subclass code (0, 1, 2...) represents them in the activity column of the *context.xlsx* file. Patient-reported data is provided as a single JSON file in each annotation folder (see

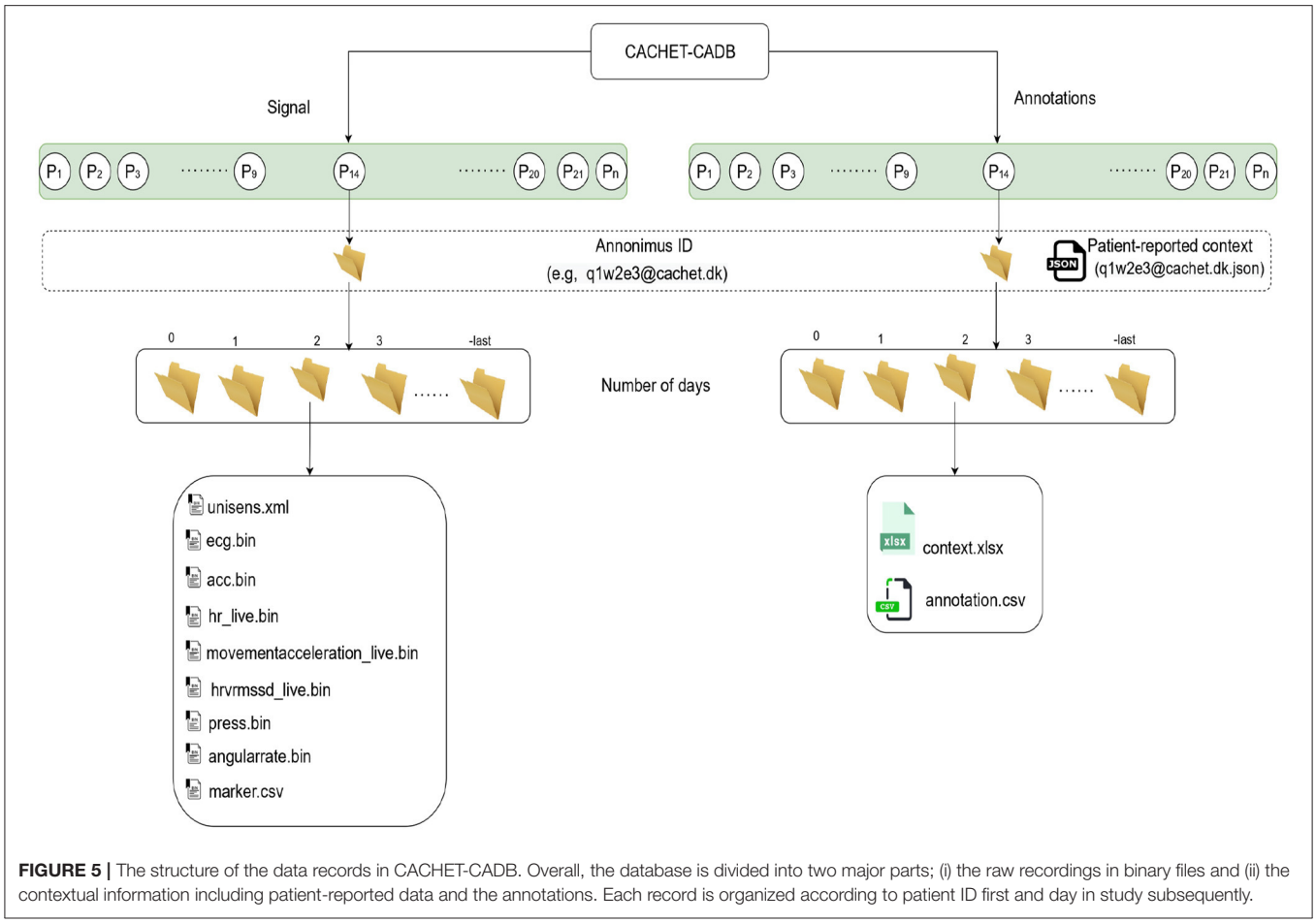

FIGURE 5 | The structure of the data records in CACHET-CADB. Overall, the database is divided into two major parts; (i) the raw recordings in binary files and (ii) the contextual information including patient-reported data and the annotations. Each record is organized according to patient ID first and day in study subsequently.

Figure 5). The JSON file contains two types of data *"dailyInfo"*, and *"event"*. Their metadata are described in **Tables 5**, **6**, respectively.

The *annotaion.csv* file contains the cardiologists' annotation of hearth rhythms. It contains the following columns: (i) the start index of 10 s long segment (*Start*), (ii) the end index of 10 s long segment (*End*), and (iii) the ECG rhythm class (*Class*). **Table 7** provides the statistics of each of the annotated rhythm classes and their associated code in the *Class* column of the *annotation.csv* file.

4. TECHNICAL VALIDATION

4.1. Quality Assessment of ECG Annotation

Although the DL models (25) was used for automatic labeling (**Figure 3**), to ensure the quality and integrity of the rhythm annotation, we have released only the annotations that have been manually checked by the two independent cardiologists. A 100% inter-rater agreement policy is followed. The ECG segments on which there was a disagreement between two cardiologists are not included in this release.

4.2. Signal Quality Assessment

For testing the validity of the collected ECG data, an ECG signal quality assessment was done using an auto-correlation-based noise detector. Subsequently, the Pan Tomkinson algorithm (34) was used to calculate QRS complex/R-peaks. The steps used in the validation process are shown in **Figure 6**. As the ambulatory ECG signal tends to get contaminated by noise and other artifacts, first, a band-pass [0.5–50 Hz] filter was applied, and the baseline was removed. A Savitzky-Golay (35) filter followed this to smoothen out the data. Thereafter, the signal was chopped into 10 s long windows, and an auto-correlation based noise detector was applied to detect the noisy signal. Finally, the Pan Tomkinson algorithm (34) was used to calculate the QRS complexes and the R-peaks for each of these 10 s windows. **Table 8** shows the number of R-peaks detected and the percentage of the noisy signal detected in each record. It should be noted that the discrepancy in the ECG noise percentage between patients (or within the same patient for different days) depended on factors such as how diligent the patients (or, in some cases, their caretakers) were in timely changing the adhesive ECG electrodes. In the ECG signal, intervals between the R-peak

TABLE 3 | Metadata for the signal files described in the *unisens.xml* file of each record.

Type	Key	Data type	Channel name	Description
	Duration	String		Total recording time in seconds
General	Timestamp Start	String		Recording start time
	Measurement Id	String		Anonymous user id
	Height	String		Height in centimeters
	Weight	String		Weight in kilograms
Patient and	SensorVersion	String		Recording device version
Device	SensorType	String		Recording device type
	Age	String		Age at recording in years
	SensorLocation	String		ECG sensors location on body
	PersonId	String		Anonymous user id
	Gender	String		Gender (M/F)
ECG	ECG.bin	Binary	ECG I	Resolution: 12 bit, Input range CM = 560 mV, DM = ±5 mV, 3 db Bandwidth 1.6–33 Hz Output rate: 1,024 Hz
Accelerometer	Acc.bin	Binary	accX, accY, accZ	3D acceleration sensor Measurement range: ±16 g Output rate: 64 Hz
Angular Rate	Angularrate.bin	Binary	AngularRateX, AngularRateY, AngularRateZ	Rotation rate sensor: Measurement range: ±2,000 dps Output rate: 64 Hz
Pressure	Press.bin	Binary	Press	Measurement range: 300–1,100 hPa Noise: 0.03 hPa Output rate: 8 Hz
Marker	Marker.csv	Integer		Contains indexes of *events* when the patient experienced unusual systems and tapped on ECG Holter. Divide the index by 64 to get the event time in seconds from the start of the recording. Output rate: 64 Hz

indicate heart rhythm's regularity. These RR intervals (RRI) features have been extensively used in DL-based AF detection models (25).

Although we did identify noise in the dataset, we did not exclude the noise from the database. This was done intentionally to allow the CACHET-CADB to reflect a realistic distribution of ECG quality as expected under free-living conditions. ECG riddled with confounding artifacts and varying signal quality is expected when performing longitudinal ambulatory arrhythmia screening. Therefore, we put forward the CACHET-DB as a resource for designing and evaluating DL-based arrhythmia detection algorithms, which work under free-living condition without generating false positives. Moreover, the database can be used for creating unsupervised learning methods, which can enable feature extraction representing ECG quality variation in ambulatory settings. As already discussed, one of the main challenges with the existing arrhythmia ECG datasets is that they are collected in a clinically controlled environment and are relatively clean. Models trained on such clean datasets may result in many false-positive cases when applied on ECG collected under free-living conditions that inevitably has low signal quality and many artifacts (36, 37).

5. DISCUSSION

This paper presents the design and development of a contextualized ECG database to support the development and generalization of ECG analysis and arrhythmia detection models. The CACHET-CADB has been developed as a part of the REAFEL (38) research project, which focuses on building mHealth and DL-based solutions for optimizing diagnosis of AF in the frail and elderly population. CACHET-CADB is particularly important for researchers who are working on bringing ECG analysis and AF detection on patient-operated wearable ECG into widespread adoption under free-living conditions. The database will be further expanded with more recordings and ECG annotation as they become available by following the data annotation and storage setup described above.

The ability to bring arrhythmia detection models in widespread adoption under free-living conditions is limited by

TABLE 4 | Contextual-data descriptor table.

Attribute	Unit	Remark
Time rel	[s]	Relative time from start of measurements in seconds
Day rel	[d]	Number of days from start of measurement
Time rel	[hh:mm:ss]	Relative time from start of measurement
Date abs	[yyyy-mm-dd]	Absolute date
Time abs	[hh:mm:ss]	Absolute time
ActivityClass	–	Activity Class (0 = unknown, 1 = lying, 2 = sitting/standing, 3 = cycling, 4 = slope up, 5 = jogging, 6 = slope down, 7 = walking, 8 = sitting/lying, 9 = standing, 10 = sitting/lying/standing, 11 = sitting, 99 = not worn)
ActivityEnergyExpenditure	[kcal/d]	Activity energy expenditure (AEE) in kcal/d
Altitude	[m]	Altitude from barometer
BodyPosition	–	Body position (0 = unknown, 1 = lying supine, 2 = lying left, 3 = lying prone, 4 = lying right, 5 = upright, 6 = sitting/lying, 7 = standing, 99 = not worn)
InclinationDown	[deg]	Inclination of sensor axis down against the vertical (0–180°)
InclinationForward	[deg]	Inclination of sensor axis forward against the vertical (0–180°)
InclinationRight	[deg]	Inclination of sensor axis right against the vertical (0–180°)
MET		MET value directly calculated from regression models
MovementAcceleration	[g]	MovementAcceleration: Raw acceleration, bandpass filtered, vector magnitude
NonWearSleepWake	–	Sleep/Wake detection (0 = wake, 1 = sleep, 2 = not worn)
NonWearTime	–	Non wear detection (0 = worn, 1 = not worn)
StepCount	[steps]	Count of steps per output interval
TotalEnergyExpenditure	[kcal/d]	Total energy expenditure (TEE = BMR + AEE)
VerticalSpeed	[m/s]	Vertical speed, calculated from barometer

The attributes are the columns of the context.xlsx file in the annotation folder of each day.

TABLE 5 | Metadata of patient-entered context data *"dailyInfo"* in JSON file.

Field name	Description
Date_time	Day for which the *"dailyInfo"* is filled
Bed_time	Bed time
Awake_time	Wake up time
Sleep_quality	Self-assessed sleep quality (1–5)
Stress_level	Self-assessed stress level (1–5)
Lunch_time	Lunch time
Lunch_weight	Lunch quantity (heavy, moderate, light)
Breakfast_time	Breakfast time
Breakfast_weight	Breakfast quantity (heavy, moderate, light)
Dinner_time	dinner time
Dinner_weight	Dinner quantity (heavy, moderate, light)
Other_time	Time of any other meal/drink
Other_weight	Meal/Drink quantity (heavy, moderate, light)

TABLE 6 | Metadata of patient-entered *"event"* field in JSON file representing patient-reported symptoms that the patient may have experienced during the recording period.

Field name	Description
Id	Unique id
Notes	Note describing the unusual experience/symptoms
Labels	n/a
Source	How was the event entered? "*Tap*": By tapping on the ECG Holter "*Self input*": Manually created in the app
Deleted[1]	Was the event Deleted? (true/false)
Comments	n/a[2]
Duration	Time in seconds for which symptoms lasted
Symptom	Symptom experienced during the unusual event (e.g., "Dizziness")
Activity	Patients activity when the unusual symptoms were experienced
Completed	Were the details of an event filled in? True: All fields were completed. False: Not filled/ Partially filled
Reviewed	n/a
Date_time	Time of the event as experienced by the patient

[1]The patient could delete an event, e.g., if it was created by accidentally tapping the ECG device.
[2]The patient's comments are removed for anonymity.

the lack of a patient-operated ambulatory ECG dataset that truly represents all the confounding contamination expected in such conditions. The models trained on benchmark datasets in **Table 1** show high performance when tested on the same datasets or similar datasets collected under clinical supervision. However, the high classification performances often obtained on these datasets are not reproducible when applied to patient-operated ECG data under free-living conditions. The patients-operated wearable-based ECG under free-living condition is often contaminated with arrhythmia mimicking artifacts and suffers from poor signal quality. The cause of the poor performance under free-living conditions is attributed to the lack

of diversity and relatively good signal quality of ECG wave forms in these benchmark databases (18).

With wearable technology advancements, single lead portable ECG monitoring has been gained attraction for arrhythmia screening under free-living conditions (39). Coupling portable patient-operated ECG monitoring with computer-aided ML and DL-based classification algorithms can help in real-time and cost-effective longitudinal arrhythmia screening under free-living conditions. To achieve high sensitivity and reproducibility under free-living conditions, the CACHET-CADB provides an opportunity to train and evaluate arrhythmia detection models on a dataset representing all the ECG morphology changes and confounding noise contamination expected in free-living conditions.

TABLE 7 | ECG annotation overview showing the class of rhythm types, its code in the *annotation.csv* file, and the number of available annotations for each class.

Class	Code	#
AF	1	747
NSR	2	615
Noise	3	221
Others	4	19

5.1. Context-Aware ECG for Explainable DL Models

One advantage of CACHET-CADB over the existing database is the availability of patients' ambulatory context corresponding to the recorded ECG. In the absence of patients' context, the

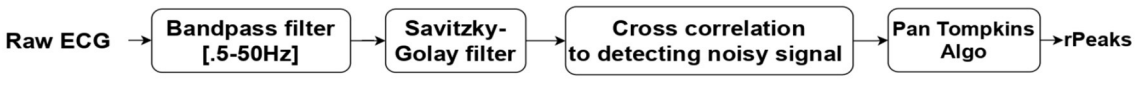

FIGURE 6 | Analysis of ECG quality, QRS complex, and R-peak detection.

TABLE 8 | Signal quality assessments and detection of QRS complex/R-peaks. Non-wear Time: Time for which device was taken off (for changing, bathing, for any other reasons).

Record	User Id	Days	No. of R-peaks	Signal duration (hours)	Noisy signal (%)	Non-wear time (hours)
P1	a2b3c4@cachet.dk	12	1,158,069	241.58	7.48	6.15
P2	t1y2u3@cachet.dk	7	673,950	139.40	6.47	1.03
P3	q1w2e3@cachet.dk	15	1,440,323	315.77	8.40	41.08
P4	p1q2w3@cachet.dk	8	739,199	173.14	5.80	10.85
P5	b1t2s3@cachet.dk	8	665,666	147.97	16.27	25.50
P7	k9v3r7@cachet.dk	12	913,892	260.16	12.43	41.91
P6	s1a2n3@cachet.dk	12	1,241,040	257.34	3.26	8.82
P8	g4v3r7@cachet.dk	22	2,895,927	479.16	9.90	77.98
P9	c1x2p3@cachet.dk	12	921,713	247.78	29.61	82.21
P10	k1x2p3@cachet.dk	16	1,297,163	359.85	31.72	80.28
P11	v2c3r4@cachet.dk	16	1,363,671	326.96	12.72	61.26
P12	r4p2n8@cachet.dk	14	1,988,086	308.91	6.88	6.31
P13	f7c4n6@cachet.dk	19	1,964,554	412.19	2.65	16.63
P14	j4y9x6@cachet.dk	12	1,035,832	262.94	29.90	111.36
P15	u3h6c1@cachet.dk	14	1,385,906	315.49	28.05	79.08
P16	i6t2v4@cachet.dk	17	1,567,938	359.86	6.29	25.71
P17	z2y4b9@cachet.dk	15	1,280,062	325.34	6.02	19.18
P18	g2v5x7@cachet.dk	5	431,256	92.95	3.23	1.54
P19	m1t2a3@cachet.dk	4	272,549	75.22	3.59	2.51
P21	y1t2r3@cachet.dk	8	778,148	168.93	10.34	12.10
P23	m1n2b3@cachet.dk	7	762,802	160.54	7.24	6.33
PNSR-1	deku_test@cachet.dk	1	105,079	24.00	0.49	0.56
PNSR-3	j5f3c2@cachet.dk	1	92,134	26.44	27.14	0.00
PNSR-4	w1y3n2@cachet.dk	2	191,867	48.00	5.63	2.05
Total		259	25,166,826	5529.94		726.57

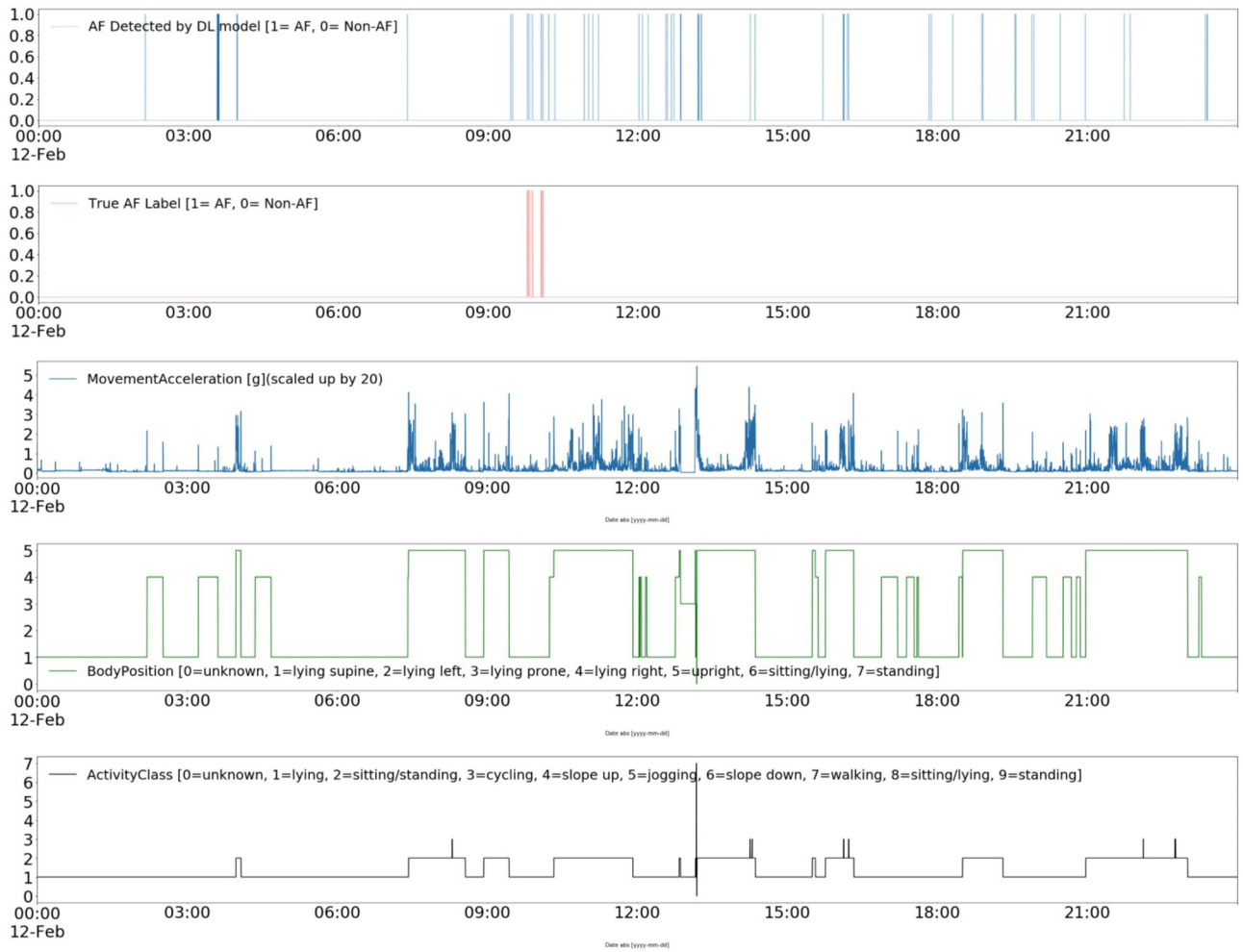

FIGURE 7 | Explainable deep learning: This Figure shows a contextualized view of a deep learning-based AF detection model Andersen's (25) performance on a single day of ECG from CACHET-CADB. In 24 h of ECG under free-living conditions, short segments of false positive in a model's output are linked to change in activity, change in body position, and sudden movement accelerations.

ECG analysis under free-living conditions is prone to misclassification and misinterpretation (6). The contextual data can also be used for multi-model input and context-based heuristics to dynamically fine-tune the models' sensitivity and specificity under different user contexts in ambulatory settings. To reduce the FPR, algorithms should be made adaptive to the user's context—i.e., the sensitivity and specificity of algorithms should be dynamically adjustable. For instance, in the elderly population, there is a significantly higher prevalence of falls in patients with AF (40). Suppose an algorithm is applied to elderly patients' data and if a fall is detected, then the algorithm should factor-in for the fall in the dynamic adjustment of its sensitivity and specificity. Similarly, information about AF triggering contexts (41) such as high stress-level, food-intake (heavy meal), drinks (alcohol, caffeine) can be utilized to make algorithms more sensitive in those contexts.

Furthermore, the contextual data can pave the way for improving the interpretability of ML and DL models (42). For instance, **Figure 7** shows a DL model's AF classification results, the "ground truth" annotations, and patient's ambulatory contexts (body position, activities, movement acceleration) for 24 h long record in CACHET-CADB. It can be inferred from **Figure 7** that the model is resulting in more FP whenever there is a change in activity, body position, and movement acceleration, which is most prominent after 09:00 o'clock. Such information can be made available to a cardiologist for the manual inspection of the dataset thereby providing a better insight into when and why the AF detection algorithm has identified an AF episode. The information can also be utilized to build post-processing heuristics around these FP prone ambulatory contexts (43). With CACHET-CADB, we aim to provide the DL research community rich longitudinal contextualized

ECG data that can help build and evaluate models which realistically work on patient-operated ECG from free-living ambulatory conditions.

5.2. Wearable ECG in Arrhythmia Monitoring and Its Economic Implications

The CACHET-CADB database is collected using the mCardia (28) system in the REAFEL (38) project, and its cost is comparable to other wearable-based single channel ECG devices. The main focus of the REAFEL study is to diagnose atrial fibrillation from patient-operated wearable ECG, away from highly controlled clinical environments, and thereby to make an accessible diagnostic tool for vulnerable populations who have difficulties in accessing to such clinically controlled measurements. Already, ambulatory wearable ECG has been found to be cost-effective in the detection of AF and reducing unnecessary hospital visits (44). However, there are significant potential economic gains in reducing manual examination of longitudinal ambulatory ECG by using automated arrhythmia detection algorithms. As pointed out by Wu et al. (14), the lack of sizable annotated and diverse ECG wearable datasets for testing and evaluating is one of the leading causes behind non/slow improvements in classification algorithms' performance. By making available the CACHET-CADB, we aim to help researchers to develop and evaluate algorithms for patient-operated wearable ECG, thereby making longitudinal ambulatory monitoring more economically robust and feasible.

6. USAGE NOTES

The design, data-descriptor, and the software tools for using CACHET-CADB are presented and made available for public use. When using this database, please cite the current publication. The new data recording and ECG annotations on the existing records will be added to CACHET-CADB periodically when they become available; details of the subsequent release will be available at CACHET's website (45).

7. CODE AVAILABILITY

Visual inspection and editing of records can be done using the UnisensViewer tool http://software.unisens.org/download/UnisensViewer/UnisensViewer_Setup.exe. Python library *pyunisens* (https://github.com/Unisens/pyunisens) can be used for reading and editing the signal programmatically. We also provide a basic code example and Jupyter Notebook in Python for using the database https://github.com/cph-cachet/cachet-ecg-db. The contextual data file context.xlsx can be loaded and viewed using the panda library (https://pandas.pydata.org/); an example code for the same can be found at https://github.com/cph-cachet/cachet-ecg-db. All software is open-sourced under an MIT license, and we welcome pull requests.

DATA AVAILABILITY STATEMENT

The datasets presented in this article can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://doi.org/10.11583/DTU.14547264.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Danish Research Ethical Committee and Mahatma Gandhi University of Medical Sciences and Technology (MGUMST), Jaipur India. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DK and JB conceived the database and implemented the technology for data collection and storage. DK conducted the data collection and manual ECG annotation process in collaboration with HD and KS. DK analyzed the data and wrote the Python scripts. DK, JB, and SP wrote the paper. JB obtained the funding. All authors reviewed the manuscript and contributed to the article and approved the submitted version.

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Cost-Effectiveness of the Pharmacist-Managed Warfarin Therapy vs. Standard Care for Patients With Mechanical Mitral Valve Prostheses: An Egyptian Healthcare Perspective

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Background: Despite warfarin therapy had been used for decades for patients with mechanical mitral valve prostheses (MMVPs), serious and life-threatening complications are still reported worldwide with a significant economic burden. This study is aimed at assessing the clinical and the cost-effectiveness of adopting pharmacist-managed warfarin therapy (PMWT) services for optimizing warfarin treatment in Egypt.

Methods: A prospective randomized trial in which 59 patients with MMVPs were randomly assigned to receive the PMWT services or the standard care and followed up for 1 year. The primary outcome was percentage time in the therapeutic range (TTR). For the cost-effectiveness analysis, a Markov cohort process model with nine mutually exclusive health states was developed from a medical provider's perspective. A lifetime horizon was applied. All costs and outcomes were discounted at 3.5% annually.

Results: The study results revealed a significantly higher median TTR in the intervention group as compared to the control group; 96.8% [interquartile range (IQR) 77.9–100%] vs. 73.1% (52.7–95.1%), respectively, $p = 0.008$. A significant association between standard care and poor anticoagulation control ($p = 0.021$) was demonstrated by the multivariate regression analysis. For the cost-effectiveness analysis, the total cumulative quality-adjusted life-years (QALYs) and total costs per patient were 21.53 and 10.43; 436.38 and 1,242.25 United States dollar (USD) in the intervention and the control groups, respectively, with an incremental cost-effectiveness ratio (ICER) of −72.5796 for the intervention group.

Conclusion: The PMWT strategy was proven to provide a significantly better anticoagulation control and to be a cost-saving approach in Egyptian patients with MMVPs. Nevertheless, the dominance of this strategy is sustained by maintaining the therapeutic International Normalized Ratio (INR) control within the recommended range.

Our findings will benefit Egyptian policy-makers who may seek novel health strategies for better resource allocation.

Clinical Trial Registration: [ClinicalTrials.gov], identifier [NCT04409613].

Keywords: cost-effectiveness, pharmacist intervention, mechanical mitral valve, warfarin, time in therapeutic range, Egypt

INTRODUCTION

Rheumatic heart disease (RHD) is the most prevalent heart condition in children and adolescents who are aged 25 or below. So far, RHD deems endemic in many low- and middle-income countries among vulnerable groups (1, 2). The highest RHD deaths were reported from Egypt, Yemen, Pakistan, Afghanistan, and Iran, which count for 80% of the total death rates for the Eastern Mediterranean Region (3). Almost 20% of patients with RHD become afflicted by congestive heart failure that requires valve surgery within 5–10 years (4). The surgical replacement of a heart valve with a mechanical prosthetic one aims to restore heart function; however, the implantation of a mechanical valve is an absolute indication for lifelong oral anticoagulation therapy to avert the risk of potential complications, such as bleeding, thromboembolic events, prosthetic valve endocarditis, and dysfunction. Moreover, the risk of extensive anticoagulation, i.e., to effectively avoid thromboembolic events, has to be weighed against another risk of bleeding complications (5, 6).

Vitamin K antagonists (VKAs) are the unique recommended option for oral anticoagulation in patients with mechanical valves (7). Among VKAs, warfarin is the most frequently prescribed drug that had been used for decades for those patients. However, it is still challenging to maintain a safe and efficient treatment (8). Major bleeding (which can be life-threatening), intracranial bleeding, and fatal bleeding are observed in 2–5, 0.2–0.4, and 0.5–1.0%, respectively, with patients on warfarin per year (9). What is more, warfarin therapy is fraught with several inherent problems, such as great diversity in dosing, delayed onset of action along with prolonged effect after discontinuation, a wide range of serious interactions, and a narrow therapeutic index. Collectively, all these problems designate warfarin as a "high alert medication" that calls for extraordinary caution and care (10–14).

There is growing evidence that the management of anticoagulation by experienced pharmacists can lead to better outcomes as compared to standard care. This is backed by data from multiple studies that reported improved clinical outcomes with the pharmacist-managed warfarin therapy (PMWT) services, such as significantly better International Normalized Ratio (INR) control, and significant reductions in rates of emergency department visits, hospitalizations, hospital length of stay, and hospital readmission rates. In consequence, cost savings have been well demonstrated in studies from different sides of the world due to decreased rates of both adverse events and complications, with subsequent impact on medical and non-medical costs (12, 15–21). The objective of this trial-based economic evaluation study was to evaluate the clinical effectiveness and the cost-effectiveness of the PMWT services for outpatients with mechanical mitral valve prostheses (MMVPs) in an Egyptian University Teaching Hospital setting.

PATIENTS AND METHODS

Study Design and Participants

This was a prospective randomized controlled study in which patients with MMVPs were recruited from the outpatients' anticoagulation clinic at the Cardiothoracic Surgery Academy, Ain Shams University, Cairo, Egypt and were randomly assigned to either the control group, who received standard medical care or the intervention group, who received the PMWT services. Patients were considered for eligibility in the study if they had met the following inclusion criteria: (1) men or women between 18 and 70 years of age, (2) post-mitral valve surgery patients with MMVPs, and (3) patients with a prescription of warfarin. Although pregnant patients, patients with double or aortic valve replacement surgery, patients with biological prostheses, and patients with congenital blood disorders were excluded from the study.

Methods

Starting 1 February 2020, a total of 107 patients were screened for eligibility in the study, of which, 48 patients were excluded, as they did not meet the inclusion criteria. Thus, a total of 59 patients were included and randomly allocated to either the intervention (patients who received the PMWT, n = 29) or the control (patients who received the standard medical care, n = 30) groups [a Consolidated Standards of Reporting Trial (CONSORT) flow diagram is provided in the **Supplementary Figure 1**]. During the first patient visit, demographic data were collected which included name, age, gender, weight, height, education, occupation, residence, and lifestyle habits (smoking and level of physical activity). Along with these data, previous and current medications, comorbidities, and INR test results were also collected. Eligible patients in both groups were followed up for 1 year.

Standard Medical Care

Standard medical care included the documentation of INR test results, and providing the patients with instructions regarding warfarin dose, regimen, any dose modification, and frequency of INR testing. All these services were provided by the anticoagulation clinic staff (which consisted of both cardiologists and nurses).

Pharmacist-Managed Warfarin Therapy Services

The PMWT services included two main pillars, which are patients' education and counseling and patients' follow-up. Patients in the intervention group (or their caregivers) received an educational session, which was aimed to ensure that the patient understands the risks, the required precautions, and the necessity for frequent monitoring. Education involves assessing the patient's understanding of his health problems, the ability to take warfarin correctly, and attitudes toward any warfarin-related complications.

Multiple methods were applied during this session, such as asking open-ended questions to evaluate the patient's understanding and subsequently, to decide what information is needed to be provided. Visual aids were also used to promote the patient's comprehension. Therefore, the information was presented as an educational leaflet (**Supplementary Figure 2**) and explained to the patient in simple language. The information provided in the leaflet included the drug's brand and generic name, purpose, anticipated onset, frequency of dosing, important precautions, lifestyle modifications, common side effects and what to do if they occur, the importance of regular monitoring and proper adherence, and the need to inform provider if the patient is planning to become pregnant, before any procedure or hospitalization and before starting any new drug. At subsequent visits, this information was briefly recalled to refresh the patient's information.

Patients were followed up from February 2020 to February 2021. They were regularly assessed through INR value recording, warfarin dose, and any warfarin-related problems, with further dose readjustment recommendations according to the patient's INR test result. Signs of warfarin overdose were also reported. The time interval for measuring INR levels was typically 1 month. However, this was not constant on a practical basis and the time interval between successive patient visits was primarily based on INR test results.

Primary End Point

The primary end point was the percentage time in therapeutic range (TTR), i.e., the proportion of time spent within the target INR range (22), and was calculated by the Rosendaal method (23). TTR below 65% was considered to be associated with poor anticoagulation control as per the 2020 National Institute for Health and Care Excellence (NICE) recommendations (24). An INR range of 2.5–3.5 was recommended as per the 2020 American College of Cardiology/American Heart Association Guideline for the Management of Patients With Valvular Heart Disease (7).

Ethical Approval

This study was performed following the principles of the Declaration of Helsinki (25). Ethical approval was granted by the Research Ethics Committee at the Faculty of Pharmacy, Ain Shams University, Cairo, Egypt (ENREC–ASU, 2019-99). Informed consent was obtained from each participant without any obligation to complete the study if they did not want to.

Sample Size Calculation and Statistical Methods

Reference to Falamić et al. (8), in which the median TTR was significantly higher in the group that received PMWT services than the standard care (93% vs. 31.2%, a difference of 61.8%), a total of 36 patients (18 per group) were required. The sample size was calculated using Stata/ES 14.2 software for windows. IBM SPSS program (version 20) was used to perform the statistical analysis. All graphs were done using Microsoft Excel 2016. All p-values were two-sided, and the difference was considered statistically significant if the p-value was ≤ 0.05 [95% confidence intervals (CI); detailed sample size calculation and statistical methods are provided in **Supplementary Figure 3**].

Economic Evaluation

Overview

Figure 1 represents a half-cycle-corrected Markov cohort process model, which is developed to reflect the real practice of patient management in Egypt and risks that change repeatedly over time, with nine mutually exclusive health states (25). The model structure and inputs were verified by clinical experts and a lifetime horizon was selected to reflect the long-term consequences. A 1-month cycle length was adopted. The model was populated with relevance to a medical provider's perspective. All costs and outcomes were discounted at 3.5% annually (26). The analysis was performed using Microsoft Excel 2016.

Model Inputs and the Likelihood of Events

Patients entered the Markov model by either receiving the PMWT services or the standard care. The health states included in the model were "within therapeutic range," "below therapeutic range," and "above therapeutic range," which were defined as INR values below 2.5, within 2.5–3.5, and above 3.5, respectively (27). The "bleeding" state was defined by a major bleeding event that required hospitalization or blood transfusion; the "thromboembolism (TE)" state was defined by the occurrence of a thromboembolic event with morbidity that included ischemic stroke/transient ischemic attack, deep vein thrombosis, and pulmonary embolism; the "reoperation" state was defined as patients who underwent reoperation; and the "recovery" state was defined as the patients recovered after an event; and death, which was defined as death from any cause (27, 28).

The transition probabilities used in the model are shown in **Table 1**. To reflect the Egyptian population, the cohort that entered the model was transitioned to within, below, or above therapeutic range states based on probabilities derived from the Cardiothoracic Surgery Academy, Cairo, Egypt. With every cycle, the patient could remain in the current state or transit between below, within, and above the therapeutic range back and forth. Afterward, the patients could stay in the no-event state or experience the following events: bleeding, TE, reoperation, or death from any cause. The model accounts for the risk of mortality at all states of any warfarin-associated events. Death risk ratios from major TE or bleeding events (i.e., additional to death from any cause) were also added to the model.

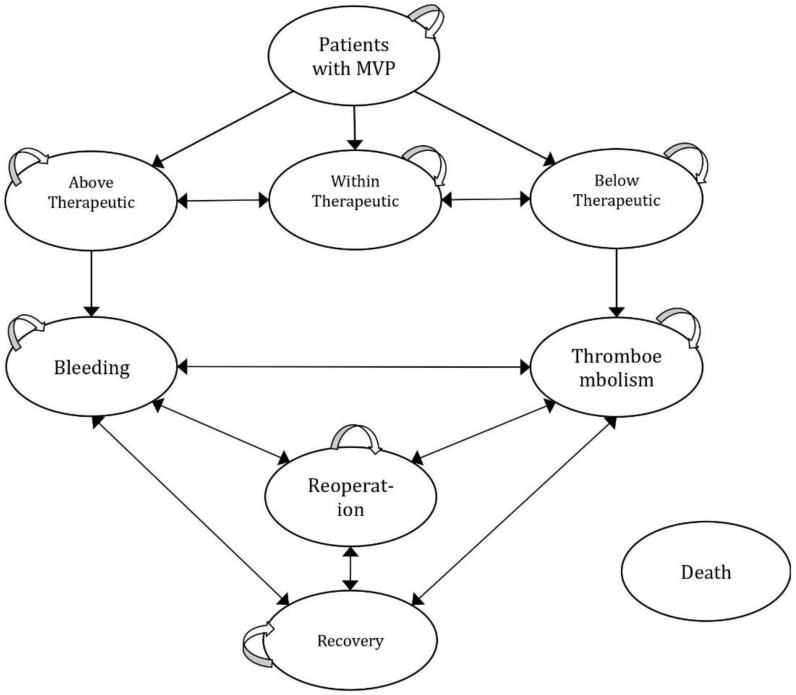

FIGURE 1 | Schematic diagram for the Markov state transition.

Due to the lack of local data, we used the probabilities of developing major TE and bleeding events, and death risk ratios after major TE or bleeding events, using published pooled data from several sources (29). The risk for reoperation was obtained from two clinical trials that included 394 and 211 patients with mitral valve replacement (MVR) and patients who were randomized to receive either biological or mechanical valves (30, 31). The probabilities of bleeding, TE, or death with reoperation were derived from a published review that compared the results of 106 patients who underwent repeat MVR with 562 control patients who underwent primary replacement using a computerized database. These risks were calculated using a multivariate logistic regression model to predict associated events or mortality (32). The risks of both major bleeding and TE events after recovery were derived from a large study that included a total of 1,608 patients who were followed for 6,475 patient-years to determine the incidence of complications of oral anticoagulation therapy in patients with mechanical valves (33). The risk of mortality after a recovery state was developed from a retrospective review of 671 patients' hospital records over 9 years (34). The transition probabilities from the recovery state to reoperation, bleeding, and TE were derived from a previous decision analysis that was modeled on Egyptian patients and assumed that these probabilities are the same as those for patients in the reoperation state (28).

Outcomes

The outcomes were measured in terms of quality-adjusted life-years (QALYs) for both groups. This generic measurement is commonly used as a summary measure for economic evaluations, which combines the impact on both the quality and quantity of life into a single parameter (35). The utilities within the therapeutic range, bleeding, reoperation, recovery, and TE states incorporated in the model were obtained from different published studies (27, 29, 36).

Costs

From a medical provider's perspective, only direct medical care costs were taken into account, i.e., the costs of bleeding, reoperation, and TE events. All cost inputs were obtained from the databases of the Cardiothoracic Surgery Academy, Ain Shams University, Cairo, Egypt. A macro-costing approach was applied. The costs of INR testing and warfarin were not included since these costs are not covered by the medical provider. We assumed no difference in resource use between the two strategies. Conversion of the local Egyptian currency to United States dollar (USD) was performed using the purchasing power parity rate. All costs were calculated in USD for the financial year of 2019 (37).

Sensitivity Analysis

To test the robustness of our model results across variations in input estimates, one-way sensitivity analyses were performed as recommended by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS): The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force report (38). The stability of the model was tested for all estimates of clinical parameters, utilities of health states, costs, and discount rates. All inputs were varied across upper and lower limits for each parameter. These parameters were delineated by CIs from the literature or reasonable ranges that were determined

TABLE 1 | Model inputs and data sources for the cost-effectiveness analysis.

Parameter	Base case	Range		Source(s)
		Low value	High value	
Initial population proportion in the intervention group (no-event states)				
Within therapeutic range	0.9942	0.8948	1.0937	CTSA
Below therapeutic range	0.0029	0.0026	0.0032	CTSA
Above therapeutic range	0.0029	0.0026	0.0032	CTSA
Initial population proportion in the control group (no-event states)				
Within therapeutic range	0.9855	0.8869	1.0840	CTSA
Below therapeutic range	0.0058	0.0052	0.0063	CTSA
Above therapeutic range	0.0087	0.0079	0.0096	CTSA
INR transition probabilities in the intervention group				
Within therapeutic to below therapeutic	0.0225	0.0203	0.0248	CTSA
Within therapeutic to above therapeutic	0.0191	0.0172	0.0210	CTSA
Below therapeutic to within therapeutic	0.4263	0.3837	0.4689	CTSA
Above therapeutic to within therapeutic	0.5712	0.5141	0.6283	CTSA
INR transition probabilities in the control group				
Within therapeutic to below therapeutic	0.0741	0.0667	0.0815	CTSA
Within therapeutic to above therapeutic	0.0383	0.0345	0.0421	CTSA
Below therapeutic to within therapeutic	0.1589	0.1430	0.1748	CTSA
Above therapeutic to within therapeutic	0.291	0.2619	0.3201	CTSA
Above therapeutic to bleeding	0.0115	0.0104	0.0127	(29)
Below therapeutic to TE	0.0023	0.0021	0.0025	(29)
TE to bleeding	0.00228	0.00205	0.00251	(28)
TE to reoperation	0.00033	0.00030	0.00037	(28)
TE to death	0.00374	0.00337	0.00412	(28)
TE to TE	0.08825	0.07942	0.09707	(28)
Bleeding to TE	0.00059	0.00053	0.00064	(28)
Bleeding to reoperation	0.00033	0.00030	0.00037	(28)
Bleeding to death	0.01078	0.00971	0.01186	(28)
Bleeding to bleeding	0.02049	0.01844	0.02254	(28)
Reoperation to TE	0.00014	0.00012	0.00015	(32)
Reoperation to bleeding	0.00028	0.00025	0.00031	(32)
Reoperation to death	0.00035	0.00031	0.00038	(32)
Reoperation to reoperation	0.00033	0.00030	0.00037	(28)
Recovery to TE	0.00059	0.00025	0.00109	(33)
Recovery to bleeding	0.00228	0.00109	0.00532	(33)
Recovery to reoperation	0.00033	0.00017	0.00075	(30, 31)
Recovery to death	0.00147	0.00131	0.00163	(34)
Death risk ratios (additional to death with no-events)				
Major TE	2.25	1.75	2.75	(27, 29)
Major bleeding	1.5	1	2	(27, 29)
Utilities				
Within therapeutic	0.987	0.967	0.998	(27)
Bleeding	0.54	0.44	0.74	(36)
TE	0.45	0.35	0.55	(29)
Reoperation	0.45	0.35	0.75	(36)
Recovery	0.668	0.61	0.76	(29)
Costs				
Cost of bleeding event (USD)	2,777.78	2,500.00	3,055.56	CTSA
Cost of TE event (USD)	2,314.81	2,083.33	2,546.30	CTSA
Cost of reoperation event (USD)	16,203.70	14,583.33	17,824.07	CTSA
Discount rate of cost	0.035	0.02	0.06	(26)
Discount rate of QALY	0.035	0.02	0.06	(26)

Transition probabilities are shown as probabilities per 1-month cycle.
CTSA, Cardiothoracic Surgery Academy, Ain Shams University, Cairo, Egypt; INR, international normalized ratio; QALY, quality-adjusted life year; TE, thromboembolism; USD, United States dollar.

TABLE 2 | Baseline demographic data of the study participants.

Parameter	Total (*n* = 59)	Intervention group (*n* = 29)	Control group (*n* = 30)	*P*-value
Age (years)	46.41 ± 10.53	46.79 ± 10.96	46.03 ± 10.28	0.785
Gender				
Males	17 (28.8%)	8 (27.6%)	9 (30%)	0.838
Females	42 (71.2)	21 (72.4%)	21 (70%)	
Weight (kg)	75 (62–85)	75 (60–85)	73 (64.5–85.25)	0.632
Height (cm)	162 (159–170)	164 (155–170)	161 (159.8–166.3)	0.819
BMI (kg/m^2)	27.84 ± 5.02	27.27 ± 4.80	28.38 ± 5.25	0.400
Residence				
Urban	26 (44.1%)	15 (51.7%)	11 (36.7%)	0.244
Rural	33 (55.9%)	14 (48.3)	19 (63.3%)	
Education				
Illiterate	26 (44.1%)	12 (41.4%)	14 (46.7%)	0.621
Primary	12 (20.3%)	5 (17.2%)	7 (23.3%)	
Secondary	14 (23.7%)	9 (31%)	5 (16.7%)	
University	7 (11.9%)	3 (10.3%)	4 (13.3%)	
Occupation				
Employed	17 (28.8%)	9 (31%)	8 (26.7%)	0.711
Unemployed	42 (71.2%)	20 (69%)	22 (73.3%)	
Smoking				
Never	47 (79.7%)	24 (82.8%)	23 (76.7%)	0.796
Former	9 (15.3%)	4 (13.8%)	5 (16.7%)	
Current	3 (5.1%)	1 (3.4%)	2 (6.7%)	
Physical Activity				
Inactive	3 (5.1%)	2 (6.9%)	1 (3.3%)	0.162
Low	22 (37.3%)	8 (27.6%)	14 (46.7%)	
Moderate	27 (45.8%)	17 (58.6%)	10 (33.3%)	
High	7 (11.9%)	2 (6.9%)	5 (16.7%)	
Comorbidities				
Number of comorbidities	1 (1–2)	1 (1–2)	1 (1–2)	—[a]
Heart failure	42 (71.2%)	19 (65.5%)	23 (76.7%)	0.344
Stroke	3 (5.1%)	2 (6.9%)	1 (3.3%)	0.530
Hepatic	0 (0%)	0 (0%)	0 (0%)	—[b]
Gastrointestinal	5 (8.5%)	4 (13.8%)	1 (3.3%)	0.137
Acute kidney injury	4 (6.8%)	3 (10.3%)	1 (3.3%)	0.275
Asthma	1 (1.7%)	1 (3.4%)	0 (0%)	0.230
Diabetes mellitus	5 (8.5%)	3 (10.3%)	2 (6.7%)	0.611
Obesity[c]				
Normal	21 (35.6%)	11 (37.9%)	10 (33.3%)	0.735
Pre-obesity	19 (32.2%)	11 (37.9%)	8 (26.7%)	
Obesity I	14 (23.7%)	5 (17.2%)	9 (30%)	
Obesity II	3 (5.1%)	1 (3.4%)	2 (6.7%)	
Obesity III	2 (3.4%)	1 (3.4%)	1 (3.3%)	

Results are expressed as mean ± standard deviation (SD), median (interquartile range), or frequency (%).
The statistical test used is the Mann–Whitney U test for numerical data or the chi-square test for categorical variables.
A p-value ≤ 0.05 is considered statistically significantly different from the control [95% confidence interval (CI)].
BMI, body mass index.
[a]*The distribution is the same across categories. No statistics are computed.*
[b]*No measures of association are computed because the variable is constant.*
[c]*Obesity was categorized according to the body mass index as follows; normal weight 18.5–24.9, pre-obesity 25.0–29.9, obesity class I 30.0–34.9, obesity class II 35.0–39.9, and obesity class III above 40 (39).*

based on different published sources. Microsoft Excel 2016 was used to perform all analyses.

RESULTS

Study Population

A total of 59 patients were included in the study, of which, 29 patients (49.2%) were included in the intervention group and 30 patients (50.8%) in the control group. Detailed demographic and clinical characteristics of the study participants are illustrated in **Table 2**. There was no statistically significant difference between both groups in terms of baseline characteristics.

Time in Therapeutic Range

By the end of the follow-up period, the median TTR was significantly higher in the intervention group than in the control

TABLE 3 | TTR outcomes at the end of the follow-up period.

Parameter	Intervention group (*n* = 28)	Control group (*n* = 27)	*P*-value	Significance
TTR (%)	96.8% (77.9–100%)	73.1% (52.7–95.1%)	0.008	**Significant**
TTR categories				
<65%	3 (10.7%)	11 (40.7%)	0.011	**Significant**
65%–75%	3 (10.7%)	5 (18.5%)	0.410	N.S
>75%	22 (78.6%)	11 (40.7%)	0.004	**Significant**

Results are expressed as median (interquartile range) or frequency (%).
The statistical test used: Mann–Whitney U test for numerical data or chi-square test for categorical variables.
A p-value ≤ 0.05 is considered statistically significantly different from the control [95% confidence interval (CI)].
TTR, time in therapeutic range; N.S, not significant.

TABLE 4 | Risk of poor quality of anticoagulation (TTR < 65%) associated with standard care: a multivariate logistic regression analysis.

Predictors	Multivariate Analysis			
	p-value	OR	95% CI for OR	
			Lower	Upper
Standard care (control group)	0.021*	6.53	1.33	32.19
Age	0.797	1.01	0.94	1.08
BMI	0.879	1.01	0.87	1.18
Number of comorbidities	0.524	0.61	0.13	2.83
Heart Failure	0.200	0.18	0.01	2.45
Stroke	0.942	0.90	0.05	17.87
Diabetes	0.956	1.11	0.03	37.14

The statistical test used: Multivariate logistic regression analysis.
**p-value ≤ 0.05 considered a statistically significant predictor [95% confidence interval (CI)].*
BMI, body mass index; CI, confidence interval; OR, odds ratio; TTR, time in therapeutic range.

group (p = 0.008) indicating that patients who received the PMWT services spent significantly more time in the therapeutic range. For TTR categories, the percentage of patients with poor INR control, i.e., TTR < 65%, was also significantly higher in the control group (p = 0.011). On the other hand, PMWT services were associated with a significantly higher percentage of patients with controlled TTR > 75% as compared to the control group (p = 0.004). TTR-related outcomes are illustrated in **Table 3** (additional figures are illustrated in **Supplementary Figures 4**, **5**). Red spots, bleeding gums, and nose bleeding were decreased in patients who received the PMWT services as compared to the control group (7.1% vs. 13.8%, 3.4% vs. 6.9%, and 6.9% vs. 10.3%, respectively); however, the differences did not reach statistical significance ($p > 0.05$).

The Association Between Standard Care and Poor Quality of Anticoagulation (TTR < 65%): A Multivariate Logistic Regression Analysis

The results of the multivariate logistic regression analysis (**Table 4**) show that receiving the standard care is significantly associated with poor INR control (dependent variable is TTR < 65%), with an odds ratio (OR) of 6.53 [95% CI (1.33–32.19)], and p = 0.021. These results were obtained while controlling other covariates, namely, age, body mass index (BMI), number of comorbidities, heart failure, stroke, and diabetes (a forest plot diagram is illustrated in **Supplementary Figure 6**).

Results of the Cost-Effectiveness Analysis

From the medical provider's perspective, the total cumulative QALY per patient for the PMWT group was 21.53 when compared with 10.43 for the standard care group. The total cumulative costs per patient for the PMWT and the standard care groups were 436.38 and 1,242.25 USD, respectively. These results yielded an incremental cost-effectiveness ratio (ICER) of − 72.5796 for the intervention group. Thus, the strategy of the PMWT services was dominant, i.e., a cost-saving strategy (**Table 5**). For the one-way sensitivity analyses, the PMWT strategy would become very cost-effective [based on the threshold stated by the World Health Organization (WHO); 3 × GDP/capita] rather than being cost-saving by a 10% reduction in the probability of remaining within the therapeutic range for the intervention group. When all other inputs were altered between the low and high values, no effects on the resultant ICER values were found. None of the extreme values of any parameter changed the results to be not cost-effective (**Figure 2**).

DISCUSSION

This study was a trial-based cost-effectiveness evaluation for adopting the PMWT services to patients with MMVPs on warfarin, which revealed that this strategy is cost-saving in the Egyptian setting. To the best of our knowledge, this is the first study to provide this evidence in Egypt. We believe that this evidence could be used to target further quality improvement efforts, which can ultimately enhance both clinical outcomes and cost-saving attempts in an era when a better allocation of scarce resources is at the precedence of healthcare policy initiatives.

As has been shown, the PMWT services have demonstrated a substantial improvement in patients' anticoagulation control as compared to standard care. This was confirmed by the significantly higher median TTR recorded with the PMWT services (96.8% in the intervention group vs. 73.1% in the control group, p = 0.008), which indicates a significant increase in time spent under the target INR range. Our study results are in accordance with the results of a recent systematic review that was conducted by Entezari-Maleki et al. (40). They studied a total of 4 randomized controlled trials (RCTs) and 20 non-RCT studies with total included patients 11,607 to compare the potential benefit of PMWT as compared to usual medical care. Their results revealed significant improvement in TTR

TABLE 5 | Decision analytic model results.

Group	Model results			
	Total cumulative costs/patient (USD)	**Total cumulative QALYs/patient**	**ICER**	**Interpretation**
The PMWT (intervention group)	436.38	21.53	**−72.5796**	**Dominant Strategy**
Standard care (control group)	1,242.25	10.43		
Difference	−805.87	11.10		

ICER, incremental cost-effectiveness ratio; PMWT, pharmacist-managed warfarin therapy; QALY, quality-adjusted life-year; USD, United States dollar.

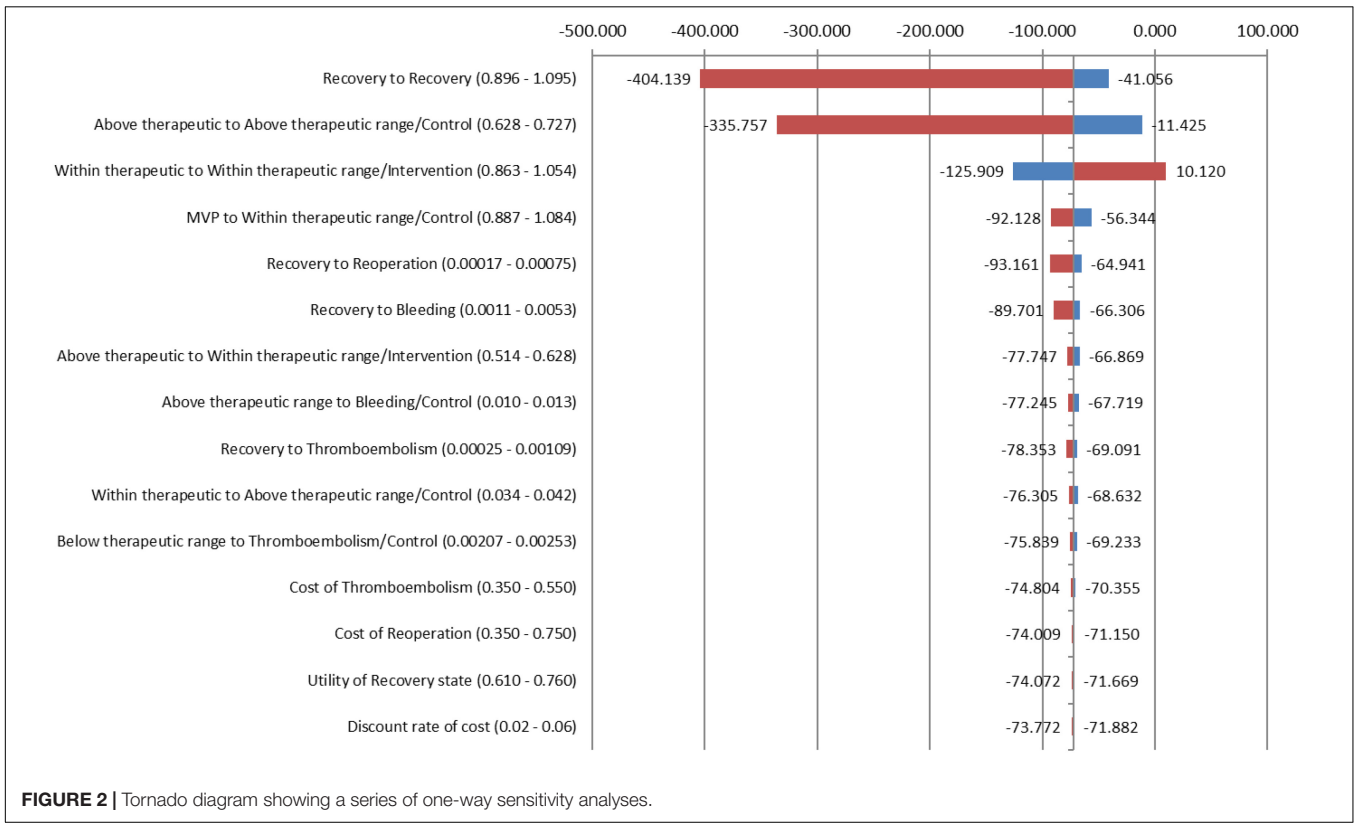

FIGURE 2 | Tornado diagram showing a series of one-way sensitivity analyses.

(72.1% vs. 56.7%; $p = 0.013$) in favor of the PMWT. Moreover, significant differences were reported in major bleeding events, thromboembolic events, hospitalization, emergency department visits in favor of the PMWT as compared to usual medical care (0.6% vs. 1.7%, $p < 0.001$; 0.6% vs. 2.9%, $p < 0.001$; 3% vs. 10%, $p < 0.001$; and 7.9% vs. 23.9%; $p < 0.0001$, respectively).

Another study was conducted by Marcatto et al. (11) to evaluate the impact of pharmacist's warfarin management in 268 patients with poor quality of anticoagulation (TTR < 50%). They applied a different design by comparing the retrospective data for the included patients with data obtained prospectively with the same patients after assigning them to receive the pharmacist's warfarin management services. The investigators reported a statistically significant increase in TTR after 4 and 12 weeks as compared to basal TTR. Furthermore, the mean TTR 1 year before (retrospective phase) was significantly lower than the TTR reported after 12 weeks of pharmacist-driven treatment (prospective phase; $p < 0.001$). Similarly, Dib et al. (41) conducted a study to evaluate the impact of the first pharmacist-managed anticoagulation clinic in the eastern province of Saudi Arabia. The authors reported that the total percentage of INR within the target range was 59% vs. 48% with the pharmacist-managed clinic vs. the traditional care, respectively. In contrast, Wu et al. (42) evaluated the impact of pharmacist interventions on INR control after MVR during the warfarin initiation phase and demonstrated a numerically higher TTR in the PMWT group as compared to the conventional group, however, the difference did not reach the statistical significance.

In this work, the results of the multivariate logistic regression analysis revealed that standard care was significantly associated with poor quality of anticoagulation; OR 6.53, 95% CI [1.33–32.19], $p = 0.021$. These results were in line with the results reported by Falamic et al. (8). They reported that the pharmacist's intervention was significantly associated with good quality of anticoagulation control (dependent variable TTR ≥ 65%); OR 77.84, 95% CI [8.25–734.14], $p < 0.001$. Our study results are

consistent with the results reported by Wu et al. (42). They revealed that PMWT was associated with achieving therapeutic INR at discharge by the multivariate regression analysis [OR 3.14, 95% CI (1.08–9.14)] and was inversely associated with achieving INRs above the target range during admission [OR 0.21, 95% CI (0.05–0.82)].

In the current study, the results of the cost-effectiveness analysis demonstrated that the PMWT strategy was dominant (i.e., less costly and more effective) as compared to standard care from the medical provider's perspective. This finding was similar to the results from previous studies conducted in other countries, such as the United States and Thailand, which strongly suggests that this intervention is cost-effective across different types of healthcare systems (15, 27, 43, 44).

In Egypt, RHD has been considered a national healthcare problem since the rate of misdiagnosis of rheumatic fever remains high. Moreover, the mitral valve is the most afflicted site among Egyptian patients (95.2% out of all valvular afflictions). In response, the Egyptian Ministry of Health has established the national RHD prevention and control program in 2006. The program was projected to save 1.7 billion USD, which represents the cost of valve replacement surgeries required for the number of RHD cases if they are neglected (45). In line with these efforts, we believe that our study results advocate for adopting a simple strategy, the PMWT strategy, that ultimately ends up with massive cost savings and better allocation of the scarce healthcare resources in Egypt. Moreover, our study was conducted from the medical provider's perspective; however, we believe that the adoption of these services will be even more cost-saving from the societal perspective.

This study included several strong points as it incorporated real-life data to demonstrate the clinical effectiveness of the PMWT services as compared to the actual care experienced by patients in day-to-day practice in Egypt. Moreover, this model is the first one in Egypt that incorporated transitions over time through INR changes and translated this in terms of increased risks of developing warfarin-associated events. Additionally, the parameters used in our analysis were derived from large RCTs (30, 31). In the used model, we explicitly accounted for uncertainties of the epidemiologic parameters, relative risks, and quality of life by using ranges and CIs based on published sources.

Our study has several limitations. We did not compare the time to achieve therapeutic INR in both arms. We believe that larger studies are needed to investigate this outcome that is strongly believed to endorse not only the clinical effectiveness of the PMWT but also the cost savings associated with this approach. In our economic model, we assumed that the rate of TE on reoperation is identical to that for patients in the recovery state due to the lack of reliable data. In this context, it is worth mentioning that the incorporation of several simplifying assumptions is considered a weak point for the model; however, this was overcome by the sensitivity analyses that adopted wide ranges for parameter values. In addition, some input parameters were derived from studies that were conducted on different populations due to a lack of local data. However, these parameters did not show any significant impact on the results in the one-way sensitivity analyses. Another additional limitation, we adopted the medical provider's perspective. Thus, we did not include the loss of productivity costs and the costs incurred by the patient (costs of the drug and the INR testing) as an out-of-pocket cost.

CONCLUSION

The pharmacist-managed warfarin therapy strategy was proven to provide a significantly better anticoagulation control and to be a cost-saving approach in Egyptian patients with MMVPs. Nevertheless, the dominance of this strategy is sustained by maintaining the therapeutic INR control within the recommended range. Our findings will benefit Egyptian policy-makers who may seek novel health strategies for better resource allocation.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committee at Faculty of Pharmacy, Ain Shams University, Cairo, Egypt (ENREC–ASU. 2019-99). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RB and IA performed the practical part at the anticoagulation clinic. RB performed the statistical and economic analysis and wrote the manuscript. SF and NS revised the manuscript. SF, IA, and NS supervised the project. All authors designed the research and read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.889197/full#supplementary-material

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Research progress on the predictive value of electrocardiographic indicators in the diagnosis and prognosis of children with vasovagal syncope

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Neurally mediated syncope (NMS) is a common type of syncope in children in clinical practice, among which vasovagal syncope (VVS) is the most frequent. In recent years, more and more studies have been carried out to assess the diagnosis and prognosis of VVS. The electrocardiographic indicators such as heart rate variability (HRV), QT dispersion (QTd), P-wave dispersion (Pd), ventricular late potentials (VLP), deceleration ability of heart rate (DC), etc., are easy to obtain and inexpensive. With the help of electrocardiographic indicators, the diagnostic procedure and individualized treatment strategies of pediatric VVS can be optimized. This article reviews the value of electrocardiographic indicators in the diagnosis and prognosis of children with VVS.

KEYWORDS

vasovagal syncope, diagnosis, prognosis, electrocardiography, children

Introduction

Syncope is a transient loss of consciousness (TLOC) and the inability to maintain the posture due to transient global cerebral hypoperfusion, and its clinical characteristics are sudden occurrence, transient, and completely spontaneous recovery (1). Hu et al. (2) reported that the incidence of syncope in children and adolescents aged 2–18 years in Changsha was 17.37%, with a peak age of 16 years. The incidence of syncope in girls was higher than that of boys [31.69% (315/994 cases) vs. 26.28% (288/1096 cases), $\chi^2 = 7.44$, $P < 0.05$], and was higher in adolescence than the school-age children [28.85% (603/2090 cases) vs. 8.32% (136/1635 cases), $\chi^2 = 243.21$, $P < 0.01$] and the preschool-age children [28.85% (603/2090) vs. 2.71% (17/627), $\chi^2 = 187.13$, $P < 0.01$]. Neurally mediated

syncope (NMS) is the most common cause of syncope, accounting for about 67% of syncope in children, and vasovagal syncope (VVS) is the most common hemodynamic type (3). According to the hemodynamic changes of the head-up tilt test (HUTT), VVS can be divided into three subtypes: vasoinhibitory vasovagal syncope (VVS-VI), cardioinhibitory vasovagal syncope (VVS-CI), and mixed vasovagal syncope (VVS-M) (4). Some children with recurrent syncope are accompanied by cardiac arrest lasting more than 3 s or severe hypotension and bradycardia, which are called malignant VVS (5, 6). The pathogenesis of VVS is still unclear. Hypovolemia, autonomic dysfunction, vasomotor dysfunction, baroreceptor reflex abnormalities, endothelial dysfunction, serotonin surges, and gut microbiota are involved in the underlying mechanism of VVS (7). At present, autonomic dysfunction is a focus of attention. It is believed that the transient abnormality of nerve reflex regulation causes decreased sympathetic tone and/or increased vagal tone, resulting in vasodilation, decreased blood pressure, and slowed heart rate, which contributes to an insufficient blood supply to the brain, causing syncope or pre-syncope to occur (8). Cardiac arrest in malignant VVS is caused by transient sinus node depression, which is caused by transiently intense vagal activity (6). For the judgment of autonomic nerve function, there are many studies on cardiac electrophysiological parameters, such as heart rate variability (HRV), QT dispersion (QTd), P-wave dispersion (Pd), ventricular late potentials (VLP), deceleration ability of heart rate (DC), etc. (7). The treatments for children with VVS mainly include non-pharmacological therapy, pharmacological therapy, and pacemaker therapy. Among these non-pharmacological therapy is the most important method, including health education, autonomic nerve function exercise, and increasing the intake of water and salt. The pharmacological therapy includes midodrine hydrochloride and metoprolol. The pacemaker therapy may be effective for children with VVS with cardiac arrest (4, 6, 9). Although VVS is a self-limiting disease and has a good prognosis, recurrent syncope attacks can seriously affect children's physical and mental health and quality of life (10). The current accepted criteria to diagnose VVS in children comprise a combination of clinical data and clinical symptoms observed during HUTT. However, the HUTT may cause episodes of syncope or asystole, usually leading to discomfort among children and adding to their psychological loads, and its widespread clinical application is thus restricted (11, 12). Therefore, novel, acceptable, safe, and simple approaches are required to optimize diagnostic procedures and individualized treatment strategies for VVS in children. Based on the electrophysiological parameters, this article reviews the prediction of different electrocardiographic indicators on the diagnosis, treatment effects, and the recurrence of VVS.

Heart rate variability in the prediction of diagnosis of vasovagal syncope in children

The variation over time of the period between consecutive heartbeats, HRV, reflects the regulation of the cardiovascular system by neurohumoral factors. Increased sympathetic nerve activity or decreased vagal nerve activity leads to an increase in the heart rate and a decrease in the HRV. On the contrary, decreased sympathetic nerve activity or increased vagal nerve activity leads to a decrease in the heart rate and an increase in the HRV (13). Therefore, HRV is often used clinically to evaluate the changes in the autonomic nervous system function. HRV includes time-domain indicators and frequency-domain indicators. In the time-domain indicators, the standard deviation of all normal-to-normal intervals (SDNN) reflects the overall tension of the autonomic nerve, the standard deviation of the average normal-to-normal intervals (SDANN), and the standard deviation of all normal-to-normal intervals index (SDNN index) reflect the sympathetic nerve activity, which is related to the slow change components of heart rate and appears to decrease with increased sympathetic nerve activity. The root mean square of differences between successive RR intervals (RMSSD) and the number of successive difference of intervals, that differs by more than 50 ms and is expressed as a percentage of the total number of electrocardiogram (ECG) cycles analyzed (pNN50), reflect the vagal nerve activity, which is related to the rapid change components of heart rate and appears to decrease with decreased vagal nerve activity. In the frequency domain indicators, total power (TP) reflects the overall tension of the autonomic nerves, ultra-low frequency (ULF), very low-frequency (VLF), low-frequency (LF), and normalized LF (nLF) reflect sympathetic nerve activity, and high-frequency (HF) and normalized HF (nHF) reflect vagal nerve activity, and the LF/HF ratio reflects the balance between autonomic nerves (14, 15).

Head-up tilt test and heart rate variability

The HUTT is often used to diagnose unexplained syncope and clarify the hemodynamic classification, mainly to simulate orthostatic stress state in the laboratory (16). Alehan et al. (17) reported that 49 children diagnosed with VVS had differences in HRV indicators during HUTT. The nLF and LF/HF in the positive HUTT group were higher than those in the negative HUTT group in the upright tilt state [nLF: (67.2 ± 17.5) nU vs. (56.4 ± 12.3) nU, $P = 0.01$; LF/HF: (3.7 ± 2.9) vs. (1.7 ± 1.0), $P < 0.01$], whereas nHF was lower [(26.6 ± 13.4) nU vs. (39.0 ± 12.3) nU, $P < 0.01$]. The nLF and LF/HF of children with positive HUTT responses were significantly increased in

the first 5 min after tilting compared with those in the supine position [nLF: (67.2 ± 17.5) nU vs. (43.9 ± 14.3) nU, $P < 0.01$; LF/HF: (3.7 ± 2.9) vs. (1.1 ± 0.8), $P < 0.01$], while nHF significantly decreased [(26.6 ± 13.4) nU vs. (48.5 ± 14.6) nU, $P < 0.01$]. Children with negative responses to HUTT also had the same changes in the first 5 min of tilting. The nLF and LF/HF were significantly increased compared to the supine position [nLF: (56.4 ± 12.3) nU vs. (39.9 ± 14.6) nU, $P < 0.01$; LF/HF:(1.7 ± 1.0) vs. (1.0 ± 0.7), $P < 0.01$] and nHF decreased significantly [(39.0 ± 12.3) nU vs. (50.4 ± 15.5) nU, $P < 0.01$]. These differences suggest that children with VVS mainly show increased sympathetic nerve activity in the supine position, and the increase in sympathetic nerve activity is more pronounced in children with positive HUTT responses than children with negative responses within the first 5 min after changing body positions, such as leaning upright. It was recommended that LF/HF > 2.7 within the first 5 min after changing body positions can be used as an indicator to distinguish positive HUTT from negative HUTT in children with VVS. The sensitivity, specificity, positive predictive value, and negative predictive value were 52%, 93%, 85%, and 41%, respectively. Evrengul et al. (18) also reported the same results that LF and LF/HF within 5 min before tilting in children with unexplained syncope were significantly higher than those of healthy children [LF:(61.1 ± 6.4) ms^2 vs. (52.8 ± 6.0) ms^2, $P < 0.01$; LF/HF:(1.88 ± 0.2) vs. (1.42 ± 0.1), $P < 0.05$], while HF was significantly lower [(36.1 ± 7.2) ms^2 vs. (44.8 ± 6.4) ms^2, $P < 0.05$]. On the other hand, LF and LF/HF were decreased significantly during syncope attacks [LF: (37.6 ± 4.8) ms^2 vs. (58.7 ± 8.9) ms^2, $P < 0.01$; LF/HF: (0.65 ± 0.2) vs. (1.63 ± 0.4), $P < 0.05$], while HF was significantly increased [(58.9 ± 6.2) ms^2 vs. (50.5 ± 2.0) ms^2, $P < 0.05$], and all of these indicated that the basic sympathetic nerve activity in children with unknown syncope was decreased before the syncope attack, but the vagal nerve activity was increased during the syncope attack. However, further statistical differences in these indicators were not observed in different hemodynamic types of VVS. Ciliberti et al. (19) observed that there was a significant statistical difference in VLF between the syncope and non-syncope groups in adults in the supine position (2421.09 ms^2 vs. 895.49 ms^2, $P < 0.01$). According to the receiver operating characteristic (ROC) curve (AUC = 0.889), VLF > 2,048 ms^2 was recommended as the best cutoff value for predicting syncope during HUTT, and its sensitivity, specificity, positive predictive value, and negative predictive value were 87.5%, 72.2%, 75%, and 89%, respectively. However, it remains controversial whether VLF is also statistically different in children. Chen et al. (20) found that VLF had a difference between NMS children and healthy children [(34668.56 ± 17039.12) Hz vs. (25391.12 ± 11040.34) Hz, $t = 2.025$, $P < 0.05$]. However, Alehan et al. (17) and Shim et al. (21) did not find a statistically significant difference in VLF between VVS children and healthy children.

Different hemodynamic types and heart rate variability

Different hemodynamic types of VVS were also associated with HRV. Zygmunt et al. (22) observed that the SDNN of VVS-CI was significantly lower than that of VVS-M children (114 ms vs. 164 ms, $P < 0.05$), suggesting that different hemodynamics may have different autonomic nerve function sensitivities. Guzmán et al. (23) found that the HF of VVS-CI and VVS-M in the supine position were significantly higher than those of VVS-VI children [(10.52 ± 0.48) $ln(ms^2)$ vs. (7.56 ± 1.3) $ln(ms^2)$, (11.09 ± 1.9) $ln(ms^2)$ vs. (7.56 ± 1.3) $ln(ms^2)$, $P < 0.01$, respectively]. Also, during the entire tilting process, the HF in the VVS-CI and VVS-M groups showed a downward trend until the syncope occurred 1 min later, suggesting that the pathogenesis of VVS-CI and VVS-M may be due to the increase in the vagal nerve activity. While the RMSSD and pNN50 of the VVS-VI children were significantly decreased [RMSSD: (18 ± 7) ms vs. (52 ± 17) ms, (18 ± 7) ms vs. (81 ± 9) ms, $P < 0.01$, respectively; pNN50: (2 ± 2)% vs. (20 ± 10)%, (2 ± 2)% vs. (25 ± 14)%, $P < 0.01$, respectively], suggesting that the pathogenesis of VVS-VI is related to the predominance of sympathetic nerve activity. Wang et al. (24) observed 85 syncope children aged 7–16 years and found that the daytime ULF (dULF), nocturnal ULF (nULF), daytime VLF (dVLF), and nocturnal VLF (nVLF) of children with VVS were significantly higher than those children with postural tachycardia syndrome (POTS). The dULF cut-off value is 36.2 ms^2 (AUC = 0.826), with a sensitivity of 73.3% and a specificity of 72.5% in distinguishing VVS from POTS.

The above HRV indicators in children with VVS have certain statistical differences in different hemodynamic types during HUTT. VLF > 993.52 ms^2 (AUC = 0.645) and dULF>36.2 ms^2 can be recommended for the initial diagnosis of patients with VVS. For the diagnosis of different hemodynamic types, further research is needed to explore the relationship between the HRV and children's diagnosis and the prediction of efficacy.

QT dispersion in the prediction of diagnosis of different hemodynamic vasovagal syncope and individualized therapy

The QT interval on the ECG represents the time from the beginning of ventricular depolarization (beginning of the QRS complex) to the end of ventricular repolarization (end of the T wave). It is affected by the heart rate and the autonomic nerve, and is shortened by increased sympathetic

nerve activity and prolonged by increased vagal never activity. Prolongation of the QT interval has been associated with arrhythmias and sudden cardiac death in several conditions, but particularly the inherited long QT syndrome (LQTS) (25–27). QTd refers to the difference between the maximum QT interval (QTmax) and the minimum QT interval (QTmin) in the ECG, which mainly reflects the inhomogeneity of ventricular muscle repolarization. It increased with the imbalance between the sympathetic nerve and the vagal nerve. QTd can be used as an indicator to predict malignant ventricular arrhythmias, sudden cardiac death, or syncope, and is often associated with arrhythmic events (such as LQTS, heart failure, coronary artery disease, post-myocardial infarction, or hypertrophic cardiomyopathy) (26, 27). Since the QT interval is affected by heart rate, corrected QT interval (QTc interval), and corrected QTd (QTcd) are often used (28). For children with VVS who have QT interval changes, it is necessary to be alert to the occurrence of arrhythmia events and the risk of sudden death. Kula et al. (29) observed syncopal children aged 8–18 and found that there was a difference in QTcd circadian rhythms between children with positive responses to HUTT, negative responses to HUTT, and healthy children. Compared with the negative HUTT group and healthy children, the QTcd in the positive HUTT group was significantly higher in the morning and night. [07:00–09:00: (76.92 ± 4.31) ms vs. (63.51 ± 4.76) ms, (76.92 ± 4.31) ms vs. (53.21 ± 4.29) ms, $P < 0.05$, respectively; 23:00–01:00: (81.84 ± 1.51) ms vs. (60.03 ± 4.91) ms, (81.84 ± 1.51) ms vs. (57.79 ± 7.0) ms, $P < 0.05$, respectively]. These results are consistent with the epidemiology that VVS mostly occurs in the morning. KarataŞ et al. (30) reported 152 children aged 4–18 with a history of syncope and 67 healthy children and found that the QTd and QTcd of the positive HUTT group were significantly higher than those of the negative HUTT group [QTd: (34.9 ± 1.4) ms vs. (27.9 ± 1.3) ms, $P < 0.01$; QTcd: (58.5 ± 2.1) ms vs. (42.5 ± 1.7) ms, $P < 0.01$], and QTd and QTcd in positive HUTT group were significantly higher than those of healthy children [QTd: (34.9 ± 1.4) ms vs. (25.8 ± 1.0) ms, $P < 0.01$; QTcd: (58.5 ± 2.1) ms vs. (37.2 ± 1.4) ms, $P < 0.01$]. Also, it was recommended to use QTcd > 50 ms as an indicator for predicting positive responses to HUTT, with a specificity and sensitivity of 76.5% and 59.5%, respectively. In this experiment, the positive HUTT group included two subtypes, VVS and POTS, and no statistical difference was found in QTcd between the two subtypes. Khalilian et al. (31) also found that the QTd in the positive HUTT group was significantly higher than that of the negative HUTT group [(42.37 ± 9.52) ms vs. (23.85 ± 4.79) ms, $P < 0.01$], and compared with VVS-VI, the QTd of VVS-M group was significantly increased [(46.74 ± 9.64) ms vs. (38.00 ± 7.29) ms, $P < 0.05$]. According to ROC, QTd > 32 ms (ACU = 0.944) and QTd > 40 ms (AUC = 0.784) were recommended as indicators for predicting positive HUTT results and VVS-M type, respectively. The sensitivity and specificity were 92% and 98% and 84%, and 63%, respectively. It suggested that VVS-CI may be more sensitive to QTd changes than VVS-VI, but the disadvantage is that the experiment did not set up a control comparison of QTd between the VVS-CI group and other subtypes. Liu et al. (32) found that the related indicators of QT interval in the VVS-CI group were longer than those in healthy children [QTmax: (414 ± 18) ms vs. (386 ± 15) ms, $t = -10.44$, $P < 0.01$; QTmin: (379 ± 17) ms vs. (364 ± 16) ms, $t = -5.892$, $P < 0.01$; QTd: (34 ± 6) ms vs. (22 ± 6) ms, $t = -12.504$, $P < 0.01$; QTcmax: (464 ± 19) ms vs. (443 ± 19) ms, $t = -7.086$, $P < 0.01$; QTcd: (38 ± 6) ms vs. (26 ± 7) ms, $t = -11.499$, $P < 0.01$], and the follow-up after non-pharmacological therapy showed that indicators of QT interval in VVS-CI children were longer in the non-response group than in the response group [QTmax: (418 ± 13) ms vs. (402 ± 16) ms, $t = 2.713$, $P < 0.05$; QTd: (37 ± 4) ms vs. (29 ± 5) ms, $t = 4.222$, $P < 0.01$; QTcmax: (477 ± 14) ms vs. (455 ± 14) ms, $t = 3.767$, $P < 0.01$; QTcmin: (435 ± 13) ms vs. (422 ± 14) ms, $t = 2.455$, $P < 0.05$; QTcd: (42 ± 4) ms vs. (33 ± 7) ms, $t = 3.745$, $P < 0.01$]. According to ROC, QTd > 28.50 ms (AUC = 0.914) and QTd < 34.50 ms (AUC = 0.906) were recommended as indicators for the differential diagnosing of VVS-CI and estimating its prognosis, respectively. The sensitivity and specificity were 86.30% and 84.95% and 90.00% and 82.35%. Wang et al. (33) observed and followed up on 40 cases of children with POTS and found that the symptoms of those with QTcd ≥ 43.0 ms were improved after physical treatment [(69.2 ± 31.2) ms vs. (43.5 ± 25.9) ms, $t/Z = 2.58$, $P < 0.05$], indicating that QTcd ≥ 43.0 ms (AUC = 0.73) can be used as a predictor of physical treatment with a sensitivity of 90% and a specificity of 60%. Subsequently, Wang et al. (34) observed and followed up on 50 children with POTS and found that the symptoms of those with QTcd ≥ 47.9 ms were improved after metoprolol treatment [(66.3 ± 20.3) ms vs. (45.7 ± 19.9) ms, Z = -3.339, $P < 0.01$], indicating that QTcd ≥ 47.9 ms (AUC = 0.822) can be used as a predictor of the efficacy of metoprolol in the treatment of POTS, with a sensitivity of 78.9% and a specificity of 83.3%. Similar to POTS, some children with VVS can also choose metoprolol therapy or physical treatment, both of which have autonomic dysfunction or high catecholamine status. Therefore, when the QTcd ≥ 43.0 ms, physical treatment can be selected. When QTcd ≥ 47.9 ms, metoprolol treatment can be recommended. In conclusion, children with VVS have abnormal QT intervals, and there are statistical differences in QT intervals between different hemodynamic types. According to ROC, it was recommended that QTd > 40 ms (AUC = 0.784) and QTd > 28.50 ms (AUC = 0.914) can be used as indicators to predict VVS-M and VVS-CI, and QTd < 34.50 ms (AUC = 0.906) can predict that treatment of VVS-CI has a good prognosis.

P-wave dispersion in the predicted diagnosis of cardioinhibitory vasovagal syncope

The P wave is the potential change that occurs when the left and right atria are depolarized. Autonomic dysfunction can cause changes in the amplitude, duration, and morphology of the P-wave. When the sympathetic nerve activity increases, the P-wave amplitude increases, forming a "pulmonary-type P-wave," and the maximum P-wave duration (Pmax) and Pd are significantly increased (35). Prolonged P-wave duration (Pwd) (Pwd > 120 ms), a marker of left atrial abnormality, has been linked with electromechanical dysfunction and poor left atrial contractility, which has been associated with myocardial fibrosis, heart failure, atrial fibrillation, and sudden cardiac death (36, 37). Pd refers to the difference between Pmax and the minimum P-wave duration (Pmin) on the surface ECG. It is a sign of inhomogeneous electrical activity in the atria and an important predictor of cardiac arrhythmias, especially atrial fibrillation (35), and is associated with sudden cardiac death and severe ventricular arrhythmias (36, 38, 39). Kose et al. (40) reported that 100 cases of VVS children had significantly prolonged Pd compared with healthy children [HUTT positive: (50.2 ± 18.5) ms vs. (32.0 ± 11.2) ms, $P < 0.05$; HUTT negative: (39.6 ± 14.2) ms vs. (32.0 ± 11.2) ms, $P < 0.05$], the Pd in the positive HUTT group was also significantly longer than that of the negative HUTT group [(50.2 ± 18.5) ms vs. (39.6 ± 14.2) ms, $P < 0.05$]. In the positive HUTT group, there were also significant differences in Pd among different VVS subtypes, and the Pd in the VVS-CI group was significantly longer than that in VVS-VI and VVS-M [(51.1 ± 23.6) ms vs. (46.9 ± 21.7) ms, (51.1 ± 23.6) ms vs. (44.4 ± 15.8) ms, both $P < 0.05$, respectively]. It verified the existence of autonomic dysfunction in children with VVS, suggesting that Pd can be used as an ECG indicator for early clinical prediction of VVS, and may be more sensitive in VVS-CI type. Wang et al. (41) reported that the P-wave related parameters of 43 cases of children with VVS-CI aged 5∼17, such as Pd, Pmax, Pwd, corrected the maximum P-wave duration (Pcmax), corrected P-wave dispersion (Pcd), were significantly longer than those of healthy children [Pd: (36 ± 7) ms vs. (26 ± 4) ms, $t/Z = 8.270$, $P < 0.01$; Pmax: (97 ± 7) ms vs. (88 ± 4) ms, $t/Z = 7.128$, $P < 0.01$; Pwd: (79 ± 7) ms vs. (75 ± 4) ms, $t/Z = 3.639$, $P < 0.01$; Pcmax: (120 ± 12) ms vs. (112 ± 7) ms, $t/Z = 3.390$, $P < 0.01$; Pcd: (44 ± 8) ms vs. (33 ± 5) ms, $t/Z = 7.043$, $P < 0.01$]. It is further verified that children with VVS-CI have autonomic dysfunction and abnormal atrial electrical activity. Pd ≥ 27.42 ms (AUC = 0.908) was recommended as an ECG indicator for early clinical prediction of VVS-CI, with the sensitivity and specificity of 95.35% and 69.77%, respectively. In addition, de Gregorio et al. (42) observed 55 syncopal patients aged 14–75 years old and found that 75% of patients with P-wave peaking (PWP, percent increase in PWP from rest to both 15-min and peak-HR) ≤50% at peak heart rate had positive responses to HUTT, while only 5% of patients with PWP ≥ 100% had positive responses to HUTT, suggesting a potential relationship between HUTT positivity and low or no PWP. However, the relevant data on children have not been retrieved yet, so the PWP indicator deserves further study. Therefore, for P-wave related indicators, Pd = 27.42 ms (AUC = 0.908) is currently recommended as an ECG indicator for early clinical prediction of VVS-CI.

T wave in the prediction of diagnosis vasovagal syncope and guide individualized treatment

T wave refers to the ventricular repolarization process on the synchronous 12-lead ECG. Since most of the repolarization potentials cancel each other during the ventricular repolarization process, the T wave actually reflects the potential difference of ventricular repolarization that has not been canceled out. Autonomic dysfunction can cause T wave changes, with an incidence of 20–40%. For example, when sympathetic nerve activity increases, T waves can appear bimodal, flat, or inverted, and the Niagara waterfall-like T wave (giant T wave inversion) may even occur when the activity of the sympathetic nerve increases excessively. When vagal nerve activity increases, the T wave height tip may appear, and T wave changes can be used as a predictor of sudden cardiac death and malignant arrhythmia (43, 44).

T wave amplitude and morphology

VVS is related to T wave amplitude and morphology. Mayuga et al. (45) found that T wave changes in leads aVF, V5, and V6 were correlated with VVS ($P < 0.05$). Kolarczyk et al. (46) observed T wave changes in 30 children with VVS, and 19 patients had T wave morphological changes after HUTT, mainly in leads V4, V5, and V6, and during the HUTT in these 19 children, the QTc and T wave peak-to-end interval (Tp-Te interval) in lead V5 were significantly longer than the syncope children without T wave morphological changes [QTc: (451.3 ± 13.4) ms vs. (434.4 ± 15.4) ms, $P < 0.01$; Tp-Te: (100.0 ± 3.3) ms vs. (88.2 ± 4.0) ms, $P < 0.01$]. Markiewicz-Łoskot et al. (47) also found that 23 of 40 children with negative HUTT VVS had T wave morphological changes in lead V5 during HUTT, and the QTc and Tp-Te intervals were significantly longer than those of VVS children without T wave changes, and there is a risk of arrhythmia. Xue et al. (48) reported that children with unexplained syncope had lower T wave amplitudes in lead V3–V6 during HUTT than healthy children, and the positive HUTT group had lower T wave

amplitudes in some leads (II, III, aVR, aVL, and aVF) during HUTT than negative HUTT group (all $P < 0.05$). Wu et al. (49) reported that the morphological changes of T wave were correlated with VVS, and the incidence of syncope can be reduced after oral β-blockers in VVS children with orthostatic T wave changes (28.6% vs. 72.7%, $P < 0.01$), suggesting that treatment of β-blocker can be recommended to VVS children with orthostatic T wave changes. Wu et al. (50) reported that the T wave amplitude in leads II, aVR, and aVF during syncope had a certain predictive value for short-term non-pharmacological therapy in children with VVS.

T wave peak-to-end interval (Tp-Te interval) and Tp-Te/QT

The Tp-Te interval refers to the total time from the peak of the T wave to the end of the T wave on the synchronized 12-lead ECG, which represents the difference between the epicardial repolarization time and the M-cell repolarization time during the cardiac repolarization process, and is an indicator of transmural dispersion of repolarization (TDR). The prolongation of Tp-Te interval has predictive values for clinical malignant ventricular arrhythmias (51–53). Tp-Te/QT reflects the proportion of Tp-Te interval in the process of repolarization. As a more sensitive indicator for judging arrhythmia, it can eliminate the influence of heart rate and individual QT interval variability on Tp-Te (54). Markiewicz-Łoskot et al. (47) found that the Tp-Te interval in lead V5 was consistently prolonged during HUTT in 40 children with VVS compared to healthy children [in supine position: 89 ms vs. 80 ms, $P < 0.01$; syncope occurred: 100 ms vs. 60 ms, $P < 0.01$; after syncope: 90 ms vs. 80 ms, $P < 0.01$]. According to ROC, Tp-Te interval > 70 ms (AUC = 1) was recommended for predicted VVS with good sensitivity and specificity (both 100%).

The above studies show that β-blockers or non-pharmacological therapy is recommended for VVS children with T-wave morphology and T-wave amplitude changes, and the diagnosis of VVS can be preliminarily predicted when the Tp-Te interval >70 ms.

Deceleration ability of heart rate in the prediction of vasovagal syncope diagnosis in different age groups

DC is an indicator to evaluate the function of the autonomic nervous system. Through the analysis of the RR interval in the Holter, the cardiac vagal nerve activity is quantitatively measured, that is, the decrease of DC reflects the decrease of the cardiac vagal nerve activity, and confirms that the DC damage is a strong predictor of mortality after myocardial infarction (55). Tong et al. (56) analyzed 90 cases of children's Holter ECG and found that children with VVS had abnormal autonomic nerve function during the asymptomatic period, and it was related to age [school-age group vs. adolescence group: (7.94 ± 0.62) ms vs. (8.59 ± 1.15) ms, $t = 2.49$, $P < 0.05$]. It was recommended that the DC of school-age (7–10 years old) is 7.72 ms (AUC = 0.717), and the DC of adolescence (11–18 years old) is 8.36 ms (AUC = 0.692) as the cutoff values have a good predictive value for the initial diagnosis of VVS, and its sensitivity and specificity were 68.8%, 68.7% and 65.5%, 62.1%, respectively.

Immediate heart rate changes to identify postural tachycardia syndrome and vasovagal syncope, and guide the application of metoprolol

Immediate heart rate change refers to the change of the patient's heart rate from supine to an upright position, including acceleration index (AI) and 30/15 ratio. AI reflects sympathetic nervous system function, and the 30/15 ratio reflects vagal nerve system function (57, 58). Tao et al. (59, 60) observed differences in AI and 30/15 ratios between children with VVS and POTS. Compared with the POTS group, the AI of the VVS group was significantly decreased, and the 30/15 ratio increased [(23.440 ± 8.693) vs. (33.495 ± 8.472), $t/Z = -4.724$, $P < 0.01$; (1.025 ± 0.084) vs. (0.962 ± 0.067), $t/Z = 3.187$, $P < 0.01$], suggesting that the pathogenesis of VVS and POTS may be different. Also, it was found that AI and 30/15 ratio can be used as indicators to distinguish POTS and VVS, with AI = 28.180 (AUC = 0.801) or 30/15 = 1.025 (AUC = 0.738) as the cutoff value, the sensitivity and specificity of differentiating POTS from VVS were 79.2%, 73.1% or 87.5%, 61.5%, respectively. After the upright training intervention, the average acceleration index of VVS children with the improved condition was lower than those without improvement [(21.10 ± 6.61) vs. (31.36 ± 9.00), $P < 0.01$], and the predictive ability was the best when AI < 26.7 (AUC = 0.827) with sensitivity and specificity of 85.0% and 69.2%. Similarly, Zhang et al. (61) found that the heart rate before a positive response to HUTT was significantly higher in the effective treatment group with metoprolol than that of the ineffective treatment group [(123 ± 15) bpm vs. (96 ± 17) bpm, $P < 0.01$], and the heart rate increment before the positive response to HUTT showed a significant difference between the two groups [(42 ± 16) bpm vs. (18 ± 13) bpm, $P < 0.01$]. Compared with the baseline value, if an increase of 30 bpm in heart rate before a positive response to HUTT was taken as a cut-off value, with respect to predicting the metoprolol efficacy in the treatment of VVS, the sensitivity was 81% and the specificity

TABLE 1 Predictors of the diagnosis of pediatric VVS.

References	ECG indicators	Cutoff values	AUC	Sensitivity (%)	Specificity (%)
Alehande et al. (17)	LF/HF	>2.7	–	52	93
Wang et al. (24)	dULF	>36.2ms^2	0.826	73.3	72.5
Karataş et al. (30)	QTcd	>50 ms	–	76.5	59.5
Khalilian et al. (31)	QTd	>32 ms	0.944	92	98
Markiewicz-Łoskot et al. (47)	Tp-Te	>70 ms	1	100	100
Tong et al. (56)	DC	School-age>7.72 ms	0.717	68.8	68.7
		Adolescence>8.36 ms	0.692	65.5	62.1
Tao et al. (59, 60)	AI	<28.180	0.801	79.2	73.1
	30/15	>1.025	0.738	87.5	61.5

LF/HF, low-frequency/High-frequency; AUC, area under curve; VVS, vasovagal syncope; VLF, very low-frequency; dULF, the daytime ultra-low frequency; QTcd, corrected QT dispersion; QTd, QT dispersion; Tp-Te, T wave peak-to-end interval; DC, deceleration ability of heart rate; AI, acceleration index.

TABLE 2 Predictors of the diagnosis of different subtypes of pediatric VVS.

References	ECG indicators	Cutoff values	AUC	Sensitivity (%)	Specificity (%)	Type
Khalilian et al. (31)	QTd	>40 ms	0.784	84	63	VVS-M
Liu et al. (32)	QTd	>28.5 ms	0.914	86.3	84.95	VVS-CI
Wang et al. (41)	Pd	≥ 27.42 ms	0.908	95.35	69.77	VVS-CI

AUC, area under curve; SDNN, the standard deviation of all normal-to-normal intervals; SDANN, the standard deviation of the average normal-to-normal intervals; SDNN index, the standard deviation of all normal-to-normal intervals index; QTd, QT dispersion; VVS-M, mixed vasovagal syncope; VVS-CI, cardioinhibitory vasovagal syncope; Pd, P wave dispersion.

TABLE 3 Predictors of individualized treatment of pediatric VVS.

References	Interventions	ECG indicators	Cutoff values	AUC	Sensitivity (%)	Specificity (%)
Liu et al. (32)	Non-pharmacological	QTd	<34.50 ms	0.906	90	82.35
Wu et al. (49)	β-blockers	T wave morphology	–	–	–	–
Wu et al. (50)	Non-pharmacological	T wave amplitude	–	–	–	–
Tao et al. (59, 60)	Upright training	AI	<26.7	0.827	85	69.2
Zhang et al. (61)	Metoprolol	Increment of HR before positive response in HUTT	30 bpm	–	81	80

QTd, QT dispersion; AI, acceleration index; HR, heart rate; HUTT, head-up tilt test.

was 80%, suggesting that β-blocker therapy is recommended for those with markedly increased heart rate before a positive response to HUTT.

Ventricular late potential in the prediction of malignant arrhythmia in children with vasovagal syncope

VLP is a high-frequency, low-amplitude fragmented electrical activity characterized by multi-shaped sharp waves caused by local delayed depolarization of the myocardium. It is caused by slow and irregular reentry activity in the ischemic myocardium, and it is an electrophysiological indicator reflecting the instability of myocardial electrical activity (62). The main detection indicators are: (1) total QRS time (TQRS, ms), which refers to the time from the start of QRS to the end of VLP on the filtered leads X, Y, and Z; (2) root mean square value (RMS40, μV), which is the voltage at the end of the QRS wave at 40 ms; and (3) the high frequency and low amplitude time limit (LAS40, ms), the time limit when the terminal voltage of the QRS after filtering is lower than 40 μV (63). Previous studies have shown that there are circadian rhythm changes in VLP associated with autonomic nerves (64, 65), and VLP is associated with the induction of malignant arrhythmias,

the prognosis of patients with myocardial infarction, and sudden cardiac death (66–68). Zhang et al. (63) found that the LAS40 of VVS children was significantly prolonged compared with healthy children [(29.04 ± 6.59) μV vs. (26.15 ± 5.82) μV, $t = 2.204$, $P < 0.05$], suggesting that VVS children have abnormal myocardial electrical activity and the risk of cardiac events, and such children should be alert to the possibility of malignant arrhythmia. Zou et al. (69) reported that the TQRS, RMS40, and LAS40 of 184 cases of VVS-VI children were longer than those of healthy children [TQRS: (84.89 ± 12.05) ms vs. (81.21 ± 8.23) ms, $P < 0.01$; RMS40: (28.73 ± 7.23) μV vs. (26.89 ± 7.36) μV, $P < 0.05$; LAS40: (62.43 ± 19.17) ms vs. (56.79 ± 18.75) ms, $P < 0.05$], and the VVS-VI group had more abnormally prolonged LAS40 (94.57% vs. 83.80%, $P < 0.01$), suggesting that monitoring VLP in children with VVS-VI can help predict the possibility of malignant arrhythmia.

Conclusion

For the clinical prediction of VVS diagnosis (**Table 1**), LF/HF > 2.7, dULF>36.2 ms^2, QTcd > 50 ms, QTd > 32 ms, Tp-Te > 70 ms, school-age DC > 7.72 ms, adolescent DC > 8.36 ms, AI < 28.18, and 30/15 > 1.025 were used as indicators to distinguish positive and negative HUTT in children, according to the maximum AUC (1.000), Tp-Te > 70 ms is recommended as a rapid identification of VVS in ECG indicator. For different hemodynamic types (**Table 2**), VVS-CI can be predicted with QTd > 28.5 ms and Pd ≥ 27.42 ms. According to the maximum AUC (0.914), QTd > 28.5 ms is recommended as the best ECG indicator for predicting VVS- CI, when QTd > 40 ms can be used to predict VVS-M. For the selection of VVS treatment measures and the prediction of efficacy (**Table 3**), QTd < 34.5 ms, AI < 26.7, heart rate before positive HUTT reaction increased by 30 bpm from basal heart rate were used as predictors for the effectiveness of non-pharmacological therapy, upright training, and metoprolol intervention.

VVS is a self-limiting disease caused by the disturbance of autonomic regulation, which usually occurs in early adolescence. ECG indicators such as HRV, Pd, QTd, Tp-Te interval, Tp-Te/QT, T-wave amplitude and shape, immediate heart rate change, DC and VLP are easily available, non-invasive, and inexpensive. However, there is still a lack of systematic large-scale, multi-center, long-term follow-up studies, and the value of some indicators needs to be further confirmed. With the help of relevant ECG indicators, individual treatment plans can be selected for patients with different hemodynamic types to improve the long-term prognosis of children and adolescents with VVS.

Author contributions

TZ conceptualized, prepared, and wrote the manuscript and made the tables. SW, MW, HC, YW, YX, and RZ participated in providing documentation. RZ and CW reviewed, edited, and revised the manuscript. All authors have read and approved the final manuscript and assume full responsibility for its contents.

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Conflict of interest

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Need for HTA supported risk factor screening for hypertension and diabetes in Nepal: A systematic scoping review

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Objective: Health Technology Assessment (HTA) is a comprehensive and important tool for assessment and decision-making in public health and healthcare practice. It is recommended by the WHO and has been applied in practice in many countries, mostly the developed ones. HTA might be an important tool to achieve universal health coverage (UHC), especially beneficial to low-and-middle-income countries (LMIC). Even though the Package for Essential Non-communicable Diseases (PEN) has already been initiated, there is a clear policy gap in the HTA of any health device, service, or procedure, including the assessment of cardiovascular risk factors (CVRFs) in Nepal. Hence, we carried out the review to document the HTA supported evidence of hypertension and diabetes screening, as CVRFs in Nepal.

Materials and methods: We searched in PubMed, Cochrane, and Google Scholar, along with some gray literature published in the last 6 years (2016–2021) in a systematic way with a controlled vocabulary using a well-designed and pilot tested search strategy, screened them, and a total of 53 articles and reports that matched the screening criteria were included for the review. We then, extracted the data in a pre-designed MS-Excel format, first in one, and then, from it, in two, with more specific data.

Results: Of 53 included studies, we reported the prevalence and/or proportion of hypertension and diabetes with various denominators. Furthermore, HTA-related findings such as cost, validity, alternative tool or technology, awareness, and intervention effectiveness have been documented and discussed further, however, not summarized due to their sparingness.

Conclusion: Overall, the prevalence of DM (4.4–18.8%) and HTN (17.2–70.0%) was reported in most studies, with a few, covering

other aspects of HTA of DM/HTN. A national policy for establishing an HTA agency and some immediately implementable actions are highly recommended.

KEYWORDS

health technology assessment (HTA), cardiovascular, risk factor, hypertension, diabetes, screening, review, Nepal

Introduction

Health technology assessment (HTA) is a multidisciplinary approach incepted during the 1970s for assessing technologies such as drugs, devices, procedures, settings of care, services or programs, including the screening in health care with the collection of data from epidemiological, clinical efficacy, quality of life, service utilization, and cost (both health systems' and patients' out of pocket payments) studies.

HTA assists in evidence informed health policy making on the introduction and use of health technologies. Since any state or country has competing priorities, policy-makers often decide what is the best buy for the available evidence-base and the budget, which can further help as suggested by the WHO, in developing the health benefit package (HBP) for any state or country (1). At least two dimensions (if not three) of universal health coverage?the proportion of the cost and the services covered are directly linked to and implicated by HTA. Countries like the USA, Australia and Canada have been benefiting from HTA for decades, whereas Asian countries like South Korea, Japan, China, and India (recently) are gaining momentum (2). As per a survey carried out by WHO in 2015, Nepal has neither rendered a national HTA body nor is there clarity on how HTA is used in decision-making (3).

According to the global burden of disease study (GBOD) conducted in Nepal in 2017, non-communicable diseases were responsible for two-thirds of all deaths (66%), while high blood pressure and high fasting blood glucose levels were responsible for 14 and 10% of all deaths, respectively (4). Screening can avert disability adjusted life years (DALYs) of 2.33–3.1 in the case of hyperglycaemia (5) and is cost-effective in both hyperglycaemia and hypertension (5, 6).

Diabetes is a metabolic disorder identified by screening using technologies like laboratory tests that include fasting plasma glucose, 2-h (2-h) post-load plasma glucose after a 75-g oral glucose tolerance test (OGTT); hemoglobin A1c (HbA1c); and random blood glucose in the presence of signs and symptoms. Diabetes is defined as fasting plasma glucose of 7.0 mmol/L (126 mg/dl), 2-h post-load plasma glucose of 11.1 mmol/L (200 mg/dl) (5), HbA1c $\geq$ 6.5% (48 mmol/ml); or a random blood glucose of $\geq$11.1 mmol/L (200 mg/ dl) in the presence of signs and symptoms. If elevated values are detected in asymptomatic people, repeat testing, preferably with the same test, is recommended as soon as practicable on a subsequent day to confirm the diagnosis (7).

Raised blood pressure can be identified at either a clinic, home-based, or ambulatory screening, and the diagnosis can be made with repeated measurements at 1–4 week intervals. In addition to this, blood tests, echocardiography, urine dipstick, albumin, and liver functions tests are other additional tests that are carried out in hypertensive suspects or diagnosed cases (8). As a part of assessing cardiovascular risk, mean systolic blood pressure should be measured over two separate occasions. For those who are already on anti-hypertensive medicine, the most recent recorded pretreatment value should be adopted as given by the National Institute for Health and Care Excellence/British Hypertension Society (NICE/BHS) guideline (9).

The population-based screening for diabetes and hypertension at a frequency ranging from every year to every 20 years was not cost-effective at the present level healthcare systems in India. However, it was estimated that screening at 3-to-5-year intervals could be cost-effective if the proportion of newly diagnosed and treated patients increased by more than 20%. Providing population-based screening of those two disease conditions through primary health centers (PHC) could be cost-effective; therefore they need to be strengthened at PHC level (10). A comparative study of BP measured in Shardaben General Hospital, India by digital and aneroid sphygmomanometers showed mean SBP as 108.92 $\pm$ 15.14 and 109.66 $\pm$ 16.81, and mean DBP as 76.20 $\pm$ 12.25 and 78.02 $\pm$ 14.35 mm of Hg, respectively, justifying that the bias for mean SBP and DBP was clinically non-significant and both instruments can be used interchangeably (11).

Diagnosing hypertension by sphygmomanometer is considered the gold standard as it has a high level of accuracy. A study from West Bengal showed that the aneroid device had better accuracy than the digital device as compared to the mercury sphygmomanometer (12). The mercury sphygmomanometer, which was widely used in the past to measure blood pressure in an office or clinic, has now been largely phased out in US hospitals, leading to the use of non-mercury, aneroid, or hybrid manometers in clinic and hospital settings (13, 14). Ambulatory monitoring was the most cost-effective strategy for all ages of men and women after an

initial raised reading at the clinic or at home for blood pressure diagnosis, and so, it should be taken as a reference standard (15, 16).

Similarly, other instruments like 12-lead portable ECG devices for the screening of cardiovascular diseases in Ahemdabad found that screening at PHC by ECG saves 2.9 lives per year at an incremental cost of 89.97 USD, yielding a cost-effectiveness ratio of 31.07 USD, so the facility to screen cardiac abnormality at PHC level is highly recommended for risk adults and symptomatic cases (17). It coincides with the US preventive services task force for screening for prediabetes and type 2 diabetes at ages 35–70 years in a primary setting, which has a moderate net benefit. It was suggested that screening every 3 years may be a reasonable approach for adults with normal blood glucose as the initial normal glucose test result is limited. The diagnosis of type 2 diabetes should be confirmed with repeated tests. Now, the US Preventive Services Task Force (USPTSF) changed their practice of 2015 recommendation and lowered the initial age of screening from age 40 to 35 among adults who were obese or overweight (18).

In Bhutan, an economic evaluation of the World Health Organization (WHO)'s Package of Essential Non-communicable diseases (PEN) found that the ambulatory but high-risk screening (where people who are overweight, obese, or >40 years for DM and/or HTN, visiting primary care facilities) represents good value for money compared to "no screening" (19). However, if performed on a regular basis and taking into account the specific population group and the existing non-disease to disease conversion rate, opportunistic high-risk approach screening may also yield high results (but may not confirm cases) (20).

The Indian diabetes risk score (IDRS) was used in a study from Tamil Nadu, India to determine the prevalence of type 2 diabetes high-risk cases. Use of the IDRS could reduce the cost of diabetes screening in India and so, being suggested to use in mass screening (21). Insulin pumps or glucose sensors appear cost-effective, particularly in populations with higher HbA1c levels and rates of hypoglycaemia. However, the cost-effectiveness for combined insulin pumps and glucose sensors was less clear (22).

A study from Kuwait assessing type 2 diabetes and hypertension using machine-learning among 89,858 diabetics, 58,745 hypertensives, and 30,522 co-morbids shows that >85 and >90% accuracies were achieved for diabetes and hypertension, respectively using simple non-laboratory-based parameters. Talking more about the prediction, ethnicity is seen as a significant factor to the predictive models such as Asian-specific models and assessments perform even better (23). Population based screening for high- risk strategies can prevent cardiovascular disease. Also, it was suggested that where resources are limited, further advice be taken to take a total risk approach to identify several risk factors targeting to high-risk group to identify hypertension. Targeting high-risk groups for screening can help reduce costs because resources are not spent on the entire population. Early detection results in timely treatment and management of risk factors, which ultimately assists in reducing morbidity and mortality and reducing health-related costs (24).

A 540-person study in rural West Virginia was designed to identify diabetic risk using an HbA1c test and a diabetes risk assessment tool. Results showed that 61.8% of participants were at high risk for diabetes. It shows that community-based screenings are an effective way to assess diabetes risk (25).

Because cardiovascular risk factors were prevalent among Nepal's rural population, comprehensive intervention targeting all risk factors should be planned and implemented to reduce the burden of CVD in Nepal (26). Nepal has yet to work to implement health policies to tackle CVD or other NCDs. Recently, CVD management has been focused on treatment as there has been a rise in the availability of interventional cardiology and cardiothoracic surgery services (27). An assessment of health facilities for the implementation of a non-communicable disease package in Nepal among 92 health facilities in Kailali and Ilam districts revealed the gaps in the capacity of health institutions and the system in terms of training, supply, equipment, and diagnostics (28).

According to WHO, HTA should include the complete range of interventions or technology, and not be limited to just one. Technologies and methods considered in HTA include safety, clinical effectiveness, equity issues, ethical issues, feasibility, and acceptability of the health care system by providers and patients (29). Based on serum HbA1c levels, diabetes screening was offered at the Durham Veterans Affairs Medical Center for people aged 45–64 years old. Participants with an HbA1c $\geq$ 6.0% were invited for a follow-up measurement of blood pressure fasting plasma glucose, and health-related quality of life (HRQoL) were measured. Those with HbA1c $\geq$ 7.0% or fasting plasma glucose $\geq$7 mmol/dl are diagnosed as having unrecognized diabetes. There was no difference in the HRQoL of patients diagnosed with diabetes and those not diagnosed with diabetes. Screening for diabetes has minimal, if any, "labeling" effect with respect to quality of life (30).

Hypertensive disorders are the risk factors for cardiovascular diseases in Nepal, and there is a wide gap and socio-economic disparity in hypertension management. In Nepal, the overall prevalence of high blood pressure was 19.6 percent. Furthermore, less than one-third of the population was treated, and <20% had their blood pressure under control. Wealth and education-based inequalities in awareness, treatment, and control measures of raised BP were significantly high in urban and rural areas (31). In this scenario, Nepal has developed PEN protocols and initiated the program in 2016 (32). These signify (but are not limited to) the systematic assessment of equity, cost, clinical efficacy, safety, ethically sound, feasible, and acceptability of health devices, procedures, and services before their population-wide applications.

TABLE 1 PICO indicators and criteria for scoping review.

PICO/Indicator	Criteria
Study design	Published qualitative and quantitative data related to blood pressure and blood sugar assessment from study designs-case series, cross-sectional studies, cohort studies, RCTs, pilot trials, screening costing and economic evaluation, health technology assessment of diabetes and hypertension screening
Population	Clinical, co-morbid or healthy population aged 18 years or above who have undergone any type of screening or assessed in survey or surveillance in Nepal
Intervention	Screening, surveillance or survey
Comparator	Having control or standard treatment or placebo or no comparator
Outcome	Any of the followings (Qualitative and/or Quantitative finding) 1. From screening: any of true positive rate (TPR), true negative rate (TNR), false positive rate (FPR), false negative rate (FNR), sensitivity, specificity, yield, positive predictive value (PPV), negative predictive value (NPV). 2. Ratio of screened +ve to screened -ve (among the total visited to surveillance center) 3. From Screening, Survey or Surveillance: Number of subjects needed to screen or survey for one case of DM or HTN 4. Costing per case identifying 5. Costing per individual screening 6. Incremental cost-effectiveness ratio (ICER) 7. Proportion of hypertension (95% CI) 8. Proportion of diabetes mellitus (95% CI) 9. Proportion of hypertension awareness among the hypertensives 10. Proportion of diabetes awareness among the diabetics 11. Proportion of taking medication among the hypertensives 12. Proportion taking medicines among the diabetics 13. Proportion of controlled BP among the hypertensives 14. Proportion of controlled sugar among the diabetics 15. Health technology assessment (HTA) 16. Ethics in screening of DM and HTN 17. Quality of life (QoL) of screening of DM and HTN 18. Willingness to pay (WTP) and cost of screening of DM and HTN 19. Capacity to pay (CTP) of screening of DM and HTN
Published duration	Last 6 years (2016–2021)

Materials and methods

Review framework

We used the following methodological framework to conduct this scoping review; (1) Identifying review questions, (2) Creating review objectives, (3) Establishing eligibility criteria, (4) Creating a search strategy and identifying search sources, (5) Screening records and data extraction, and (6) Evidence synthesis.

Search strategy

A comprehensive search was conducted using PubMed, Google Scholar, and the Cochrane databases, with publication date limits of the last 6 years (2016–2021). We also searched for reports, theses, and abstracts in gray literature and in citation searches.

A search strategy was finalized after developing a search strategy in consultation with the experts in the field. We searched with keywords such as screening, hypertension, diabetes, hyperglycaemia, Nepal, non-communicable, review, raised blood pressure, surveillance in the title, abstract, and keywords (ti; ab; kw); and with the medical subject heading (MeSH) descriptors such as heart disease risk factor, diagnostic techniques, blood pressure, diabetes mellitus. We searched on the basis of outcome indicators as illustrated in Table 1.

Study selection

After the strategy was finalized among all, a researcher, having trained and previous experience in systematic search and evidence synthesis, independently screened studies for eligibility and relevance. Studies were considered to be eligible if they had any of the outcome indicators as illustrated in

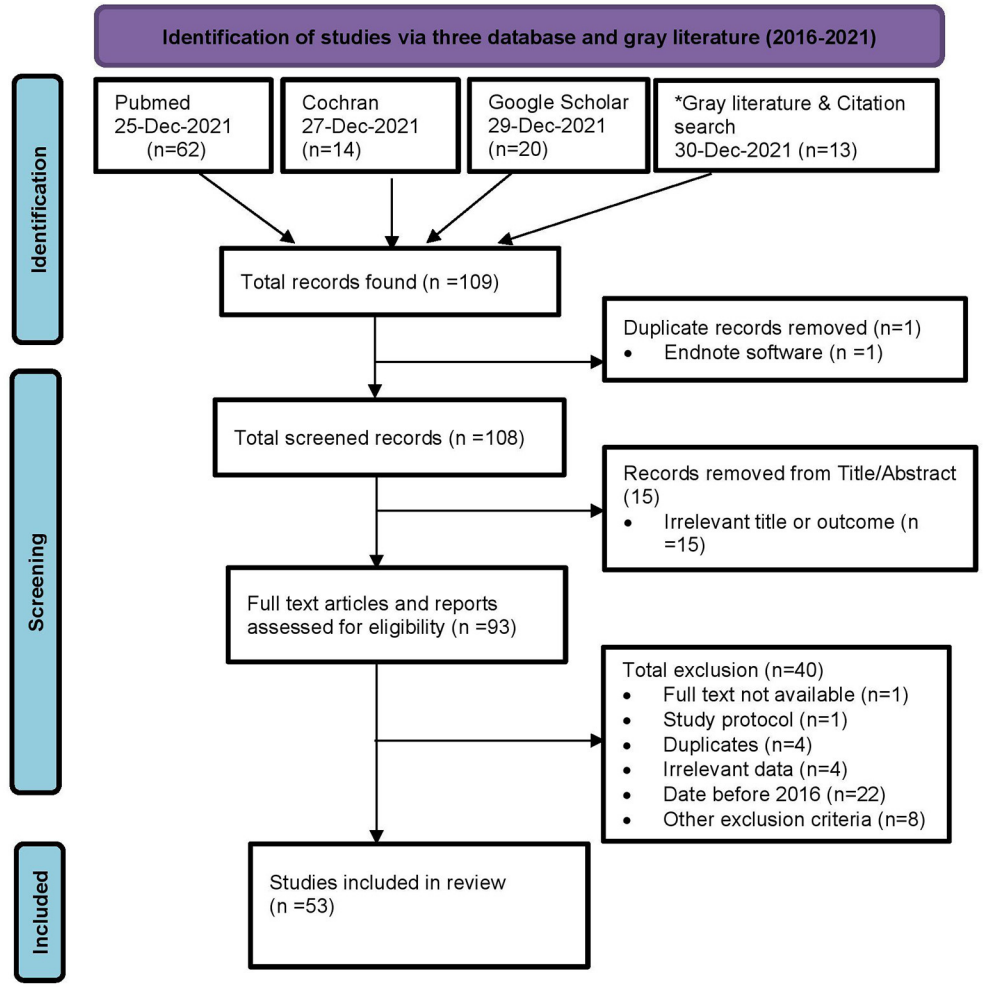

FIGURE 1
PRISMA chart of screening and included studies. *Gray literature search includes Shahid Gangalal National Heart Center (2), Mrigendra Samjhana Medical Trust (MSMT) (1), National Health Research Council (2), Ministry of Health and Population, Dept. of Health Services (3), Others (3), and Citation search (2).

Figure 1, including abstracts and reports. However, we excluded the protocols.

Data extraction and data synthesis

Three different data extraction grids were developed by two review authors (CA and KS) and then sent to two authors (LMA and BP) for data extraction, from whom CA again obtained and compiled the data. Information regarding authors, country, study year, study type, sample size, geography, sex, age, ethnicity, and outcomes measures (Table 2), including key findings, and strengths and limitations (Table 3), was extracted from 53 individual studies (Figure 1), which were included in the review.

Results

After excluding duplicates, irrelevant studies, and further eligibility assessment, 53 articles were included in the scoping review.

Of the 53 included studies, 11 reported both DM and HTN prevalence. Participants aged 50 years and older from Bagmati Province and Terai had a higher prevalence of DM. Similarly, people aged 60–69 years from Karnali Province and urban hills had a higher prevalence of HTN. A higher DM prevalence was reported among the clinical participants. For HTN, it was higher among both healthy and clinical participants. Similarly, studies/screenings carried out in ambulatory settings had a higher prevalence for DM, but for HTN, it was reported to be higher in the camps. Males had a higher prevalence among participants with DM and HTN, and co-morbidity for

TABLE 2 Characteristics of the included studies.

SN	References	Study type (Screening/survey/ surveillance) and/or cross-sectional/longitudinal	Study detail (sample)	Study detail (geography/ districts)	Population characteristics (Sex, age)	Population characteristics (caste/ethnicity)	Population characteristics (healthy, clinical)	Outcome measured	Remarks (publication type)
1	Acharya et al. (33)	Opportunistic screening campaign	11486	Nepal	18 years and above, female- 6,568 (57%)	Not available (NA)	Healthy and clinical (on medications), both	• Proportion of hypertension; • Proportion of hypertension awareness among the hypertensives; • Proportion of persons on medication among the hypertensive	Conference abstract book
2	Adhikari (34)	Screening of cardiac patients using the invasive and non-invasive technology, Cardiac Camps (through May measurement month screening)	Varying (depends upon the screening technology)—For May measurement month screening Camps-1857	Nepal (facility-based)	All ages	Not available (NA)	Clinical and healthy	• Proportion of hypertension-camp based	Annual report
3	Agho et al. (35)	Secondary analysis of NDHS 2016	14,857 (males: 6,245 and females: 8,612)	Nepal	15 years and above	Not available (NA)	Clinical and healthy	• Prevalence of prehypertension and hypertension	Original article
4	Bhattarai et al. (36)	Secondary analysis	NA	Nepal	General population	NA	Clinical and healthy	• Proportion of contribution of CVD in mortality and DALYs	Original article
5	Bist et al. (37)	Survey	5593	Nepal	15–69 yrs.	NA	Clinical and healthy	• Proportion of raised blood pressure • Proportion of raised blood glucose	Original article
6	Brewis et al. (38)	Secondary analysis of NDHS 2016	14842	Nepal	General population	NA	Clinical and healthy	• Proportion of raised blood pressure	Research article
7	Aryal et al. (39)	Survey	521	Mustang and Humla (Mountain)	30 years and above	Tibetans and Khas-Aryas.	Clinical and healthy	• Proportion of raised blood pressure • Proportion of prediabetic and diabetic	Research article
8	Das Gupta et al. (40)	Secondary analysis of NDHS 2016	13,393	Nepal	18 years and above	General population	Clinical and healthy	• Proportion of hypertension awareness among the hypertensive • Proportion of using antihypertensive use among the hypertensive • Proportion of controlled BP among the hypertensive	Research article
9	Das Gupta et al. (41)	Secondary analysis of NDHS 2016	13,393	Nepal	18 years and above	General population	Clinical and healthy	• Prevalence of prehypertension and hypertension	Research article
10	Datta and Humagain (42)	Secondary analysis of NDHS 2016	3,778	Nepal	15–49 years married women	General population	Clinical and healthy	• Prevalence of prehypertension and hypertension	Research article
11	Dhungana et al. (43)	Secondary analysis of NCD Survey 2018	8,931	Nepal	20 years and above	General population	Clinical and healthy	• Prevalence of comorbidity with hypertension and diabetics	Research article
12	Dhungana et al. (44)	Survey	347	Sitapaila VDC, Kathmandu	18–70 years excluding self-reported CVD and pregnant women	General population	Clinical and healthy	• Prevalence of hypertension • Prevalence of diabetes	Research article

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TABLE 2 Continued

SN	References	Study type (Screening/survey/ surveillance) and/or cross-sectional/longitudinal	Study detail (sample)	Study detail (geography/ districts)	Population characteristics (Sex, age)	Population characteristics (caste/ethnicity)	Population characteristics (healthy, clinical)	Outcome measured	Remarks (publication type)
13	Ene-Iordache et al. (45)	Secondary analysis of 12 countries (LMICs)	Total = 75,058; Nepal = 21066	12 countries	18 years or older	General population	Clinical and healthy	• Prevalence of hypertension • Prevalence of having awareness of disease onset (HTN and Diabetes)	Research article
14	Ghimire et al. (46)	Secondary analysis of STEPS 2013	526	Nepal	60–69 years	General population	Clinical and healthy	• Prevalence of hypertension • Prevalence of diabetes	Research article
15	Ghimire et al. (47)	Secondary analysis of STEP Survey 2013	4,200	Nepal	45–69 years	NA	General population	• Prevalence of raised blood pressure	Research article
16	Gyawali et al. (48)	Review article	34 studies	Nepal	NA	NA	NA	• Costing per case treatment • Prevalence of DM type 2	Research article
17	Paudel et al. (49)	Descriptive cross-sectional study	977 family members of 290 households	Kaski district, Nepal.	• Male 46.4%, Female 53.6% • Adult 79.5%, Elderly 20.5%	Brahmin 41.4%, Chhetri 17.4%, Dalit 88%, Gurung 18.2%, Others 14.2 %	Healthy and clinical (on medications), both	• Proportion of hypertension • Proportion of hypertensive patients under medication • Proportion. of hypertensive patients who had their blood pressure under control after taking the medications	Research article
18	Peoples et al. (50)	Mixed-method Survey	114 Quantitative; 20 Qualitative	Ten PHC facilities across two regions of Nepal: five in Kailali district and five in Sindhuli district.	• Male (51%) female (49%) of over 18 years of age	NA	Have ever been diagnosed with at least one of the following conditions: heart disease, stroke, hypertension, and/or diabetes	• Assessment of the use and perception of PHC services in Nepal among people living with Cardio metabolic diseases for primary and secondary prevention of cardiovascular disease	Research article
19	Rana et al. (51)	Secondary analysis of NDHS 2016	13,436	Nepal	Male = 5,645, Female = 7,790, Population of age 18 years and above	NA	Healthy	• Prevalence of hypertension • Factors associated with hypertension	Published article
20	Rai et al. (52)	Cross-sectional	1,905	Kathmandu, Nepal	Male = 60.3%, Female = 39.7%	NA	Clinical	• Proportion of hypertension • Proportion of diabetes • Proportion of combined diabetes and hypertension	Research article
21	Rauniyar et al. (31)	Secondary analysis of NDHS 2016	802,167 (787,713 in India, 14,454 in Nepal)	India and Nepal	Nepal • (Male = 58.2%, Female = 41.8%) • Age between 15 and 49 years	NA	Healthy and clinical (on medications), both	• Prevalence, awareness, treatment, and control of hypertension • Wealth-based inequality in prevalence and management of hypertension	Research article
22	Sainju et al. (53)	Cross sectional	1,243	Sindupalchowk district	Female 70%, Male 30%, 18 and above age	NA	Healthy	• Prevalence of pre hypertension and hypertension.	Research article
23	Saito et al. (54)	Cross-sectional	9,177 individuals residing in 1,997 households	Kathmandu, Nepal	• Female 49.1%, Male 51.0% • All ages	NA	Healthy	• Prevalence of non-hypertension and diabetes	Research article

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TABLE 2 Continued

SN	References	Study type (Screening/survey/ surveillance) and/or cross-sectional/longitudinal	Study detail (sample)	Study detail (geography/ districts)	Population characteristics (Sex, age)	Population characteristics (caste/ethnicity)	Population characteristics (healthy, clinical)	Outcome measured	Remarks (publication type)
24	Paudel et al. (55)	Secondary analysis of STEPS 2013	1,977	Nepal	15–69 years	NA	Healthy and clinical (on medications), both	• Prevalence of type 2 diabetes mellitus • Factors associated withType-2 Diabetes Mellitus	Journal Pre-proof document
25	Gyawali et al. (56)	Population-based cross-sectional survey	2,310	Lekhnath Municipality of Nepal	(Female 68%, Male 32%) 25 years or above	Upper caste = 54%, Janajati = 32%, Others = 14%	Healthy	• Prevalence of type 2 diabetes • Factors associated with Type 2 diabetes Awareness, treatment, and control status of type 2 diabetes	Research article
26	Shrestha et al. (57)	Systematic review	15 studies were included in the qualitative and quantitative analysis	Nepal		NA	Having prevalence of T2DM and/or details such as risk factors	• Prevalence of T2DM, pre-diabetes, and impaired glucose tolerance • Factors associated with T2DM	Research article
27	Shrestha et al. (58)	Review	14 eligible studies that comprised a total of 44,129 participants and 3,517 diabetes cases	Nepal	≥20 years old	NA	Healthy, clinical (on medication) l	• Prevalence of Prediabetes and diabetes awareness, treatment and control of diabetes	Research article
28	Shrestha et al. (59)	Hospital based cross sectional	2,256	Bhaktapur district, Nepal	Age: Between 40 and 69 years old.	NA	Outpatients	• Prevalence of hypertension and pre-pre hypertension • Factors associated with hypertension and pre-pre hypertension	Research article
29	Silvanus et al. (60)	Community based, cross-sectional, analytical study	256	Budhanilkantha Municipality, Kathmandu district	170 female, 86 male Age: 50 years old and above	NA	Healthy	• Prevalence of diabetes • Classification of risk for developing diabetes	Research article
30	Silvanus et al. (61)	Community based, cross-sectional, analytical study	162	Budhanilkantha municipality in Kathmandu District		NA	Healthy	• Prevalence of undiagnosed diabetes and prediabetes	Research article
31	Tan et al. (62)	Qualitative study	23 IDIs and 1 FGD	Kavre district, Nepal		NA	Individuals with hypertension	• Hypertension awareness and treatment. • Health system-related barriers and facilitators of hypertension care utilization.	Research article
32	Tang et al. (63)	Secondary analysis of May Measurement Month	Total = 52,180; Nepal = 14,795	USA, India, and Nepal	Age: 18 years or older	All	Healthy	• Misclassification rates of 1st, 2nd, and contrasting 1st with second (given that 1st measures ≥130/80) by taking at least two measurements	Research article
33	Timilsina (64)	Mixed method study	212	Kathmandu and Kailali district	16 years above	All	Tuberculosis patients	• Prevalence of DM among TB patients	Research article

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TABLE 2 Continued

SN	References	Study type (Screening/survey/ surveillance) and/or cross-sectional/longitudinal	Study detail (sample)	Study detail (geography/ districts)	Population characteristics (Sex, age)	Population characteristics (caste/ethnicity)	Population characteristics (healthy, clinical)	Outcome measured	Remarks (publication type)
34	Sharma et al. (65)	Cross-sectional	320	Morang district	15 years and above Male = 214, Female = 96	NA	Clinical	• Prevalence of diabetes • Predictors of the risk factors of Diabetes among the Tuberculosis Patients	Research article
35	Yadav et al. (66)	Interventional time-series of cases	258	Dharan	Male = 123, Female = 135	NA	General OPD patients	• Prevalence of hypertension	Research article
36	Hassan et al. (67)	Secondary analysis of NDHS 2016	3,334	Nepal	>18 years	NA	Hypertensive patients	• Proportion of hypertension awareness among the hypertensive	Research article
37	Kadaria and Aro (68)	Survey (clinic based)	270	Two clinics of Lalitpur and Kaski districts	30–70 years	NA	type 2 diabetes patients	• Prevalence of physical activity; 52% were moderately active and 28% highly active.	Research article
38	Karmacharya et al. (69)	Survey	1,073	Dhulikhel	≥18 years	NA	healthy and clinical	• Proportion of hypertension awareness among the hypertensive • Proportion of taking medication among the hypertensive • Prevalence of Control of HTN	Research article
39	Khanal et al. (70)	RCT	125	Birendranagar municipality of Surkhet district	≥30 years	NA	Hypertnsive patients	• Proportion of taking medication among the hypertensives • Prevalence of Control of HTN	Research article
40	Khanal et al. (71)	Survey	1,159	Birendranagar Municipality of Surkhet district	≥30 years	NA	Clinical and healthy	• Prevalence of HTN • Proportion of hypertension awareness among the hypertensives • Proportion of taking medication among the hypertensives • Proportion of controlled BP among the hypertensives • Prevalence of DM	Report
41	Kibria et al. (72)	Secondary analysis of NDHS 2016	13,519	Nepal	18 years or older	NA	Clinical and healthy	• Prevalence of HTN (as per JNC and ACC/AHA criteria) • Proportion of hypertension awareness among the hypertensives • Proportion of taking medication among the hypertensives • Proportion of controlled BP among the hypertensives	Research article
42	Koirala et al. (73)	Screening at community based setting	140	Community of Dharan	≥18 years	Aryans and Mangolians	Hypertnsive patients	• Proportion of controlled BP among the hypertensives	Research article
43	Koirala et al. (74)	Survey	188	Tsarang village, of Mustang district	≥18–80 years	Highlanders	healthy and clinical	• Prevalence of HTN • Prevalence of DM	Research article
44	Kushwaha and Kadel (75)	Camp survey	114	Community hospital of Kathmandu	>14 years	NA	healthy	• Prevalence of DM	Research article
45	Mehata et al. (76)	Nationally representative cross-sectional study	4,200	Mountain, Hill, and Terai	Adults aged 15–69 years	NA		• Prevalence of metabolic syndrome • Determinants of MetS	Research article

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TABLE 2 Continued

SN	References	Study type (Screening/survey/ surveillance) and/or cross-sectional/longitudinal	Study detail (sample)	Study detail (geography/ districts)	Population characteristics (Sex, age)	Population characteristics (caste/ethnicity)	Population characteristics (healthy, clinical)	Outcome measured	Remarks (publication type)
46	Mehata et al. (77)	Secondary analysis of NDHS 2016	13,598	Mountain, Hill, and Terai	Adults aged 15–69 years	NA	Healthy	• Proportion of Hypertension; • Proportion of hypertension awareness among the hypertensives • Proportion of hypertension treatment among the hypertensives • Proportion of hypertension control among the hypertensives	Research article
47	Mishra et al. (78)	Secondary analysis of NDHS 2016	14,823	Mountain, Hill, and Terai	15 years and above (6,245 males and 8,612 females)	NA	Healthy	• Examine the socio-economic inequalities in prevalence, awareness, treatment, and control of hypertension	Research article
48	Mizuno et al. (79)	Cross-sectional study	Total, 1,899; Nepal, 700	Bangladesh, Indonesia, Nepal, and Vietnam	Female (54%) male (46%	NA	Healthy	• Association between urinary heavy metal concentrations and blood pressure among residents of four Asian countries (Bangladesh, Indonesia, Nepal, and Vietnam)	Research article
49	Bista et al. (80)	Secondary analysis of NDHS data 2016	6,396	Mountain, Hill, and Terai	Women of age 15–49 years	Advantage (31.3%) group, Dalit (12.6%), Janjati (36.6%), Other (19.5%)	Healthy	• Prevalence of non-communicable diseases risk factors among reproductive aged women of Nepal • Determinants of non-communicable diseases risk factors	Research article
50	Neupane et al. (81)	Cross-sectional study	123 Female community health volunteers (FCHVs)	Lekhnath municipality, Nepal	20 years and above	Dalit (4.4%), Disadvantaged Janjati (5.3%), Relatively advantaged janajati (9.7%), Upper caste (80.5%)	Healthy	• Knowledge of diagnosis, risk factors, and complications • Attitude toward hypertension and its risk factors • Attitude toward community behavior related to hypertension • Attitude toward future involvement in hypertension management	Research article
51	Neupane et al. (82)	Community-based, open-label, two-group, cluster-randomized controlled trial	1,638 participants (939 assigned to intervention; 699 assigned to control)	Nepal	Adults 25–65 years	NA	Healthy	• Mean systolic blood pressure at 1 year	Research article
52	Neupane et al. (83)	Cross-sectional study	2,815 households	Semi urban area of Lekhnath Municipality,Nepal	Adult population (≥18 years) Female (63%), Male (37%)	NA	Healthy	• Calculate prevalence, awareness, treatment and control level of hypertension.	Research article
53	Niraula et al. (84)	Hospital based cross-sectional study	204 diagnosed patients (102 males and 102 females) with T2DM and 102 healthy controls were enrolled in the study	BPKIHs, Dharan, Nepal			Newly diagnosed and follow-up cases of T2DM v	• Reveal the adenosine deaminase activity in type 2 diabetes mellitus	Research article

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TABLE 3 Key findings, strengths, and limitations of included studies.

SN	References	Key findings	Strengths and limitations
1	Acharya et al. (33)	• About 31.3% (3592/11481) participants had hypertension. • Among the hypertensive persons, 40.2% (1,444/3,592) were aware of their hypertension status. • Among these who were aware, 79.4% (1,146/1,444) were taking antihypertensive medicine. • However, the overall proportion of hypertensive patients taking medicine was 32.0% (1,146/3,592). • The BP was controlled among 46% (527/1444) of participants who were under medication.	• At least three measures were taken, from which the last two were recorded • Representativeness of the sampling is not mentioned • Geography, caste/ethnicity and age distribution of the participants are not described
2	Adhikari (34)	• Hypertension proportion (Camp) is 70% (1,301/1,857; Pre-HTN, HTN1 and HTN2) • Proportion of hypertension among in-patients is 13.7%	• The report is service coverage based rather than outcome based.
3	Agho et al. (35)	• Prevalence of prehypertension and hypertension was 26.9 and 17.2% respectively • Prehypertension was present in 30.4% (95%CI: 28.7, 32.2) of males and 24.3% (95% CI: 23.1, 25.6) of females, while hypertension was present in 20.4%, (95% CI 18.9, 22.0) of males and 14.8%.	• Nationally representative sample • Lack of temporal relationship with the risk factors and outcome • Limited risk factors considered for study • Post-earthquake situation which might interfere in psychosocial status interfering pre/HTN
4	Bhattarai et al. (36)	• CVDs contributed to 26.9% of total deaths and 12.8% of total DALYs • Ischemic heart disease and stroke were the predominant CVDs, contributing 16 4% (UI, 18.2–14.6) and 7.5% (UI 8.6–6.7) to total deaths and 7.5% (UI, 8.7–6.3) and 3.5% (UI, 4.0–3.0) of total DALYs, respectively.	• This is the first study to report on trends and distribution of the CVD burden at a national level in Nepal.
5	Bist et al. (37)	• The prevalence of raised blood pressure was 24% • The prevalence of raised blood sugar was 5.8% • The prevalence of raised cholesterol was 11% • The proportion of overweight was 24%	• Nationally representative sample
6	Brewis et al. (38)	• The proportion of raised BP is 25.4% among male and 19.3% in female	• Nationally representative sample • The relationship between de/hydration and BP and the direction of effect was measured
7	Aryal et al. (39)	• Proportion of hypertension (including under treatment) is 46.1 and 40.9% in urban and rural areas of Mustang, respectively; and 54.5 and 29.1% in urabn and rural areas of Humla • 30.9% of participants are prediabetic • 6.9% were diabetic • Prevalence of pre-diabetes was significantly higher in rural settings compared to urban settings ($p < 0.01$)	• Selection bias on sampling the survey used non-fasting blood samples for determination of a lipid profile which might interfere with the TG level.
8	Das Gupta et al. (40)	• Prevalence of hypertension was 21% (JNC7) and 44% (2017 ACC/AHA) • Prevalence of hypertension awareness was 37.1 and 43.9% in male and female, respectively. • Prevalence of antihypertensive medication was 47.5 and 50.1% in male and females, respectively • Prevalence of control of hypertension among the hypertensive was 53.5 and 49.2% among male and female, respectively.	• Blood pressure was measured three times in a single day for the study whereas JNC7 guideline recommends longitudinal measurement • Possibly misclassification bias • Robust association between the outcome variables and caste could not be obtained due to missing data
9	Das Gupta et al. (41)	• Overall prevalence of hypertension was 21.1%	• Three blood pressure measurements were recorded; all were done in a single visit within a 5-min interval
10	Datta and Humagain (42)	• Overall prevalence of prehypertensive and hypertensive women were 24.30% and 10.86 whose husband did not consume alcohol • 4.5% point gap in hypertension prevalence between wives of alcohol-consuming husbands and those of husbands not consuming alcohol • Likelihood of being hypertensive of Nepalese women was 12.8%	• Husband's alcohol consumption, as a factor of wives' hypertension status.
11	Dhungana et al. (43)	• The most prevalent comorbidity of hypertension and diabetes was 5.7% followed by HTN and COPD (4.8%), and HTN and CKD (4%)	• Secondary analysis of the data from the NCD survey 2018 • Chronic disease multimorbidity determinants and patterns study
12	Dhungana et al. (44)	• Prevalence of hypertension was 34.6% and diabetes 10.5% • 23.2% were not taking any antihypertensive medications among the aware hypertensive patients • 47.2% had controlled blood pressure level among the hypertensive medicine users • Among the Diabetics, only 59.3% were taking medication	• Cross-sectional study • Recall bias while recording dietary and medication history and assessing seven days physical activities
13	Ene-Iordache et al. (45)	• Prevalence of hypertension was 23% in the general population and 38% among high risk cohorts (Framingham risk score) • Prevalence of awareness being onset of disease is 59 and 71% for HTN and Diabetes (74 vs. 56% for HTN and 80 vs. 69% for Diabetes among high risk cohorts and general population) • Self-reported of onset of having disease is 11 and 4%, respectively among high risk cohorts and general population	• Individuals were screened based on convenience sampling, section bias on recruiting volunteers who will provide the testing
14	Ghimire et al. (46)	• Proportion of Hypertension was 57.2% • Proportion of Diabetes was 15%	• Nationally representative survey data • Age group of only 60–69 years, though >30% population is over 70 years, so generalizability is limited.
15	Ghimire et al. (47)	• Prevalence of raised blood pressure was 31.4%	• Self-reporting of disease status • Non-response rate-21.84%
16	Gyawali et al. (48)	• Mean cost case treatment was ranged from 484.8 to 445.9 USD per annum and per visit 5.1–16.2 USD • Prevalence of DM Type 2 ranges from 4.5% to as high as 19% in urban Nepal and rural prevalence ranging from 0.3 to 2.5%	• Costing study of DM • Limited to the selected database source • Urban-focused

(Continued)

TABLE 3 Continued

SN	References	Key findings	Strengths and limitations
17	Paudel et al. (49)	• Almost one-fourth (29.49%) of the adult population in the community suffered from hypertension. • Less than half (43.2%) of the hypertensive patients were aware of their conditions • 94.9% were taking antihypertensive medication and 68.4% had their blood pressure controlled	• This study is one of the few studies of Kaski district, Nepal to assess the awareness, treatment and control status of hypertensive patients. • This study limits its scope as the causal inferences could not be drawn. • This study is based on one district of Nepal and is not representative of the whole country due to the high ethnic, dietary, cultural, and geographical variation in the country
18	Peoples et al. (50)	**Quantitative finding** • Medicine cost was rated "too expensive" by 52 and 63% of rural and urban participants, respectively. • Perceived poor bedside manner was tied to negative perceptions of PHC quality, and vice versa. • Lack of resources and excessive barriers to care were mentioned by every interviewee. **Qualitative finding** • PHC use was high and satisfaction was low. • Most of the people were found unaware and didn't have any idea how to manage the disease when they were interviewed	• The study is claimed to be the first to examine perception and use of PHC services for Cardiometabolic diseases (CMDs) in Nepal. • The use of only two districts of Nepal as study sites, the use of cluster convenience sampling, and the limited sample size.
19	Rana et al. (51)	• Women were having lower prevalence of hypertension compared with men for both measured (16.0%, 95% CI: 14.8, 17.3 vs. 22.8%, 95% CI: 21.2, 24.5) and medical hypertension (21.7%, 95% CI: 20.4, 23.0 vs. 29.1%, 95% CI: 27.4, 30.8) and the differences were significant statistically in both measurements ($p < 0.001$). • People living in urban areas were having higher prevalence of hypertension compared with people living in rural areas for both measured (19.5%, 95% CI: 18.7, 20.4 vs. 17.9%; 95% CI: 16.9, 19.0) and medical (26.2%, 95% CI: 25.2, 27.1 vs. 22.7%; 95% CI: 21.6, 23.8) hypertension and the differences were significant statistically ($p < 0.001$) only for medical hypertension. • There was an overall 21% increase in the prevalence of hypertension, with the highest increase in the male population (23%)	• Assessed the association between SES and hypertension according to standard hypertension JNC7 guideline and a new guideline recommended by the ACC/AHA 2017. • The study could not assess the causality of the associations between Socio Economic Status and hypertension due to the cross-sectional nature of the data
20	Rai et al. (52)	• Hypertension was the common systemic disease associated in 40.8% of the cases, followed by diabetes in 32.5% and combined diabetes and hypertension in 20.2%. • Wealthy urban population in Nepal had higher prevalence, awareness, treatment and control than the poorer and poorest population. • The odds of being hypertensive was higher in men compared to women 1.96 (1.59–2.44) for Nepal)	• Recorded data was analyzed for HTN and DM, of the eye patients visiting a tertiary eye care center • Ocular co-morbidities have not been included, so a certain proportion might have been missed
21	Rauniyar et al. (31)	• Prevalence of hypertension in Nepal was 19.6%. • Less than one-third (20.2%) of the hypertensive population received treatment and 10.4% among them had their blood pressure controlled. • The odds of being hypertensive was higher in men compared to women1.96 (1.59–2.44). • Prevalence of hypertension was 7.1 (2.9–11.4) percentage points higher in affluent populations compared to the disadvantaged ones in Nepal.	• Provides detailed information on existing inequalities in prevalence and management of hypertension • The study cannot be generalized to population aged 50 years and above
22	Sainju et al. (53)	• Pre-hypertension and hypertension were seen in 11.02 and 30.17% of the study population, respectively • Almost three-fifths of the obese participants were hypertensive	• Sample is not nationally representative • Single episode of measurement of blood pressure (three readings) was taken, which may not be sufficient to diagnose hypertension in the population. • There could be an error due to observer variation in hearing the Koratkoff sound in crowed places
23	Saito et al. (54)	• Prevalence of hypertension (36.7%) • Prevalence of diabetes (14.4%)	• Self-reported assessment of illness may be biased • Face-to-face interview (only by asking) may not suffice to assess all the NCD risk factors • Data was collected in winter season, which might have affected the prevalence
24	Paudel et al. (55)	• 9% had diabetes with the prevalence higher among males (12.7%) than females (6.9%) • Overweight and obesity, Waist Circumference >102 cm (males) or >88 cm (females), a triglyceride level ≥150 mg/dL and total 14 cholesterol ≥190 mg/dL were associated with Type 2 Diabetes Mellitus	• Measurement and modeling of multiple behavioral, socio-economic and biological risk factors assessed • STEP survey data of 2013 re-analyzed for 40–69 yrs age group
25	Gyawali et al. (56)	• Prevalence of type 2 diabetes 11.7% (95% CI: 10.4–13.1) • Prevalence of prediabetes 13.0% (95% CI: 11.8–14.5) • Nearly two-fifths (35%) unaware of their disease • Nearly 94% of those aware were receiving some kind of treatment such as insulin or oral anti-diabetic medications and counseling • Control rate was less than one quarter of those who were receiving treatment (21%)	• One of the few studies on the awareness, treatment and control of diabetes in Nepal through validated STEPS questionnaire and fasting blood glucose measurements according to the WHO recommendations • The use of self-reported physical activity measures that are subjected to recall bias and over-reporting could have increased the possibility of exposure misclassification
26	Shrestha et al. (57)	• The prevalence of T2DM, pre diabetes, and impaired glucose tolerance in Nepal was estimated to be 10, 19.4, and 11%, respectively. • Normal waist circumference, normal blood pressure and no history of T2DM in a family has 64.1, 62.1, and 67.3%, respectively	• Heterogeneity in the studies due to variation in the T2DM diagnostic criteria and different demographics of the population
27	Shrestha et al. (58)	• Prevalence of prediabetes and diabetes was 9.2% (95% CI 6.6–12.6%) and 8.5% (95% CI 6.9–10.4%), respectively. • 52.7% (95% CI 41.7–63.4%) were aware of their diabetes status. 45.3% (95%CI 31.6–59.8%) were taking antidiabetic medications.	• High heterogeneity between the reported diabetes prevalence across the included studies

(Continued)

TABLE 3 Continued

SN	References	Key findings	Strengths and limitations
		• Nearly one-third of those under antidiabetic treatment (36.7%; 95% CI 21.3–53.3%) had their blood glucose under control	
28	Shrestha et al. (59)	• Prevalence of hypertension and pre-pre hypertension was 40.67 and 36.77%, respectively • Age AOR for being hypertensive for males compared with females was 0.86 (95% CI 0.72–1.02) • Sex AOR for being hypertensive was 1.61 (95% CI 1.35–1.91) for the age group 55–69 compared with age group 40–54 years. • Participants with WC measures greater than the cut-off value were twice as likely to be hypertensive (2.02; 95%CI 1.66–2.45) than people with normal WC	• Waist to height ratio and waist circumference were also included for picking up obesity with higher cardiovascular risk despite normal body mass index • Underlying causes and co-morbidities are not included
29	Silvanus et al. (60)	• Prevalence of known diabetes (50/306) was an estimated 16.34% (95% CI: 12.62% to 20.90%) • 46.09% were classified as high risk, 44.53% as moderate risk and 9.38% as low risk for developing diabetes • The tabulated sensitivity (true positive rate) of the IDRS cut-off score ≥60 (high risk classification) was found to be 84.21% with a specificity (true negative rate) of 55.24% • The false positive rate and false negative rate was 44.76 and 15.79%, respectively. • The positive predictive value was 20.0% and negative predictive value was 96.34%	• Community-based study design to screen for undiagnosed diabetes, the step wise approach including the non-invasive tool and estimation of RCBG and the use of both FPG and the 2 h PG following a 75 g OGTT to identify diabetes and prediabetes • A community-based screening program can attract persons who have the health condition, those with a propensity to seek health care or who are more interested in their health which can introduce a selection bias
30	Silvanus et al. (61)	• Prevalence of undiagnosed diabetes was 4.32% (95% CI 1.75–8.70%) and that of prediabetes was 7.14% (95% CI 3.89–12.58%) • The overall prevalence of persons with "raised blood glucose" was 11.73% (95% CI 5.64–21.28%) • All of the persons with prediabetes ($n = 12$) had IGT	• Recognizing the use of glucometer and capillary sampling in low- and middle-income countries • Two glucometers were used during the screening camp, within glucometer variation was not studied
31	Tan et al. (62)	• Most individuals with hypertension could link hypertension to its causes, symptoms and complications • Some individuals with hypertension occasionally stopped medication due to forgetfulness, negligence, laziness, and affordability issues	• First qualitative study in Nepal involving a range of stakeholders to gather multidimensional insights into hypertension management • Qualitative design and small sample size limit the generalizability of the study findings
32	Tang et al. (63)	• The range of 8.2–12.1% and 4.3–9.1% missed and overidentified hypertensive, respectively found when only 1st measurement was taken. • The range of 4.9–6.4% and 2.0–4.4% missed and overidentified hypertensive, respectively, found when only 2nd measurement was taken but for this, all the participants needed to go through screening. • The range of 3.8–8.1% and 2.0–3.9% missed and overidentified hypertensive, respectively, found when 2nd measurement was taken only for those having BP ≥ 130/80 during 1st screening. The range (%) of the participants needed to screen in the conditional screening (BP ≥ 130/80) for 2nd time is only 33.8–59.8% • Hence, resource cost is reduced by 40.2–66.2% when conditional sequential screening is carried out	• Comparison of 1st, 2nd, and conditional 3rd screening was carried out so as to assess the difference in resources used • Survey data of USA is taken from 1999–2016 whereas findings from opportunistic screenings of May Measurement Month of 2017–18 for India and Nepal were used
33	Timilsina (64)	• Prevalence of DM among TB patients was 18.84%.	• Sample was taken purposively
34	Sharma et al. (65)	• The prevalence of diabetes, pre-diabetic and glucose intolerance among tuberculosis patient was 11.9, 17.2, and 17.8%, respectively. • Current alcohol consumer as the significant predictor of diabetes among the tuberculosis patient	• The Fasting Blood Sugar and 2-h Post-Prandial Blood Sugar were assessed by the glucose oxidase method • Facility-based DOTS center sample was taken
35	Yadav et al. (66)	• 56% were diagnosed as hypertensive; • 29% were pre-hypertensives; • 16.3% had 1st stage hypertension and 11% had 2nd stage hypertension	• The study sample was obtained from the tertiary level teaching hospital • Less generalizability at population
36	Hassan et al. (67)	• Among the total hypertensive participants, identified only in NDHS 2016 survey but not by professionals earlier, prevalence of diagnosed hypertension was - Total, 49.6%; - Province 1, 53%; Madhesh Province, 53.1%; Bagmati Province, 52.7%; Gandaki Province, 46.9%; Lumbini Province, 45.4%; Karnali Province, 39.8%; SudurPaschim Province, 41.9% • Mountain, 47.1%; Hill, 48.3%; Terai, 51.4% • Prevalence of undiagnosed hypertension was 50.4% • Proportion of hypertension awareness among the hypertensives was 49.6%. • Undiagnosed hypertension was disproportionately higher among lower socioeconomic status groups (Concentration Index, $C = -0.18$, $p < 0.001$).	• Nationally representative, cross-sectional data to determine the prevalence • Other behavioral and lifestyle factors potentially relevant to undiagnosed hypertension, for example, physical activity, dietary patterns and family history of hypertension, that were not explored in this study.
37	Kadaria and Aro (68)	• 52% were moderately active • 28% were highly active	• Facilitators and barriers physical activity were assessed • Self reporting and its recall bias on measure of physical activity
38	Karmacharya et al. (69)	• Proportion of hypertension awareness among the hypertensives was 44.7% • Prevalence of taking antihypertensive treatment was only 76.1% (among the known hypertensives and 33.2% among the total) • Prevalence of control of hypertension was 35.3% among the known hypertensive and 11.7% of the total	• Spectrum of awareness, treatment and control of hypertension • BP was taken in home setting and single day measurement cause false readings and affect the study • The targeted study was conducted at Dhulikhel which has teaching hopsital that could impact on level of awareness and control of HTN among the participants.
39	Khanal et al. (70)	• Proportion of participants controlling Systolic BP increased to 58.3% from 3.3% compared to only to 40% among the intervention vs. control group • Percentage of the controlled Diastolic BP increased by 30% after the intervention compared to only 20% on usual care (control)	• The study was study was conducted in one municipality and high number of female respondents thus limited generalization. • The blood pressure measured twice at 3-min interval in a single visit
40	Khanal et al. (71)	• Prevalence of hypertension was 38.9%2 • 53.4% were aware about their HTN status	• The study was conducted in one municipality and high number of female respondents thus limited generalization

(Continued)

TABLE 3 Continued

SN	References	Key findings	Strengths and limitations
		• 29% on treatment among the hypertensive, and • 8.2% had controlled blood pressure among the treated • Self-reported prevalence of Diabetes was 6.9%	• The blood pressure measured twice at 3-min interval in a single visit • Presence of diabetes was determined as reported by participants without blood sugar measurement
41	Kibria et al. (72)	• HTN prevalence, 44.2% (as per 2017 ACC/AHA) but only 21.2% (as per JNC 7 guideline) • HTN awareness proportion, 40.4% (as per 2017 ACC/AHA) but only 23.6% (as per JNC 7 guideline) • 20.4 vs. 9.8% (as per JNC vs. 2017 ACC/AHA category) of those who would have been considered hypertensive were taking antihypertensive medications • Among the hypertensives, about 9.7 and 7.2% had a controlled blood pressure level, respectively (as per JNC vs. 2017 ACC/AHA category)	• The survey data was nationally representative • Blood pressure of the participants was measured 3 times in a single day while both guidelines recommend the longitudinal measurement • Comparison and effectiveness of two methods of BP measurement and classification
42	Koirala et al. (73)	• Proportion of controlled BP among the hypertensives was 75%	• Sample size is low and generalizability is limited.
43	Koirala et al. (74)	• 20.7% of participants were hypertensive Proportion of Intermediate Hyperglycemia was 31.6 and 4.6% was of DM based on Hba1C measure	• Sample size is low and generalizability is limited due to single village taken for sampling • Fasting blood sugar was not taken for confirming DM diagnosis
44	Kushwaha and Kadel (75)	• Prevalence of diabetes mellitus was found as 4.38%.	• Glucometer with glucose sticks was used to measure the random blood sugar level which was not recommended in respect to fasting blood glucose with biochemistry method
45	Mehata et al. (76)	• The overall prevalence of MetS is 15 and 16% according to Adult Treatment Panel III (ATP III) and International Diabetes Federation (IDF) criteria, respectively • Triad of low HDL-C, abdominal obesity and high BP was the most prevalent (8.18%), followed by abdominal obesity, low HDL-C cholesterol and high triglycerides (8%)	• Provides the first nationally representative estimates on prevalence, disaggregated by sub-groups, and factors attributed to metabolic Syndrome among adult population of Nepal
46	Mehata et al. (77)	• Prevalence of hypertension was 18% (95% CI 16.7–19.2) • Among the total hypertensive individuals, only 38% were aware of their hypertensive status • 18% were taking antihypertensive medication • Half of the hypertensive participants on treatment (52%) had their blood pressure under control.	• Based on a large national sample consisting of both urban and rural populations in Nepal • Dietary habits, alcohol intake or physical activity as the major determinants of hypertension status could not be explored
47	Mishra et al. (78)	• Prevalence of hypertension was 19.5% (95% CI: 18.3–20.7) • Of total hypertensives, the prevalence of hypertension awareness, treatment and control was 40.0% (95% CI: 37.5–42.6), 20.2% (95% CI: 18.0–22.2) and 10.5% (95% CI: 8.8–12.2), respectively	• First nationwide study to examine socio-economic disparities in hypertension burden and cascade of services
48	Mizuno et al. (79)	• Hypertension was 23% • The urinary lead concentrations were positively associated with both systolic and diastolic blood pressure. • Urinary selenium concentrations were negatively associated with both systolic and diastolic blood pressure.	• Wide variation of data (17 communities with various characteristics across four Asian countries) • Association of heavy metals (Pb and Se) were associated with hypertension
49	Bista et al. (80)	• 22.2% were overweight and obese • 11.5% of the participants were hypertensive. • Around 6% of participants had co-occurrence of two NCDs risk factors.	• Adjusted prevalence ratio (APR) was calculated from multiple poisson regression method • Secondary data analyzed for reproductive aged women
50	Neupane et al. (81)	• Low, medium, and high levels of knowledge about hypertension were 43, 24, and 31%, respectively • No significant differences were observed in the knowledge and attitudes related to hypertension in relation to demographic characteristics of FCHV. • A majority of FCHV agreed that smoking (69.8%), alcohol (77.8%), low physical activity (42.4%), high salt intake (65.4%), high fat intake (78.7%), and genetics (53.9%) are major risk factors for hypertension.	• The study was conducted only among FCHV based in 1 municipality in Nepal
51	Neupane et al. (82)	• HTN was 29.6%, $M = 55.4\%$; $F = 24.1$ • Pre-HTN was 20.6% • The mean systolic blood pressure at 1 year was significantly lower in the intervention group than in the control group for all cohorts: the difference was −2·28 mm Hg (95% CI −3·77 to −0·79, $p = 0·003$) for participants who were normotensive, −3·08 mm Hg (−5·58 to −0·59, $p = 0·015$) for participants who were prehypertensive, and −4·90 mm Hg (−7·78 to −2·00, $p = 0·001$) for participants who were hypertensive	• First cluster-randomized controlled trial to report systolic blood pressure among normotensive, prehypertensive, and hypertensive populations through an existing network of community health workers
52	Neupane et al. (83)	• The age and sex adjusted prevalence of hypertension was 28% • Among hypertensive participants, 46% were aware of their preexisting hypertension, 31% were on hypertensive medication, and 15% met BP control targets • Increasing age (1.07, 95% confidence interval: 1.06; 1.08), higher body mass index (OR: 1.09, 95% CI: 1.06; 1.12), men (OR: 1.63, 95% CI: 1.25; 2.14), harmful alcohol intake (Or: 2.46; 95% CI: 1.73; 3.51), family history of hypertension (OR: 1.42; 95% CI: 1.14; 1.76), and diabetes (OR: 2.08, 95% CI: 1.30; 3.33) were independently associated with hypertension	• High response rate, adequate representation of both sexes, utilizing average of two BP measurements preceded by a first disregarded measurement and detailed information on the history of hypertension, and pharmacological treatments.
53	Niraula et al. (84)	• Serum ADA levels (U/L) was significantly raised in Uncontrolled Diabetic patients (49.24 ± 16.89) compared to controlled population (35.74 ± 16.78) and healthy controls (10.55 ± 2.20), p-value < 0.001 • A significant positive correlation was obtained between Serum ADA and HbA1c, Fasting Plasma Glucose and Post-prandial Glucose respectively	• Serum Adenosine deaminase (ADA) level can also be used as a biomarker in predicting glycemic control in diabetic patients • ADA level also indicates the presence of other diseases • Hospital based comparative cross-sectional study • Convenient sampling

TABLE 4 Disease-wise summary prevalence/proportion (range*) of included studies.

SN	Study characteristics and demographics	DM		HTN	
		Min-Max	Ref	Min-Max	Ref
1	**Samples**				
	Primary studies	114–9,177	[55, 76]	123–11,486	[33, 82]
	Secondary analysis	526–21,066	[45, 46]	526–21,066	[45, 46]
2	Total (M; F)	114–14,857 (58–6,245; 56–8,612)			
3	**Study types**				
	Total ($n = 53$)$^{\$}$	21		44	
	Primary study ($n = 31$)	15		22	
	Secondary analysis ($n = 21$)	4		20	
	Review studies ($n = 3$)	1		2	
	Interventional studies ($n = 3$)	0		3	
	Qualitative ($n = 1$)	0		1	
	Mixed-methods studies ($n = 2$)	2		1	
4	**Sex-wise distribution**				
	Male	12.7	[56]	22.8–55.4	[51, 83]
	Female	6.9	[56]	10.9–43.9	[40, 42]
5	**Age**				
	General (all)	4.4–18.8	[65, 75]	17.2–70.0	[34, 35]
	15–49 yrs	-		10.9–19.6	[42, 53]
	15–69 yrs	9.0	[56]	8.2–31.4	[47, 77]
	18 yrs+	4.6–11.7	[57, 75]	5.7–54.5	[39, 43]
	18–70 yrs	-		34.6	[44]
	40–69 yrs	-		40.6	[60]
	50 yrs+	16.3	[61]	-	
	60–69 yrs	15.0	[46]	57.2	[46]
6	**Geographic distribution**				
	National (more than 1 province)	5.7–15.0	[43, 46]	5.7–70.0	[34, 43]
	Province 1	11.9	[66]	56.0	[67]
	Madhesh	-		53.1$^{\#}$	[68]
	Bagmati	4.4–32.5	[52, 76]	30.2–40.8	[52, 54]
	Gandaki	4.6–11.7	[57, 75]	20.7–46.1	[39, 75]
	Lumbini	-		45.4$^{\#}$	[68]
	Karnali	6.9		29.1–54.5	[39]
	Sudur-Paschim	18.8	[39]	41.9$^{\#}$	[68]
	Urban	-	[65]	46.1–54.5	[39]
	Rural	-		29.1–40.9	[39]
7	**Ecological belts**				
	Mountain	4.6–6.9	[39, 75]	20.7–54.5	[39, 75]
	Hill	4.4–16.3	[61, 76]	28.0–56.0	[67, 84]
	Terai	11.9–18.8	[65, 66]	51.4$^{\#}$	[68]
8	**Participants**				
	Healthy	4.4–16.3	[61, 76]	18.0–36.7	[55, 78]
	Clinical	18.8	[65]	13.7–56.0	[34, 67]
	Both	5.7–15.0	[43, 46]	5.7–70.0	[34, 43]
9	**Types of study/screening settings**				
	Survey/evidence synthesis	5.7–14.4	[43, 55]	5.7–57.2	[43, 46]

(Continued)

TABLE 4 Continued

SN	Study characteristics and demographics	DM		HTN	
		Min-Max	Ref	Min-Max	Ref
	Ambulatory	11.9–18.8	[65, 66]	40.6–40.8	[52, 60]
	Opportunistic	-		31.3	[33]
	Camp	4.4	[76]	70.0	[34]
10	**Disease awareness and control**				
	Awareness	35.0–80.0	[45, 57]	23.6–74	[73, 45]
	On medication (among aware)	45.3–94.0	[57, 59]	9.8–94.9	[49, 73]
	BP/Sugar control (by medicine)	21.0–36.7	[57, 59]	8.2–52.0	[72, 78]
	BP/Sugar control (overall)	-		9.7–68.4	[49, 73]
	On medication (overall)	59.3	[44]	18.0–66.8	[44, 78]
11	**Pre-and undiagnosed proportions**				
	Pre-diabetes/pre-HTN	9.2–31.6	[59, 75]	11.2–36.8	[54, 60]
	Undiagnosed Pre-DM/HTN	7.1	[62]		[68]
	Undiagnosed DM/HTN	4.3	[62]	50.4[#]	
12	**Co-morbid status**				
	HTN and DM	5.7–20.2	[43, 52]		
	HTN and COPD	4.8	[43]		
	HTN and CKD	4.0	[43]		

[*]In some variables, only single value could be extracted.
[$]Some studies were common for DM and HTN.
[#]Among the total hypertensive participants, identified only in NDHS 2016 survey but not by health professionals earlier, as diagnosed and undiagnosed.

both diseases ranged from 5.7 to 20.2%. Interestingly, pre-HTN and pre-DM were reported among about one-third of the participants, and importantly, for both DM and HTN, a minimum of one-fourth were unaware, and among those on medication, a maximum of only about half had their diseases under control (Table 4; Figure 2).

Validation and alternative use of the technology

The Indian Diabetes Risk Score (IDRS) is a simple tool that includes four statements to screen for diabetes and, with a cut-off score of 60, among the Nepalese population, revealed a sensitivity and a specificity of 84.2 and 55.2%, respectively, and hence could be a suitable alternative for diabetes and prediabetes screening (60). A hospital-based study revealed that measurement of serum Adenosine Deaminase (ADA), a biomarker, can be an alternative tool for glycaemic control and monitoring. It showed a significant correlation with HbA1c, fasting blood sugar (FBS) and post-prandial glucose (84). Similarly, a simple technological change in classification in the national guideline, changing the category of (130–140)/(80–90) mm of Hg as pre-HTN as defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) to HTN as newly defined by the American Heart Association/American College of Cardiology (AHA/ACC), can reduce cardiovascular and related health problems by early detection and thereby save more lives and money (40). Another application of sequential screening, BP ≥130/80 mm of Hg, if assessed a second time (without assessing all for a second time), would give almost the same result but reduce the cost (time, human resources) by 40–60% during the camp and other opportunistic screenings (63). Moreover, the relationship of heavy metals with BP indicates that we need to address the problems of NCD prevention and control from a different perspective. On the other hand, HTN and DM are both webbed with multiple risk factors. For example, the triad of HDL-C, abdominal obesity and HTN was found among nearly 1 in 10 (8.2%) persons (76), and 6% women of reproductive age had co-occurrence of two NCD risk factors. This implies that these problems the rather be addressed with multiple and complex interventions, along with some feasible policy interventions (Figure 2).

Cost, DALYs, and equity

The prevalence of HTN was found to be more than seven (7.1) times higher among the wealthy than among the poor (31) but undiagnosed HTN was found to be disproportionate (1.6 times higher) among those with lower

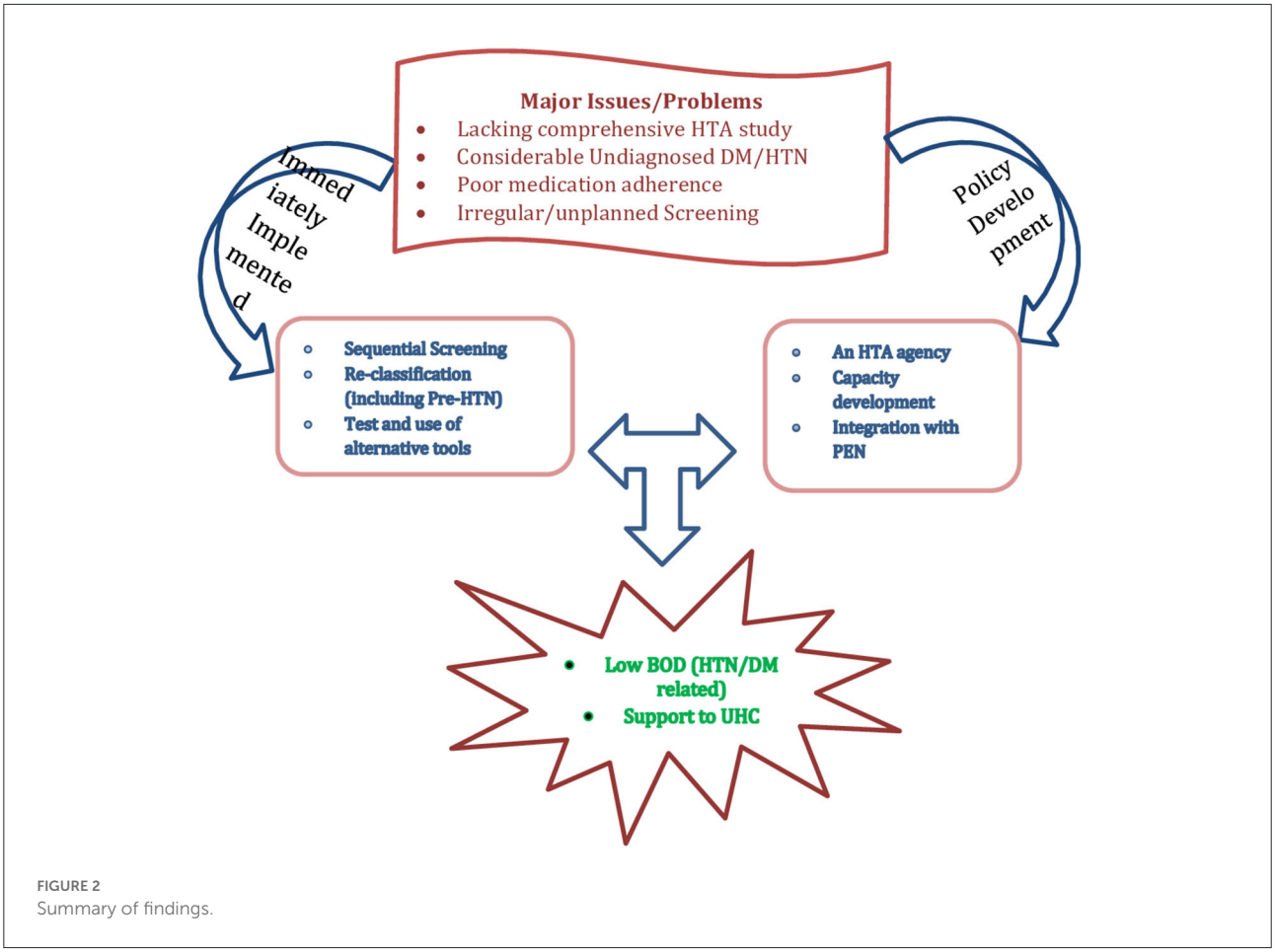

FIGURE 2
Summary of findings.

socioeconomic status ($C = -0.18$, p 0.001) (67). According to a qualitative finding, 52% of rural and 63% of urban people considered the medicine used to treat HTN and DM to be expensive (50). A review of costing studies showed that in DM, USD 445.9 (±27,535), 16.2 and 5.1 are needed per annum per patient, per prescription, and per visit per patient, respectively (48), thus, implicating medication non-adherence (Figure 2).

Awareness, medication adherence, and intervention efficacy

Nine out of every 10 people have moderate to high chances of developing DM (60), which indicates the importance of early interventions. HTN medication was missed due to forgetfulness, negligence, and unaffordability (62), which could be attributed to a lack of or poor HTN knowledge among community members (50) and the female community health volunteers (FCHVs) (81). However, when these cadres were trained and prepared as change agents, the intervention could reduce a mean blood pressure by 2.3–4.9 mm Hg and increase the proportion of BP control and knowledge of the community members (70, 82).

Discussion

Overall, the prevalence of high blood pressure was found to be as low as 5.7% (43) and as high as 70% (46) nationally, and up to 55% (39) in Karnali province and in urban areas. Similarly, DM was found to be between 5.7 (43) and 15% (46) nationwide, though it was as low as 6.9% (39) and as high as 32.5% (52) in Karnali and Bagmati provinces, respectively. Similarly, there is also a wide variation in DM (45–94%) and HTN (9–95%) awareness (49, 56, 58, 72), disease/disorder controlled by medicine (56, 58, 71, 77) in the population. This variation should be considered when planning and implementing the relevant programs for coverage and efficacy (Figure 2). A combined study of systematic review and expert consultation carried out in eight European countries found that the incorporation of additional social value judgments beyond clinical benefit assessment and economic evaluation could help further explain heterogeneity in coverage

recommendations and decision-making (85). Similarly, it would be wise to compare the cost in lieu of the yield and the diagnoses that the screening strategies give. In an ambulatory high-risk approach carried out in the Bhutan PEN evaluation study (19), a 10% of eligibility and around 23% of diagnosis for HTN and a 10% of eligibility and 26% of diagnosis for DM may be contrasted with a 13% of eligibility and 17% of diagnosis for HTN and a 19% of eligibility and 22% of diagnosis in an opportunistic high-risk screening approach carried out in Karnataka, India (20). In these two studies, number of diagnoses was higher in ambulatory high-risk approach but yield was higher in opportunistic high-risk approach.

Producing HTA capacity in a country like Nepal may run up against different problems at various stages, such as policy sensitization, development and implementation, expertise development, and overall management. A similar program carried out by the Health Intervention and Technology Assessment Program (HITAP) of Thailand in India, Colombia, Myanmar, the Philippines, and Vietnam revealed experiences suggesting that it is not only technical capacity, such as analytical techniques for conducting economic evaluation, but also management, coordination, and communication capacity should be strengthened (86). Inequality in HTN was observed to have up to 1.6 times higher prevalence among the poorest and underprivileged (31, 67). A combined study of documentary review and interviews carried out by Ciani et al. in Italy during the early stage of HTA development, argued that not only the central agency should be in place, but also a fully coordinated and harmonized multi-level structure of HTA was imperative (87). Then, the Italian National Healthcare System was one of the most decentralized systems since the devolution reform approved in 2001, and Nepal is more or less, at present, in a similar situation with devolution of power to the local levels with a 3-tier governing system.

Regarding the universal health coverage (UHC) and social health security program (SHSP) that are underway, we are adopting and scaling-up different benefit packages by assessing only a few to many, but not all components. The early results of Thai universal coverage in 2009–10 showed that HTA is helpful for informing coverage decisions for health benefit packages because it enhances the legitimacy of policy decisions by increasing the transparency, inclusiveness, and accountability of the process (88). The National Institute for Health Research HTA programme also suggests that synthesized evidence, rather than depending upon clinical trials, should be taken into account, for decision analysis and that the findings of a trial be linked to systematic reviews and meta-analyses (89).

Limitations

The included studies' principal limitations were costing comparisons of technologies in light of comparative validity and precision. Furthermore, there was a lack of ethical, ICER, quality of life, and willingness and capacity to pay for various technologies.

Conclusion

Overall, 53 studies, including some secondary analysis and the reviews, mainly reported the prevalence of DM of 4.4–18.8% and HTN of 17.2–70%. In addition to establishing an HTA national agency, some immediate actions and a systematic HTA of both diseases, covering a representative sample, is highly recommended before warranting.

Author contributions

CA, KSh, RD, and LA conceptualized the review, developed the search strategy, the data extraction grids, and edited. CA, LA, and BP curated data. CA, KSh, and KSu carried out the formal analysis. CA, BP, LA, and AT extracted the data. CA and KSh administered, supervised, and validated the project. CA, RD, LA, BP, KSu, AT, YA, and KSh wrote the draft. All authors reviewed the final manuscript and agreed for submission.

Conflict of interest

Author LA was employed by HERD International.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Machine learning for predicting acute hypotension: A systematic review

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An acute hypotensive episode (AHE) can lead to severe consequences and complications that threaten patients' lives within a short period of time. How to accurately and non-invasively predict AHE in advance has become a hot clinical topic that has attracted a lot of attention in the medical and engineering communities. In the last 20 years, with rapid advancements in machine learning methodology, this topic has been viewed from a different perspective. This review paper examines studies published from 2008 to 2021 that evaluated the performance of various machine learning algorithms developed to predict AHE. A total of 437 articles were found in four databases that were searched, and 35 full-text articles were included in this review. Fourteen machine learning algorithms were assessed in these 35 articles; the Support Vector Machine algorithm was studied in 12 articles, followed by Logistic Regression (six articles) and Artificial Neural Network (six articles). The accuracy of the algorithms ranged from 70 to 96%. The size of the study sample varied from small (12 subjects) to very large (3,825 subjects). Recommendations for future work are also discussed in this review.

KEYWORDS

digital health, hypotension, hypertension, intensive care unit, anesthesia, obstetric and gynecologic, emergency and critical care, low blood pressure

Introduction

It is widely accepted that hypotension is defined as absolute mean arterial pressure (MAP) below 60–65 mmHg (1). The incidence of hypotension is estimated to affect around half of the population worldwide (2, 3). While chronic low blood pressure without symptoms is usually not concerning, health problems may occur when blood pressure drops suddenly.

An acute hypotensive episodes (AHE) is defined as lasting for 30 min to 1 h or longer during which at least 90% of the MAP is at or below 60 mmHg. While this definition is widely used, it is not based on consensus or is not part of a medical guideline; rather, it is from the 10th PhysioNet/CinC Challenge (2009) (4). It has also been noted that intra-operative hypotension should be defined as a relative difference from baseline MAP (5, 6). AHE often happens in the intensive care unit (ICU) or operation rooms, commonly caused by sepsis, myocardial infarction, cardiac arrhythmia, pulmonary embolism, hemorrhage, dehydration, and anaphylaxis (4). Hypotension reduces the

oxygen supply, resulting in cell and tissue injury and loss of function. Therefore, AHE requires an immediate and appropriate intervention. Without this, patients are at an increased risk of irreversible organ damage and even death.

Currently, several scoring systems are used to predict critical medical events; however, these systems have not been specifically developed for AHE (7, 8). The symptoms of AHE may not be noticeable, and they might last only a few seconds. Hence, an adequately early prediction or warning system is desired to give nurses and physicians enough time to administer preventive care. This is especially important in an ICU setting, as often there is a shortage of nurses.

The importance of predicting AHE was first noted in the European AVERT-IT (Advanced Arterial Hypotension Adverse Event prediction through a Novel Bayesian Neural Network) project in 2008, which was funded by the European Commission to develop a novel bedside monitoring and alerting system to predict AHE (9). In 2009, in the 10th PhysioNet/CinC Challenge, using an automated method, the participants were expected to predict which patients in the challenge dataset (MIMIC II) would experience an AHE (4). Since the challenge, there has been continuous interest in this topic, and more researchers have studied it.

This paper reviews the relevant literature published between 2008 and 2021. Before 2008, there were very few studies in this area, and the methodologies were mainly statistical models rather than machine learning algorithms. Given the advances in machine learning in the last decade, we are re-visiting this topic with a focus on answering the following questions: (1) How well do machine learning algorithms perform in predicting AHE? and (2) What is the potential of these current ML algorithms in the clinical setting?

Methods

Study guidelines

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) (10). A prior review protocol was drafted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (11) for internal use amongst the research team but it was not externally published or registered prospectively.

Search strategy and study eligibility

The PubMed, IEEE database, Embase, and Google Scholar were searched for articles published between January 1, 2008, and January 1, 2022, for all English-language papers using the following keywords: (hypotensive or hypotension or low blood pressure) and (ECG or electrocardiogram or MIMIC) and (automatic detection or machine learning or artificial intelligence or deep learning or prediction) were used. The detailed strategy was discussed in Supplementary material. Gray literature was not included in this review in an attempt to only include peer-reviewed studies. This timeframe was chosen to reflect advances in artificial intelligence technologies and applications in medicine. The search for this review was completed in May 2022.

Inclusion and exclusion criteria

Articles were excluded (a) if the focus was not on hypotension, (b) if ECG data were not used, (c) if a machine learning algorithm was not used, (d) if the article was a review, a book chapter, or a thesis, and (e) if the article did not address the topic (predicting hypotension). One reviewer (AZ) conducted the literature search and two reviewers (AZ and ME) screened the titles, abstracts and full-texts independently for potentially eligible studies. Reference lists of eligible studies were also hand-searched but no additional studies were included on this basis.

Study selection and data extraction

One author (AZ) conducted the literature search, and two authors (AZ and ME) independently screened the titles and abstracts for potentially eligible studies. Each potential study for inclusion underwent full-text screening and was assessed to extract study-specific information and data. For each of the included articles, we extracted information from the below perspectives: the year the paper was published, author(s), number of subjects, gender split of the subjects, the signal used, sampling frequency, features extracted, machine learning algorithms evaluated in the study, training data window length, prediction window length, data source, evaluation metric(s) of the machine learning algorithms.

Results

Search results

As shown in Figure 1, a total of 485 records were identified with the above-mentioned keywords and year range in the four databases. After comparing the literature titles and authors, 48 duplicates were confirmed and removed, resulted in 437 search records. With the five exclusion criteria mentioned in the Methods section, 354 of the 437 records were excluded after reading the abstract: 40 studies did not use electrocardiogram (ECG) as one of the signals; 161 studies did not investigate hypotension; 63 studies did not aim for blood pressure

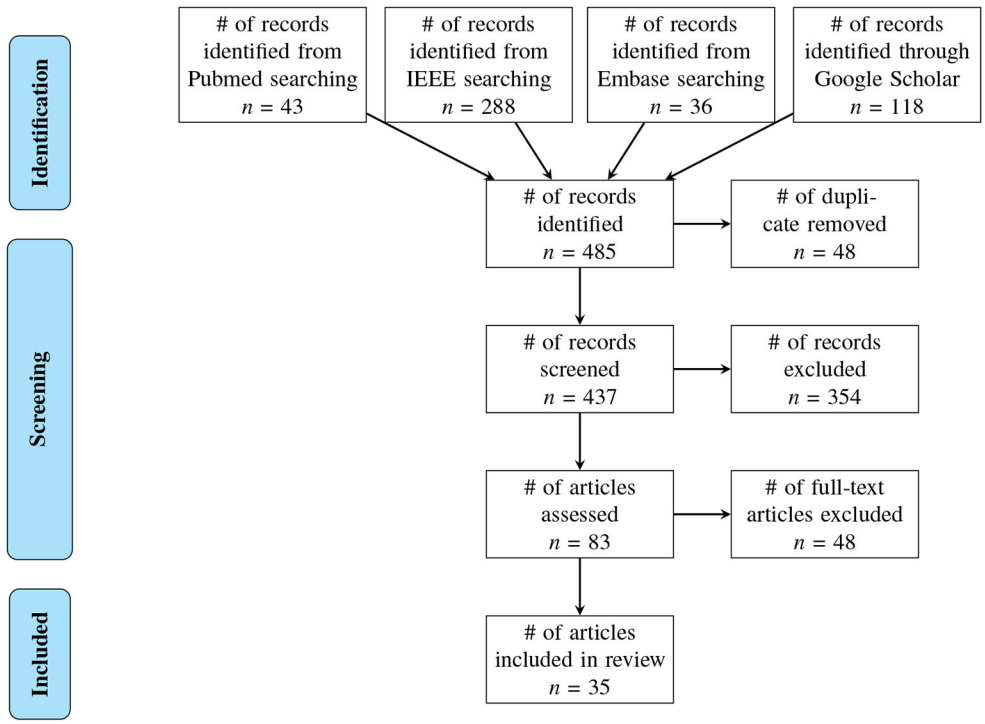

FIGURE 1
Flow chart of the methodology used to screen the articles. Thirty-five articles published between 2008 and 2021 were included in the review.

prediction; 89 were a review article or chapter in a book or a thesis; fiver were excluded because they were either not written in English or the full text was unavailable.

The full text was assessed in 83 articles. Of those, 48 articles were further excluded: 11 studies did not use machine learning as a forecasting method; 16 studies focused on blood pressure estimation rather than prediction; six studies forecasted blood pressure in general but not as a way to predict AHE; six studies used blood pressure to forecast other diseases; three studies aimed to determine which feature has the greatest predictive power, rather than to assess an algorithm; one study used an animal model, one focused on developing a new sensor, one aimed to detect artifacts, and one focused on photoplethysmography rather than ECG. Ultimately, 35 articles were included in this systematic review.

Characteristics of included reviews

We read and summarized the included articles based on (a) the year in which the article was published, (b) how many subjects were included in the study and the gender info, (c) what signal(s) was/were used, and the sampling frequency used to obtain the signal, (d) what features were extracted, (e) what machine learning algorithm(s) was/were evaluated in the study, (f) the evaluation metrics of the machine learning algorithm, (g) the duration of the observation window and prediction window, and (h) what data source the authors referred to, as shown in Table 1.

Overall, as shown in Figure 2, the articles were published during the years of the search range; most of the articles were published in 2010 ($n = 5$), followed by 2009, 2016, 2017, 2021 ($n = 4$, each). In 2019 and 2020, three articles were published each year. In 2011, 2013, and 2014, only two papers were published on this topic. In 2015 and 2018, only one article was published each year.

Results of studies

Most of the studies (37%, 13 out of 35) were large-scaled (1,110–4,000 patients were included). However, small-sized studies were also common: seven studies included 60–100 patients, six studies included 12–50 patients, and five studies included 110–500 patients. Medium-sized studies were relatively rare; only three studies had 510–1,000 patients. Of the 35 articles, 31 did not report the gender of the subjects; of those that did report on gender, the percentage of females was 40% ($n = 2$), 44.8% ($n = 1$), and 52.5% ($n = 1$). More than half of the articles ($n = 18$) used the arterial blood pressure (ABP) signal

TABLE 1 Overview of studies included in the systematic review.

References	Subject	Gender split	Signal	Samp Freq	Feature	ML algorithm	Training window	Predicted length	Data source	Evaluation metric
Zhang et al. (12)	1,055	$F = 425$	ABP	N/R	Max, min, avg, median, STD, skewness, kurtosis, upper quartile, avg absolute deviation, range, variance	• LR • AdaBoost • SVM • RF • XGBoost • Gradient boosting • Ensemble	5 h	60 min	MIMIC II (13)	Accuracy(%) • LR = 77.8 • AdaBoost = 82.0 • SVM = 80.1 • RF = 81.0 • XGB = 80.4 • GB = 81.0 • Ensemble = 82.2
Ribeiro et al. (14)	3,825	N/R	HR, RR, SpO2, SBP, DBP, MAP time series, PP, CO	N/R	Interquartile range, max, min, mean, median, skewness, kurtosis, linear slope, SD, variance, wavelet energy, cross-correlations between signals	Layered Learning (LL), the adopted classifier in each layer was a Light Gradient Boosting Machine	60 min	60 min	MIMIC III (15)	Accuracy (%) = 75.9 ± 4.2
Tang et al. (16)	30	N/R	Patient's NE infusion rate per unit weight, ECG, ABP	125 Hz	HR, PP, KR	• Physiology based approach (our method) • RRLS • IIR filter • ARMAX	1.3–6.67 h	3.33–20 min	Inter-mountain Medical Center, MIMIC-III (15)	Mins to 5 mmHg RMSE • Our method = 11.5 • RRLS = 9.5 • IIR = 8 • ARMAX <3
Lee et al. (17)	3,301	$F = 1,479$	• Invasive: AP+ECG +PPG+EtCO2 vs. AP • Non invasive: ECG+ PPG+EtCO2 vs. PPG	100 Hz	N/R	DL consisted of seven convolutional layers	30 s	5, 10, 15 min	VitalDB database (18)	AUROC(%) • Invasive: 89.7 vs. 89.1 • Non invasive: 76.2 vs. 69.4

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TABLE 1 Continued

References	Subject	Gender split	Signal	Samp Freq	Feature	ML algorithm	Training window	Predicted length	Data source	Evaluation metric
Moghadam et al. (19)	1,000	$F = 396$	ABP, HR, SBP, DBP, Resp, SpO2; PP, MAP, CO, MAP2HR, RR	N/R	33 scalar feature	• LR • SVM • KNN • Decision tree • Discriminant analysis • Naive Bayes • Ensemble	5 min	30 min	MIMIC III (15)	Accuracy(%) • LR = 95 • SVM = 94 • KNN = 92 • DT = 93 • DA = 93 • NB = 88 • Ensemble = 93
Lee et al. (20)	282	$F = 148$	Non invasive BP, HR, Mechanical Ventilation data, Bispectral index	N/R	Min, max, mean, std. Experiment performed 3-fold: 27, 56, 67 features then sum and dim reduction to get 98, 45, 20, 29. Best performance are 56 for 1st experiment and 20 for 2nd experiment	• RF • Xgboost • CNN	4–1 min before intubation	1 min	Soonchunhyang University Bucheon Hospital database	Accuracy (%) Raw feature vs. plus statistics features: • RF =70.3 vs. 74.9 • CNN = 72.6 vs. 69.0 • Xgboost = 64.6
Moghadam et al. (21)	1,000	N/R	ABP,HR,SBP, DBP, Resp, SpO2; PP, MAP, CO, MAP2HR, RR	N/R	33 scalar features. PCA optimize the feature set and resulted into 11 combined features	• LR • SVM • KNN • DT • Discriminant analysis • Naive Bayes • Ensemble	5 min	30 min	MIMIC III (15)	Accuracy(%) • LR = 95 • SVM = 94 • KNN = 92 • DT = 93 • DA = 93 • NB = 88 • Ensemble = 93
Xiao et al. (22)	2,866	N/R	ABP	N/R	decompose MAP with SW and ensemble EMD, then a 3-layer auto encoder to get 50 outputs	Multiple gene expression programming classier	2 h	60 min	MIMIC II (13)	Voting combination strategy vs. 10-fold cross validation (%) • Accuracy = 85.7 vs. 86.2 • Sensitivity = 86.4 vs. 86.8 • Specificity = 85.5 vs. 85.9

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TABLE 1 Continued

References	Subject	Gender split	Signal	Samp Freq	Feature	ML algorithm	Training window	Predicted length	Data source	Evaluation metric
Shin et al. (23)	207	N/R	MAP	N/R	• LR: mean, slope, SD of MAP of past 5, 10, 20, 30, 45, 60 min • AR: MAP values with t and preceding 5 min time-steps were computed as the median MAP	• Logistic regression (LR) • Auto-regressive model (AR)	60 min	30 min	MIMIC II ("Hospital 1") (13), Mass General Hospital ("Hospital 2")	• LR predicted on average 7.0 min before onset (Hospital 1) and 2.5 min before (Hospital 2) • AR predicted 10.5 and 2.0 min before
Chan et al. (24)	538	N/R	MAP, HR, SPO2	N/R	N/R	Long Short-Term Memory, three layers each with 100 units	10–60 min	10–60 min	Kingston General Hospital	• Accuracy(%) = 80 • AUC(%) = 87
Angelotti et al. (25)	86	N/R	ABP and ECG containing at least one ECG lead	N/R	SBP statistical moments; LF, HF, VLF spectral powers (for both RR and SBP); LF/HF (for both RR and SBP); Baroreflex amplitude; Baroreflex frequency	• 4 classification trees • 6 SVM • 6 KNN • LR	20 min	10 min	MIMIC III (15)	AUC(%) with vs. w/o BRFX: • Trees = 67 vs. 63 • SVM = 68 vs. 62 • KNN = 64 vs. 57 • LR = 62 vs. 54
Pathinaru-pothi et al. (26)	30	N/R	MAP	N/R	Use MAP severity quantizer, Consensus motif extractor, SVM based prediction engine for feature extraction	SVM	15 min	2.75 h	MIMIC II (13)	F1 score (%) = 82
Kim et al. (27)	2,291	N/R	MAP	N/R	N/R	Collision Frequency Locality Sensitive Hashing	5 h	60 min	MIMIC II (13)	Accuracy (%) in the range (93, 96)
Hamano et al. (28)	100	N/R	MAP, EtCO2, MAC, HR, SpO2, and body temperature	N/R	Each variable is mapped *via* the similarity-based approach, and trial and error to get 6,000 combinations	Spiking neural networks	15 min	5 min	OR of a tertiary hospital, Auckland NZ	37.6% of the experiments had an SNR above 0, which means better prediction than the naive method

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TABLE 1 Continued

References	Subject	Gender split	Signal	Samp Freq	Feature	ML algorithm	Training window	Predicted length	Data source	Evaluation metric
Jiang et al. (29)	2,866	N/R	MAP	1 Hz	55 feature incl peak, mode, skewness, kurtosis, and Shannon entropy from original time series, first 9 IMFs and last IMF	Multi GP	2 h	60 min	MIMIC II (13)	Accuracy (%) = 82.9 in the training set and 79.9 in the testing set
Ghosh et al. (30)	50	N/R	MAP	N/R	A gap-constrained sequential contrast pattern P is required (1) Positive Support: countP (D+, g) >= alpha (2) Negative Support: countP (D-, g) <= delta	Sequential pattern mining	30, 60 min	60, 120 min	MIMIC II (13)	Accuracy (%) single mode performance with 10 symbols vs. multi mode performance with 15 symbols: • 30 min = 82.3 vs. 81.3 • 60 min = 83.6 vs. 80.9
Ghosh et al. (31)	528	N/R	MAP	N/R	Utilize sequential contrast patterns as features to build classification models	SVM	60, 90 min	30, 60 min	MIMIC II (13)	Accuracy (%) = 85.8
Kim et al. (32)	2,291	N/R	MAP	N/R	N/R	LSH with two variants, the bit sampling based (L1LSH), the random projection based (E2LSH)	5 h	60 min	MIMIC II (13)	Accuracy (%) • L1LSH >95 • E2LSH >90
Jiang et al. (33)	2,866	N/R	MAP	1 Hz	EMD to decompose MAP into 77 IMFs. Statistical features: min, mean, max, median, variance, max instantaneous freq, HF/LF energy ration	• Multi GP • SVM	2 h	60 min	MIMIC II (13)	Accuracy (%) • MGP = 79.1 in training set and 78.0 in testing set • SVM = 76.2 and 75.5
Fan et al. (34)	1,599	N/R	ABP	125 Hz	EMD to extract 77 features then group to 30. Extracted features: min,mean,max, median,variance. Calculated features: max instantaneous freq, HF/LF. Also, the 12th percentile, skewness, kurtosis, mode of the last IMF	RF based on GP	30 min	N/R	MIMIC II (13)	Accuracy (%) = 77.6

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TABLE 1 Continued

References	Subject	Gender split	Signal	Samp Freq	Feature	ML algorithm	Training window	Predicted length	Data source	Evaluation metric
Kim et al. (35)	2,291	N/R	ABP	125 Hz	The first and second differences, 20-min variance and slope	• Dynamic Bayesian network • KNN	30 min	30, 60 min	MIMIC II(13)	Accuracy (%) • DBN = 80 • KNN = 82
Jiang et al. (36)	110	N/R	MAP	N/R	EMD was used to calculate MAP time series and BW of the AM, FM, power of IMF	GP	2 h	60 min	MIMIC II (13)	Accuracy (%) = 83.4 in the training set and 80.6 in the testing set
Zhang et al. (37)	12	N/R	MAP, HR, SBP, and DBP	N/R	MAP, HR, SBP, and DBP	ANN with one hidden layer	30 min	60 min	MIMIC II (13)	Median Absolute Difference between the predicted and actual HI was 0.070, ranged from 0.012 to 0.175
Sun et al. (38)	2,863	N/R	MAP	1 Hz	The 2 cluster centers, x1Mean and x2Mean, the 2 cluster ratios, x1Ratio and x2Ratio, the average of 15 min MAP signal before T0	SVM	60 min	60 min	MIMIC II (13)	• Accuracy = 81.2% • Sensitivity = 83.2% • Specificity = 80.4%
Janghorbani et al. (39)	95	N/R	HR, SAP, DAP, MAP	N/R	• LR: 10% DAP, mean MAP, max ECO; • LR+GA: same as LR, 95% ECO, skewness dHR, mean ECO slope, 5% ECO slope, mean MAP slope, mean DAP slope; • SVM+GA: HR/SAP IPR 10-5%, 50% HR/MAP, 95% dHR, skewness dHR, mean MAP slope, 5% MAP slope, 5% SAP slope;	• LR • SVM	30 min	60 min	MIMIC II (13)	Accuracy (%) • LR = 80 • LR+GA = 86 • SVM+GA = 88
Rocha et al. (40)	311	N/R	MAP	125 Hz	N/R	Neural network multi-models	12 h	60 min	MIMIC II (13)	• Sensitivity = 82.8% • Specificity = 78.4%

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TABLE 1 Continued

References	Subject	Gender split	Signal	Samp Freq	Feature	ML algorithm	Training window	Predicted length	Data source	Evaluation metric
Sun et al. (41)	1,500	N/R	SBP, DBP, MAP, SpO2, HR	N/R	top-10 wavelet coefficients as the features	Locally Supervised Metric Learning (LSML)	60 min	60 min	MIMIC II (13)	Accuracy (%) = 85.51
Lee et al. (42)	1,357	N/R	HR, SBP, DBP, MAP	N/R	Mean, median, SD, variance, interquartile range, skewness, kurtosis, linear regression slope, and relative energies in different spectral bands. A total of 45 features, whose space dim was reduced *via* PCA to 15–16	Feed-forward, three-layer artificial neural networks (ANNs)	30 min	1–4 h	MIMIC II(13)	Accuracy (%) • 1 h = 87.3 ± 0.8 • 2 h = 84.2 ± 1.4 • 3 h = 83.5 ± 1.7 • 4 h = 81.0 ± 1.9
Afsar (43)	60	N/R	ABP	125 Hz	SBP and Area under SBP wave along with the 1st, 3rd, and 6th principle component averaged over beats in each 60 s interval	Linear support vector machine (LSVC)	1.5 h	60 min	MIMIC II (13)	Accuracy (%) • No Feature Reduction = 79.4 • Using GA Features = 93.7
Wang et al. (44)	70	N/R	MAP	N/R	db3 as wavelet mother function to decompose the MAP signal at three levels to get the LF coefficient cA3 and HF coefficients cD1, cD2, and cD3. Then extract median and maximum	SVM	60 min	60 min	MIMIC II (13)	Accuracy (%) = 90
Rocha et al. (45)	110	N/R	ABP	N/R	The filtered signals are down-sampled by 2 and the results are called approximation and detail coefficients	Feed-forward neural Networks with two hidden layers	2 h	60 min	MIMIC II (13)	• Sensitivity = 94.7% • Specificity= 93.6% • Accuracy = 94.0%
Fournier et al. (46)	60	N/R	ECG, PAP, ABP, central venous pressure, HR, RR, SpO2, CO, and alarms annotations	N/R	Use KL divergence to identify the most discriminative features	Nearest neighbors (NN)	30 min		MIMIC II (13)	Accuracy (%) = 80

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TABLE 1 Continued

References	Subject	Gender split	Signal	Samp Freq	Feature	ML algorithm	Training window	Predicted length	Data source	Evaluation metric
Jousset et al. (47)	50	N/R	MAP	N/R	N/R	SVM	2 h	60 min	MIMIC II (13)	Accuracy (%) = 75
Chiarugi et al. (48)	60	N/R	ECG,ABP	125 Hz	HR, SBP, mean ABP (ABPM), DBP, MAP	Decision tree	10 h	2 h	MIMIC II (13)	Accuracy (%) 91.7 in the training set and 75 on test set
Henriques et al. (49)	50	N/R	ABP	N/R	N/R	Generalized regression neural network	6 h	60 min	MIMIC II (13)	Accuracy (%) 100 for test set A, 92.5 for test set B

Overview of the included papers in this study. STD/SD, standard deviation; LR, logistic regression; SVM, support vector machine; RF, random forest; ABP, arterial blood pressure; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; CO, cardiac output; NE, norepinephrine; KNN, K-nearest neighbors; SW, sliding window; EMD, empirical mode decomposition; GP, genetic programming; IMF, intrinsic mode functions; GA, genetic algorithm.

to focus on MAP, while some (n = 10) used more than three data sources. A few studies (n = 7) used ABP+ECG as the signal inputs. The majority of the articles (n = 25) did not mention what sampling frequency was used to acquire the signals. Of those that did report on this factor, 125 Hz was most frequently used (n = 6), followed by 1 Hz (n = 3) and 100 Hz (n = 1). Some (n = 8) of the 35 articles did not mention the features extracted because they simply used the raw data. Five articles described the methodology used to extract the features, but did not mention the exact number of features. Seven articles described the methodology and provided the final number of features, but they did not mention what the features were. Fifteen articles provided a list of the features that were extracted.

Statistics of the raw signal (e.g., maximum, minimum, mean) were the most common features extracted; this was adopted by 13 out of the 27 studies that described the methodology to extract the features, followed by clinical equations that were calculated based on the raw signal (n = 7), Empirical Mode Decomposition (n = 5), wavelet transform (n =3), and contrast sequential pattern and sliding window (n = 2 each). Only five of the 27 studies also conducted feature reduction, and Principal Component Analysis was the only methodology used by more than one study (n = 2).

Most of the studies (n = 24) only investigated one machine learning algorithm. A few of the studies (n = 6) evaluated three to seven machine learning algorithms and a few (n = 5) compared two machine learning algorithms. Of the type of machine learning algorithms used, Support Vector Machine (SVM) was the most studied (n = 12), followed by Logistic Regression (LR) and Artificial Neural Network (ANN) (n = 6 each). Other common machine learning algorithms include Nearest Neighbors (KNN) (n = 5), Genetic Programming (GP) (n = 4), Random Forest (RF), Gradient Boosting Machine, Decision Tree, Naive Bayes (NB), or Dynamic Bayesian Network (n = 3, each), and Locality Sensitive Hashing (LSH) (n = 2). The least examined algorithms were Deep Learning, Spiking Neural Network, Sequential Pattern Mining, and Long-Short-Term Memory (n = 1, each).

Most of the articles (n = 27) reported accuracy as the evaluation metric for the machine learning algorithm(s) that were studied. Eight other articles had their own way of measuring performance without assessing accuracy; those methods included F1 score, area under the curve (AUC), sensitivity (SE), and specificity (SP), prediction time, and the absolute difference between the prediction and the actual hypotension index.

The length of the prediction window depends on the time the AHE is expected to happen. Among the 35 articles, most of the studies (n = 30) focused on predicting AHE in the ICU, where the most common prediction window was 60 min prior to the onset of the event (n = 21), followed by 30 min (n = 4), 120 min (n = 2), or 165 and 10 min (n = 1, each). Some articles looked at a time range, for example 10–60 min or 1–4 h (n = 1,

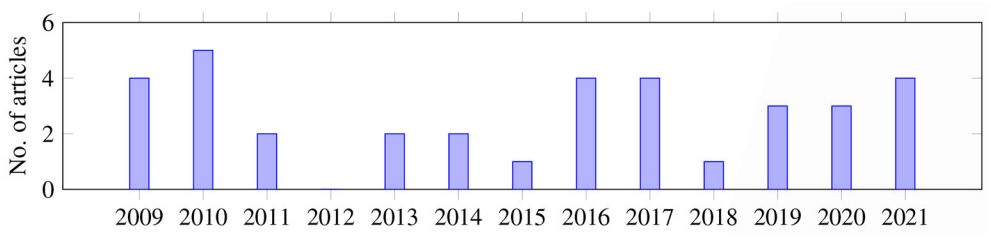

FIGURE 2
Number of publications by year.

each). Two studies did not report prediction window, assuming that the prediction window occurred right after the observation window.

A second type of prediction looked at intra-operative AHE; but only three studies focused on this area. Therefore, the prediction window is very short, either 1 min ($n = 1$), 5 min ($n = 1$) or 5, 10, or 15 min ($n = 1$), because intra-operative AHE occurs during anesthesia and only after intubation. The last type of study checked AHE that occurred during medication against septic shock. Data from patients given vasopressor infusion ($n = 1$) or norepinephrine infusion ($n = 1$) were studied to predict AHE. The prediction window for this type of forecast was 30 min ($n = 1$) or 3–20 min ($n = 1$) before the onset of the AHE.

Similarly, the observation window depends on whether the AHE is post-operation, intra-operative, or occurs when taking medication. For the first type of AHE, the observation window values, ranging from most common to least common, are 30 min ($n = 7$), 60 min ($n = 6$), 2 h ($n = 6$), 5 h ($n = 3$), 5 min ($n = 2$), 90 min ($n = 2$), 15 min ($n = 1$), 20 min ($n = 1$), 10 h ($n = 1$), 12 h ($n = 1$), 6 h ($n = 1$), or 10–60 min ($n = 1$). For intra-operative AHE prediction, the observation windows are 1–4 min before intubation, 30 s and 15 min ($n = 1$, each). For the AHE prediction during medication, the observation window is either 60 min or 1.3–6.67 h ($n = 1$, each).

The MIMIC-II database ($n = 26$) was the most frequently used data source, followed by the MIMIC-III database ($n = 4$), or a hospital database that is not public ($n = 3$). The Vital DB was rarely used ($n = 1$); it is a public database. One study used both the MIMIC-II database and a hospital database.

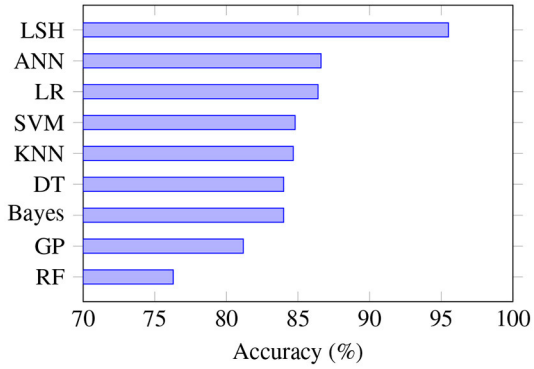

FIGURE 3
Prediction accuracy based on the type of algorithm. LSH is the most accurate algorithm, although only a few studies used it. SVM is the algorithm that was most often studied, and RF is the least accurate algorithm. RF, random forest; GP, genetic programming; DT, decision tree; KNN, K-nearest neighbors; SVM, support vector machine; LR, logistic regression; ANN, artificial neural network; LSH, locality sensitive hashing.

Discussion

The sample sizes of the studies varied greatly, ranging from a very small-scaled analysis with only a few dozen patients to very large-scaled studies that include several thousand people. Such a large variation in the number of subjects means that a comparison of different studies is not possible or could be strongly biased. Kim et al. (35) demonstrated that the performance of both of the chosen algorithms improved up to a point when the size of the training dataset increased. Patient information, including gender, age, comorbidity, medication, etc., was not reported in most of the reviewed studies, and these factors could have an impact on whether an AHE could occur.

The MIMIC database was mostly often used in the reviewed studies, probably due to its freely accessible nature. There might be data quality concerns regarding this database, for example, missing data. Moreover, the database is continuously updated, meaning that different studies, although all referring to the same database, might not have used the same data.

Since accuracy was the performance measure mostly often reported, we compared the performance of different machine learning algorithms based on this evaluation metric (Figure 3). LSH has the highest average accuracy; however, only two studies used this algorithm, and both had the same first author: Kim and O'Reilly (32). In contrast to some other algorithms that are better established and more widely studied, the performance of LSH needs to be further assessed in future studies. Kim and O'Reilly

TABLE 2 Summary of the prediction window.

Type	Time length (mins)	Number of study
Post-operative AHE	10	1
	30	4
	60	21
	120	2
	165	1
Intra-operative AHE	1	1
	5	2
	10	1
	15	1
AHE during medication	3–20	1
	30	1

Most studies focused on predicting post-operative AHE. A 60 min prediction time length was the most common. Fewer studies aimed to predict AHE during an operation or when taking medication.

(32) observed that LSH variants have very different robustness against data irregularities, and noted that further work is needed to develop an effective data representation that can be integrated into the general LSH framework.

AHE prediction

When researchers use the same data but different prediction window, as shown in Table 2, they will get different results even with the same machine learning algorithm. In our analysis, we found there is no standard prediction window consensus in this area yet. Thus, the choice of prediction window is mostly subjective. Zhang et al. (12) analyzed the impact of prediction gaps on six machine learning algorithms and concluded that some methodologies are less impacted than others when the prediction gaps change. Lee et al. (42) studied the gap window size ranging from 1 to 4 h and showed that, in general, the overall performance degrades as the gap size increases.

Regarding the training data time length, Lee et al. (20) studied the intra-operative AHE scenario and found 3 min of data performed better than 2 and 1 min. It is not difficult to imagine that a shorter prediction window and a longer training data time would provide better prediction accuracy, but a prediction window that is too short would be clinically less valuable to healthcare providers in terms of providing them with sufficient time to check the patient's situation and decide if an intervention is needed.

Summarization frequency may also impact the accuracy performance. In Pathinarupothi et al. (26) summarization was done once every 5 and 10 min; they found that a 10 min summarization can predict AHE with at least a 10% better F1 score, on average.

Feature extraction

Feature selection is the process of trying to fit the dataset. As mentioned in the previous three sub-sections, the missing patient background information, the diversity in the sample size and the prediction window, and the dynamics of the database can impact the data to be studied, while directly impacting the features to be selected.

However, the way in which the features were extracted also varied in the studies. While many studies described what methodology was used to extract the features (27 out of 35 articles), as shown in Figure 4 (left panel), eight articles did not provide details, mostly because raw data were applied and not processed. Kim et al. (35) found that the performance of the models utilizing derived features was worse than the performance of the models simply using the raw time series. In the study of Zhang et al. (12) feature reduction did not impact the accuracy or AUC performance of the selected machine learning algorithms. Afsar (43) reported that using dimensionality reduction effectively improved the prediction accuracy, and only five features were needed for the calculation. Note that the most used number of features is between 2 and 9, as shown in Figure 4 (right panel). Lee et al. (20) compared the use of vital records with the use of vital records plus electronic health records (EHR), and found that for the convolutional neural network model, EHR improves the accuracy by 0.39%; however, for other algorithms, such as RF, Xgboost, and deep neural network, the differences were negligible. Therefore, with these completely different findings, it is difficult to conclude which methodology is the best for extracting the features, what features are universally effective no matter what algorithms are applied, or how feature reduction impacts prediction performance.

When considering the different combinations of feature extractions and time windows, the situation could become very complicated. Ghosh et al. (30) studied different combinations of observation windows (30, 60 min), prediction windows (60, 120 min), and feature classification methods (single mode, multi-mode). They found that the prediction accuracy was the highest when both the observation window and prediction window times were 60 min for a single mode extraction mechanism, but the highest prediction accuracy occurred when the observation window was 30 min and the prediction window was 60 min for the multi-mode classification method.

Evaluation metrics

As shown in Figure 5, most of the studies ($n = 27$) reported accuracy as one of the evaluation metrics, followed by sensitivity ($n = 17$) and specificity ($n = 16$).

However, Ribeiro et al. (14) and Moghadam et al. (21) mentioned that the common ways of measuring performance (including accuracy, sensitivity, specificity, etc.) might not be

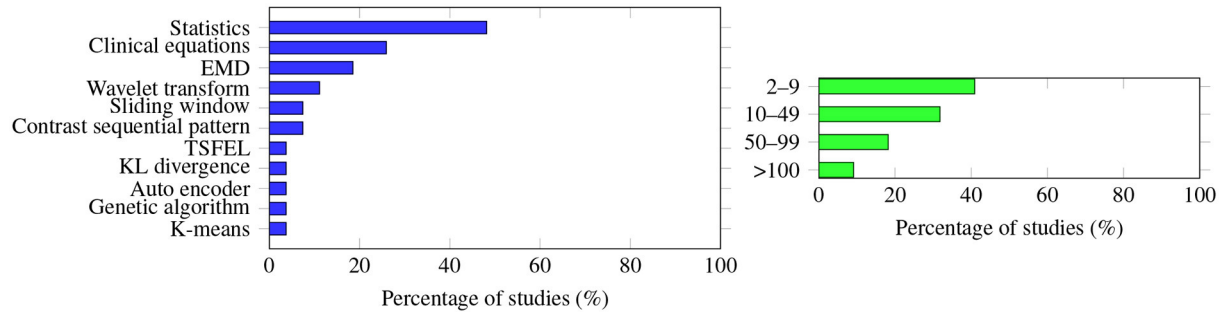

FIGURE 4
(Left) The methodology used to extract the features was very diverse; no single methodology accounts for more than half of the studies. Statistics (e.g., maximum, minimum, mean values of the raw data) are the extracted features most often studied, followed by clinical equations (apply raw data to the equation to calculate some of the derived information, e.g., cardiac output, MAP to HR ratio). **(Right)** Graph showing how many features were extracted to predict AHE. The number varies greatly among the studies, with a single feature extraction being the most common.

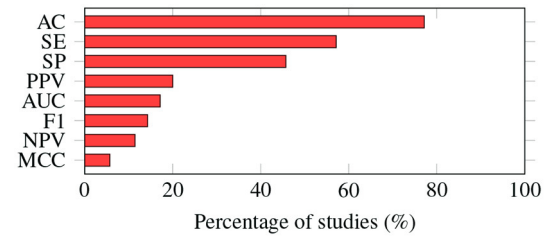

FIGURE 5
Evaluation metrics. The way in which the performance of machine learning algorithms is evaluated varies from study to study. Accuracy is the most common metric; it was adopted by almost 80% of the studies. AC, accuracy; SE, sensitivity; SP, specificity; PPV, positive predictive value; AUC, area under the ROC curve; F1, F1-score; NPV, negative predictive value; MCC, Matthews correlation coefficient.

sufficient to evaluate the performance of an algorithm in predicting AHE, as the data are highly skewed. In Moghadam et al. (21) the Naive Bayes (NB) algorithm raised 17,271 false positive alarms; true positive was only seen in 23,552 cases. However, the accuracy, sensitivity, and specificity of NB were 88, 85, and 88%, respectively. Based on those results, NB is a good machine learning algorithm candidate. However, in clinical practice, such a high false alarm rate means the healthcare providers would gradually lose confidence in the accuracy of the alarm and may not react when a true positive incident occurs. Both authors suggested using positive predictive value (PPV) or the F1 score to evaluate the machine learning algorithm to predict AHE, but PPV and F1 scores are missing in many of the current studies.

Deep learning models have generated great interest due to breakthroughs in fields like image analysis and speech recognition. However, we noticed that as regards to predicting AHE, deep learning algorithms were not so widely studied, and the performances were not better than other traditional methods (17, 24, 37). One possible explanation could be that deep learning models require a massive dataset for learning, which is usually lacking in the ICU setting; therefore, the interest in exploring deep learning's potential in predicting AHE is less prominent. Another reason might be that deep learning is known to be good at learning from features. At the same time, some research (35) has shown that for predicting AHE, raw data could sometimes be even better, probably because MAP itself is already a good indicator. Thus, a simpler but faster model could be sufficient to fulfill the expectation in AHE prediction.

Recommendation for future work

Summarizing the study findings, we recommend that researchers consider the following aspects when designing future studies:

1. Use a large number of subjects (>100) balanced in gender, age, and ethnicity. Moreover, the health status of the subjects needs to be stated, such as comorbidities.
2. Examine a consistent prediction window, precisely 30, 60 min, or both.
3. Elaborate on the feature selection phase, including the number of features extracted, how the feature extraction was done, and what the features are, since these aspects would impact the algorithm performances.
4. Report different evaluation metrics such as accuracy, sensitivity, specificity, Matthews correlation coefficient (MCC), and F1 score is essential for objective assessment.

Limitations

Due to time constraints, we searched only four databases. It is, therefore, possible that we missed some articles available

in other databases. The keyword choice might also lead to the omission of relevant research. Some studies checked applications of machine learning algorithms in multiple areas, which could include but are not limited to AHE prediction.

Conclusion

This review summarizes the application of machine learning algorithms for predicting AHE in articles published from 2008 to 2021. Most of the studies included in the review focused on the prediction of post-operative AHE 30 or 60 min before the onset utilizing ABP signals from the MIMIC database. The machine learning algorithm showed an accuracy between 76.3 and 96.5%. The machine learning algorithms perform well when evaluated with metrics like accuracy, sensitivity, and specificity. However, some researchers (14, 21) reported high false positives in some algorithms, when using metrics like PPV or F1 score. As many of the studies currently do not report MCC or F1 score, it is difficult to say if and which of the machine learning algorithms are ready to be used clinically.

By examining the metrics and machine learning algorithms used in previous studies, this review aimed to enable future researchers to better design experiments and pave the way for the findings to be adopted in a clinical environment. Little evidence is currently available for a meta-analysis due to the variations in the scope and methodologies used in previous studies. Further research is needed to evaluate the technology in real life and examine its impact on patients and healthcare providers.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

ME designed and led the study. AZ, ME, and CM conceived the study. All authors approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.937637/full#supplementary-material

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QT interval is correlated with and can predict the comorbidity of depression and anxiety: A cross-sectional study on outpatients with first-episode depression

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Object: Patients with depression are at an increased risk for developing cardiovascular diseases. The associations between electrocardiogram (ECG) abnormalities and the severity of psychiatric disorders, such as depression and anxiety, have not been clearly elucidated. The present study aims to investigate the associations between depression and anxiety symptoms with ECG indices, and to predict the severity of depression and anxiety using ECG indicators.

Methods: 61 outpatients with first-episode depression from the Shanghai Pudong New Area Mental Health Center were selected and met the diagnostic criteria of DSM-IV. All participants provided self-reported scores on the Zung Self-Rating Depression Scale (SDS) and Zung Self-Rating Anxiety Scale (SAS) and underwent the standard 12-lead ECG assessment.

Results: Among the 61 included outpatients (mean [standard deviation, SD] age: 37.84 [13.82] years; 41[67.2%] were female), there were 2 (3.3%) outpatients without depression symptoms, 16 (26.2%) with mild depression, 19 (31.1%) with moderate depression, and 24 (39.3%) with severe depression. Ten (16.4%) outpatients did not have anxiety symptoms, 19 (31.1%) exhibited mild anxiety, 20 (32.8%) exhibited moderate anxiety, and 12 (19.7%) exhibited severe anxiety. Only 1 (1.6%) outpatient exhibited neither depression nor anxiety, 9 (14.8%) and 1 (1.6%) outpatients only exhibited depression and anxiety, respectively, and most outpatients (50 [82.0%]) had comorbid depression and anxiety symptoms. In the correlation analysis, depression and anxiety severity levels were significantly positively correlated ($r = 0.717$, $p < 0.01$). Moreover, categorical anxiety significantly differs in QT interval ($p = 0.022$), and continuous SAS scores were significantly correlated with QT interval ($r = 0.263$, $p = 0.04$). In addition, the correlations between ECG measurements and both categorical depression and continuous SDS scores were not statistically significant. The comorbidity of anxiety and depression was significantly correlated with heart rate ($p = 0.039$) and QT interval ($p = 0.002$). Disorder status significantly differed with different QT intervals ($p = 0.021$).

In the prediction analysis, QT interval was the only significant predictor ($p = 0.01$, b = 0.058, Odds Ratio = 1.059) for comorbid anxiety and depression symptoms.

Conclusion: This study found that comorbid symptoms of depression and anxiety were significantly associated with QT interval and heart rate. Additionally, QT interval could predict the comorbidity of these two psychiatric disorders. Further prospective research in a larger and high-risk population is needed.

KEYWORDS

depression disorders, anxiety disorders, psychiatric symptoms, ECG abnormalities, cardiovascular disorders

Introduction

Psychiatric disorders, including depression and anxiety, are common in patients with coronary artery diseases, which are a major cause of death around the world (1). Previous research found that depression and heart disease are very common and often coexist (2). Similarly, anxiety is associated with an increased risk of cardiovascular diseases, especially heart failure (3–5). One explanation for the widely observed associations between cardiovascular diseases and depression and anxiety is that depression and anxiety lead to altered inflammation status and sympathetic nervous system activity that may adversely affect the cardiovascular system (2, 6).

Electrocardiogram (ECG) is a non-invasive measure of cardiovascular functions that can reflect the balance between the sympathetic and parasympathetic divisions of the autonomic nervous system. Researchers have found significant correlations between ECG indices and psychological disorders (7). For example, prolongation of QT interval has been related to depression symptoms in female patients with acute coronary syndrome (8). In addition, anxious participants were found to have a significantly lower respiratory sinus arrhythmia (RSA) compared with healthy controls (9). Since there has been strong comorbidity between anxiety and depression (10–12), both of them were found to be related to decreased heart rate variability (HRV) (13–15). However, the impact of depression and anxiety symptoms on ECG measurements may depend on the type of anxiety (e.g., general anxiety or heart-focused anxiety) and the stage of depression (e.g., onset, maintenance or recurrent) (16). Additionally, researchers developed a model based on recurrent neural network (RNN) (a deep learning-based model) and long short-term memory (LSTM) autoencoder to predict the risk of depression based on ECG measurements (17). This model could differentiate between "normal," "abnormal," and "risky" heartbeats, which correspond to different severity levels of depression. Although many studies have evaluated the associations of psychiatric disorders with ECG measurements, they only focused on a few ECG indices.

Given that mental impairments can influence physiological functions, we assume that physiological presentations may in turn reflect mental health conditions. Moreover, compared with other depression and anxiety severity physiological evaluation methods (e.g., EEG, EMG, saliva tests, and Dermal electricity), the use of ECG is much more convenient and accessible, and a link between ECG to anxiety and depression symptoms could help us form a straightforward understanding of the psychosomatic disease. To our knowledge, how ECG measurements predict psychiatric disorders has been less studied previously. Therefore, we tried to fill this knowledge gap by predicting the severity of depression and anxiety symptoms based on main ECG indices.

In this cross-sectional study, we conducted correlation analyses of psychological and physiological data to investigate the association of depression and anxiety symptoms with ECG indices (namely heart rate, PR interval, QT interval, corrected QT interval [QTC], and QRS complex). Then we performed prediction analyses to evaluate whether the extracted ECG indices can predict symptom severity of depression and anxiety.

Materials and methods

The present study involving human participants was reviewed and approved by the Shanghai Pudong New Area Mental Health Ethics Committee. The outpatients/participants provided their written informed consent to participate in this study.

Recruitment of participants

In this study, 61 outpatients were originally recruited from the Shanghai Pudong New Area Mental Health Center. The

following were the inclusion criteria: (1) met the diagnostic criteria for depression in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV); (2) aged between 18 and 70; (3) were male or female; (4) had no history of head trauma, obvious intellectual disability, or other serious or uncontrolled stable physical illness. The outpatients with asthma or respiratory allergy, sensitivity to plant extracts, olfactory problems, nasal injury, other comorbid psychological diseases, previous cardiovascular diseases, and history of myocardial infarction, those who had undergone coronary artery bypass surgery and percutaneous transluminal coronary angioplasty, those who had previously experienced arrhythmia (atrial fibrillation, ventricular atrial block, left and right heart block, etc.), had chronic bronchitis, atelectasis, and other chronic respiratory diseases, and those who had or were receiving other psychotropic-relevant medications (sodium channel blockers, QTc-prolonging drugs, first-generation antipsychotics, second-generation antipsychotics, antidepressants, cardiovascular drugs (nitrates, β-blockers, calcium channel antagonists, antithrombotics), and lipid-lowering drugs, etc.) before the ECG recordings were excluded. Enrollment and assessment were conducted from January 2021 to September 2021. Data were collected from October 2021 to January 2022 for analysis.

The G* Power (Version 3.1) – *Post Hoc* power analysis (two-tails) revealed that the present sample size ($n = 61$) was sufficient for the detection of a correlation coefficient of r = 0.40 and a moderate effect size (0.25) difference among individuals with different severity levels of psychological disorders, with a power (1-β) level of 0.90 and a significant α level of 0.05.

Demographic and clinical information, including age, sex, education level, self-reported depression and anxiety scores, and five ECG indices (heart rate, PR interval, QT interval, QTC, and QRS complex), was collected.

Instruments and assessment

Assessment of the severity of depression

The severity of depression was assessed using the Zung Self-Rating Depression Scale (SDS) (18). The SDS consists of 20 items with a 4-point Likert-type scale for each item. Therefore, the total raw score of this scale ranges from 20 to 80. The total raw score will then be multiplied 1.25 times to give rise to an SDS score. Based on the SDS score, subjects are classified as normal (<53), having mild depression (53 to 62), having moderate to major depression (63 to 72), and having severe to extreme major depression (>72).

Assessment of the severity of anxiety

The Zung Self-Rating Anxiety Scale (SAS) was utilized to assess participants' anxiety severity (19). The SAS includes 20 items covering a variety of anxiety symptoms, both psychological (e.g., "I feel afraid for no reason at all" and "I feel like I'm falling apart and going to pieces") and somatic (e.g., "My arms and legs shake and tremble" and "I feel my heart is beating fast"). Responses are given on a 4-point scale. Participants are instructed to answer the questions based on their experiences (either negative or positive) over the last week, with positive experiences being reversely scored from 4 to 1. The total raw score for SAS ranges from 20 to 80 and will be multiplied 1.25 times to yield an SAS score. Based on the SAS score, subjects are classified as normal (<50), experiencing mild anxiety (50 to 59), experiencing moderate to major anxiety (60 to 69), and experiencing severe to extreme major anxiety (>69).

ECG measurements

Participants were subject to the standard 12-lead and a 5-min ECG to assess cardiac functions. ECGs were recorded using a standard 12-lead tracing at rest in the supine position with a speed of 25 mm/s, an amplitude of 10 mm/mV, and a sampling frequency of at least 500 Hz. We collected the PR interval (ms), QRS interval (ms), and QT interval (ms) as ECG data. The PR interval was the time from the onset of the P wave to the start of the QRS complex. This is an indication of atrioventricular node conduction. The QT interval was the time from the start point of the QRS complex, expressed as ventricular depolarization, to the return point (visualized) of the T wave. It results from ventricular repolarization. The corrected QT (QTc) interval was obtained by the tangent method and corrected for heart rate using Bazett's formula: $QTc = QT/\sqrt{RR}$ (20). This formula has been commonly used and well established in previous research (21–23). Automated analysis was performed through a digitized multi-channel computer-assisted program (GE 12SL ECG Analysis), which uses validated algorithms for ECG parameters measurement. ECG analysis is described elsewhere (24).

Statistical analysis

Software packages Statistical Product and Service Solutions (SPSS, Version 26.0) and R (Version 4.0.3) were used for all statistical analyses. Prior to analysis, variables were screened for accuracy of data entry, missing values, outliers and compliance with the assumptions of univariate analysis, such as normality test. Missing values were imputed with the median for continuous variables. For descriptive analysis, clinical and demographic data are presented as mean ± standard deviation or mean ± standard error of the mean for continuous variables, and number (percentage) for categorical variables. Two-tailed $P < 0.05$ was considered statistically significant.

Coding for the participants' basic information

The gender of the participants was coded as follows: "1" for male and "2" for female. The education level of the participants was coded as follows: "1" for primary school-educated; "2" for junior high school or equivalent-educated; "3" for high school or equivalent-educated; "4" for junior college-educated; "5" for undergraduate-educated; and "6" for postgraduate-educated. Categorical values of depression and anxiety were determined based on the symptom severity according to the classification criteria for continuous SDS and SAS scores mentioned above as follows: "1" for normal; "2" for mild symptom; "3" for moderate symptom; and "4" for severe symptom. The disorder status (anxiety only, depression only, comorbid anxiety and depression, and no symptom/low severity of both anxiety and depression) was coded based on comorbidity: 1 for anxiety-only, 2 for depression-only, 3 for comorbid anxiety and depression, and 4 for no symptom/low severity of both.

Determination of the associations of demographic indicators with depression, anxiety, and ECG measurements

As for the correlation between demographic indicators and ECG measures, Pearson product-moment correlation was conducted for the relationship between age and ECG measures. Independent sample *T*-test was used to assess the association between participants' sex and ECG measures, and One-way ANOVA was performed to evaluate the relationship between education levels and ECG measures.

In terms of demographic indicators and symptom scores, Pearson correlation was conducted for the relationship between age and continuous SDS and SAS scores. Independent sample *T*-test was used to assess the association between participants' sex and continue SDS and SAS scores. One-way ANOVA was performed to evaluate the relationship between education levels and continue SDS and SAS scores, and age and categorical SDS and SAS values. Moreover, a chi-square test was carried out for the association between sex and categorical SDS and SAS values, and education levels and categorical SDS and SAS values.

Determination of the associations of depression and anxiety with ECG measurements

Associations between anxiety and depressive symptoms, respectively, and ECG outcomes, and between anxiety and depressive symptoms collectively, and ECG outcomes were determined. Participants were categorized into several groups according to the severity of depression and anxiety symptoms. Associations of continuous SDS and SAS scores with ECG indices were examined using Pearson product-moment correlation coefficients and multivariate regression analysis. One-way ANOVA was performed to estimate the associations of anxiety only, depression only, comorbid anxiety and depression, and no symptom/low severity of both anxiety and depression with ECG measurements before and after adjusting for demographics (sex, age, and education level). Covariates included sociodemographic characteristics. Analyses of covariates were performed to adjust for potentially confounding factors (i.e., demographic characteristics including age, sex, and education level).

Prediction analysis

Logistic regression analysis was used to predict the severity of depression and anxiety based on the collected ECG indices.

Results

Participants' characteristics

A total of 61 outpatients were included. Of these participants, 9 (14.75%) did not provide SDS and SAS scores. Given the small sample size, we retained the missing reports and replaced them with the mean values. Descriptive analyses of the participants' demographic and clinical characteristics are presented in Table 1. Among the 61 outpatients (mean [standard deviation, SD] age: 37.84 [13.82] years; 41[67.2%] were female), there were 2 (3.3%) outpatients without depression symptoms, 16 (26.2%) with mild depression, 19 (31.1%) with moderate depression, and 24 (39.3%) with severe depression. Ten (16.4%) outpatients did not have anxiety symptoms, 19 (31.1%) exhibited mild anxiety, 20 (32.8%) exhibited moderate anxiety, and 12 (19.7%) exhibited severe anxiety. Only 1 (1.6%) outpatient exhibited neither depression nor anxiety, 9 (14.8%) and 1 (1.6%) outpatients only exhibited depression and anxiety, respectively, and most outpatients (50 [82.0%]) had comorbid depression and anxiety symptoms. Table 1 also displays the ECG measurements, including heart rate (73.16 ± 11.06 BPM), PR interval (153.12 ± 19.13 ms), QT interval (375.67 ± 24.80 ms), QTC (415.95 ± 22.52 ms), and QRS complex (92.13 ± 11.07 ms), of the participants. The interrelationships between ECG indices for these participants were as follows: heart rate and QT interval were significantly negatively correlated ($r = -0.547$, $p < 0.01$); QTC and heart rate were significantly positively correlated ($r = 0.321$, $p = 0.012<0.05$); QT interval and QTC were significantly positively correlated ($r = 0.489$, $p < 0.01$).

TABLE 1 Demographic and clinical characteristics of outpatients.

Characteristic	Total	Depression group					Anxiety group					Symptom group					Comorbid group	
		SDS-1	SDS-2	SDS-3	SDS-4		SAS-1	SAS-2	SAS-3	SAS-4		NONE	depression-only	anxiety-only	co-occurrence		No co-occurrence	
	(*n* = 61) mean ± sd; n (%)	(*n* = 2) mean ± sd; *n* (%)	(*n* = 16) mean ± sd; *n* (%)	(*n* = 19) mean ± sd; *n* (%)	(*n* = 24) mean ± sd; *n* (%)	*p-value*	(*n* = 10) mean ± sd; *n* (%)	(*n* = 19) mean ± sd; *n* (%)	(*n* = 20) mean ± sd; *n* (%)	(*n* = 12) mean ± sd; *n* (%)	*p-value*	(*n* = 1) mean ± sd; *n* (%)	(*n* = 9) mean ± sd; *n* (%)	(*n* = 1) mean ± sd; *n* (%)	(*n* = 50) mean ± sd; *n* (%)	*p-value*	(*n* = 11) mean ± sd; *n* (%)	*p-value**
Demographics																		
Age (years)	37.8 ± 13.8	45.5 ± 10.6	43.8 ± 14.3	38.6 ± 16.5	32.6 ± 9.4	0.065	36.1 ± 12.4	41.0 ± 15.1	41.3 ± 13.4	28.5 ± 9.8	0.044	38	35.9 ± 13.1	53	37.9 ± 14.1	0.719	37.6 ± 12.8	0.958
Sex (Female, n (%))	41 (67.2%)	2 (100%)	8 (50%)	11 (57.9%)	20 (83.3%)	0.082	6 (60%)	14 (73.7%)	13 (65.0%)	8 (66.7%)	0.886	1 (100%)	5 (55.6%)	1 (100%)	34 (68.0%)	0.672	7 (63.6%)	0.78
Education attainment																		
% Primary school educated	2 (3.3%)	0	1 (6.3%)	1 (5.3%)	0	0.762	0	0	1 (5.0%)	1 (8.3%)	0.682	0	0	0	2 (4.0%)	0.638	0	0.499
% Junior high school or equivalent educated	14 (23.0%)	0	4 (25%)	7 (36.8%)	3 (12.5%)		3 (30%)	3 (15.8%)	5 (25.0%)	3 (25.0%)		0	3 (33.3%)	0	11 (22.0%)		3 (27.3%)	
% High school or equivalent educated	17 (27.9%)	1 (50%)	4 (25%)	4 (21.1%)	8 (33.3%)		1 (10%)	6 (31.6%)	6 (30.0%)	4 (33.3%)		0	1 (11.1%)	1 (100%)	15 (30.0%)		2 (18.2%)	
% Junior college educated	8 (13.1%)	0	3 (18.8%)	2 (10.5%)	3 (12.5%)		2 (20%)	3 (15.8%)	3 (15.0%)	0		0	2 (22.2%)	0	6 (12.0%)		2 (18.2%)	
% Undergraduate educated	16 (26.2%)	1 (50%)	2 (12.5%)	5 (26.3%)	8 (33.3%)		2 (20%)	5 (26.3%)	5 (25.0%)	4 (33.3%)		1 (100%)	1 (11.1%)	0	14 (28.0%)		2 (18.2%)	
% Graduate educated	4 (6.6%)	0	2 (12.5%)	0	2 (8.3%)		2 (20%)	2 (10.5%)	0	0		0	2 (22.2%)	0	2 (4.0%)		2 (18.2%)	
ECG measures																		
Heart rate (bpm)	73.2 ± 11.1	70.5 ± 3.5	77.1 ± 12.9	73.3 ± 8.5	70.7 ± 11.7	0.356	80.0 ± 15.0	69.2 ± 9.9	72.9 ± 10.1	74.2 ± 8.7	0.092	68	81.3 ± 15.3	73	71.8 ± 9.8	0.114	79.4 ± 14.4	0.039
P-R interval (ms)	153.1 ± 19.1	154.5 ± 10.6	151.3 ± 16.6	155.3 ± 21.2	152.5 ± 20.3	0.937	152.4 ± 19.9	154.8 ± 17.7	153.5 ± 22.8	150.4 ± 15.8	0.941	162	151.3 ± 20.7	147	153.4 ± 19.4	0.942	151.9 ± 18.9	0.82
QT interval (ms)	375.7 ± 24.8	365.5 ± 2.1	366.1 ± 29.9	381.4 ± 23.0	378.4 ± 22.3	0.26	354.6 ± 22.4	382.9 ± 26.6	379.1 ± 21.3	376.1 ± 22.1	0.022	367	353.2 ± 23.3	364	380.1 ± 23.4	0.021	355.5 ± 21.4	0.002
QTC (ms)	416.0 ± 22.5	397.0 ± 8.5	412.6 ± 25.2	420.9 ± 25.2	415.8 ± 18.7	0.452	406.7 ± 19.9	417.1 ± 23.9	418.4 ± 26.0	417.8 ± 15.5	0.572	391	408.4 ± 20.3	403	418.1 ± 22.9	0.4	406.4 ± 18.9	0.12
QRS complex	92.13 ± 11.1	87.5 ± 9.2	93.2 ± 12.7	91.6 ± 12.9	92.2 ± 8.8	0.915	90.3 ± 13.1	90.5 ± 10.7	94.5 ± 11.5	92.3 ± 9.6	0.665	81	91.3 ± 13.5	94	92.5 ± 10.8	0.779	90.6 ± 12.5	0.625
Psychological measures																		
SDS	68.8 ± 11.4	44.5 ± 2.1	56.6 ± 2.5	67.2 ± 2.5	80.3 ± 5.8	0.000	56.4 ± 6.6	65.0 ± 10.9	72.0 ± 5.4	79.9 ± 10.4	0.000	43	57.9 ± 4.9	46	71.7 ± 10.0	0.000	55.5 ± 7.0	0.000
SAS	59.6 ± 12.7	46.0 ± 17.0	49.6 ± 9.1	58.2 ± 9.4	68.6 ± 10.6	0.000	40.1 ± 5.2	55.0 ± 2.8	62.9 ± 3.3	77.9 ± 7.6	0.000	34	40.8 ± 5.0	58	63.6 ± 9.9	0.000	41.7 ± 7.3	0.000

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TABLE 2 Differences in ECG measures of depression and anxiety severity.

ECG measures	SDS			SAS		
	F	p	η^2	F	p	η^2
Heart rate (bpm)	1.102	0.356	0.055	2.253	0.092	0.106
P-R interval (ms)	0.138	0.937	0.007	0.132	0.941	0.007
QT interval (ms)	1.373	0.260	0.067	3.454	0.022	0.154
QTC (ms)	0.889	0.452	0.045	0.673	0.572	0.034
QRS complex	0.171	0.915	0.009	0.527	0.665	0.027

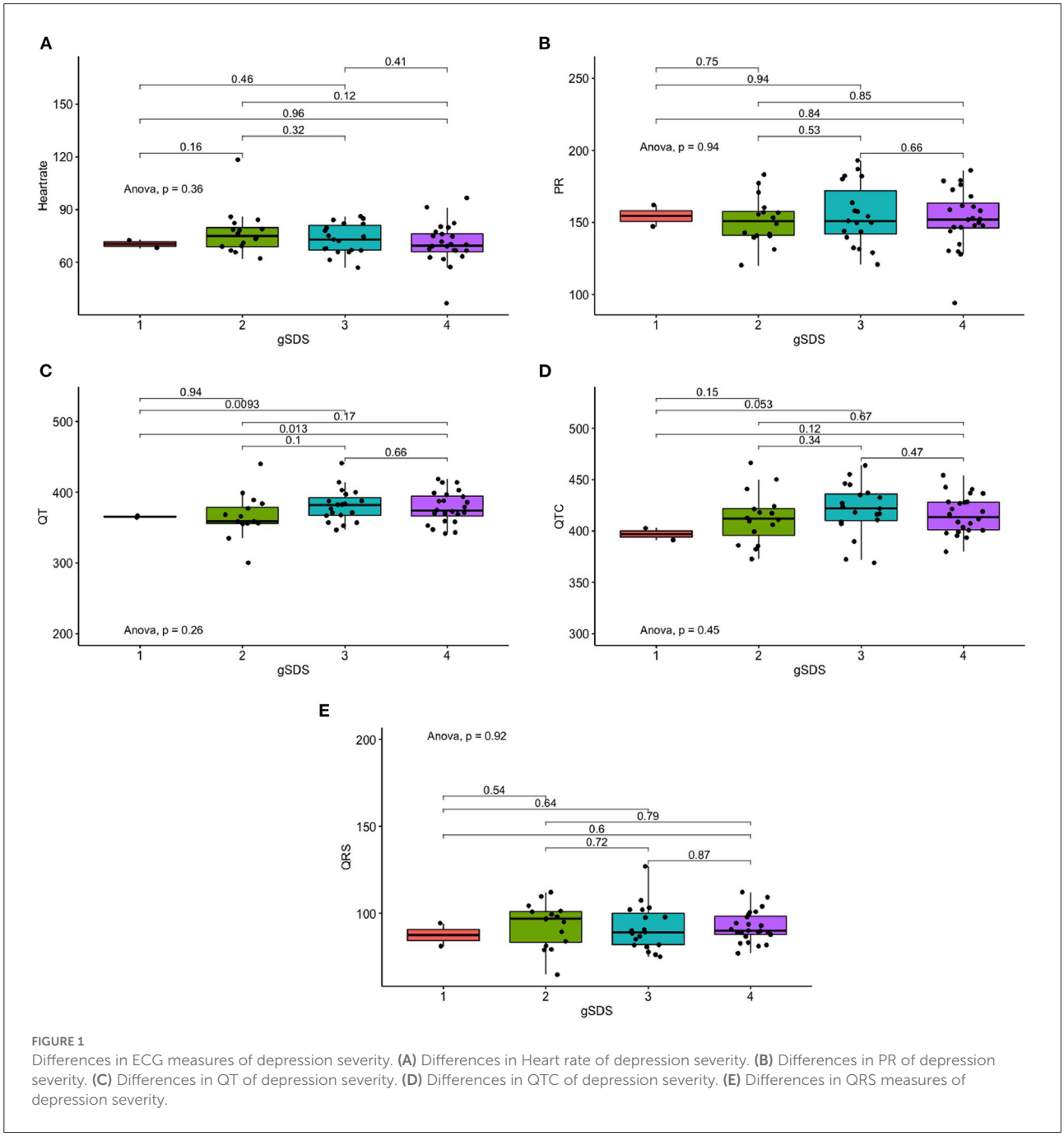

FIGURE 1
Differences in ECG measures of depression severity. **(A)** Differences in Heart rate of depression severity. **(B)** Differences in PR of depression severity. **(C)** Differences in QT of depression severity. **(D)** Differences in QTC of depression severity. **(E)** Differences in QRS measures of depression severity.

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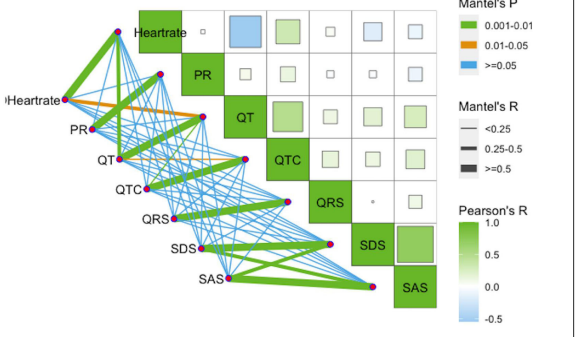

FIGURE 2
Correlation between ECG measures and psychological variables.

Correlations between the participants' demographic characteristics and ECG measurements

Correlations between demographic characteristics and ECG measurements were analyzed because previous studies have suggested that sex, age, and education level were related to ECG measurements (25–27). Independent *t*-tests showed that male outpatients had significantly higher QRS complex amplitude than females ($p = 0.002$). No significant differences were found in other ECG indices between genders. Pearson correlation analysis indicated that age was only significantly associated with QTC interval ($r = 0.450$, $p < 0.01$). No associations were found between education level and ECG indices as revealed by one-way ANOVA.

Correlations between the participants' demographic characteristics and psychological measurements

Correlations between demographic characteristics and psychological measurements were also analyzed. Age was found to be significantly correlated with SDS scores ($r = -0.294$, $p = 0.021$), but not with continuous SAS scores ($r = -0.173$, $p = 0.182$). However, age was significantly related to anxiety severity ($p = 0.044$) but not with depression severity ($p = 0.065$).

Chi-squared tests were used to examine relationships between gender, education level and SDS score, SAS score, and disorder status. There was no significant association between sex and SDS score ($p = 0.082$), SAS score ($p = 0.882$), disease status ($p = 0.672$) and the status of comorbidity ($p = 0.780$). The associations between education level and SDS score ($p = 0.762$), SAS score ($p = 0.682$), disease status ($p = 0.638$), and the status of comorbidity ($p = 0.499$) were also not significant.

TABLE 3 Association between depression severity and ECG measures.

ECG measures	Unadjusted mean					Adjusted mean*				
	SDS-1 mean ± sem	SDS-2 mean ± sem	SDS-3 mean ± sem	SDS-4 mean ± sem	P[a]	SDS-1 mean ± sem	SDS-2 mean ± sem	SDS-3 mean ± sem	SDS-4 mean ± sem	P*
Heart rate (bpm)	70.5 ± 2.5	77.063 ± 3.215	73.263 ± 1.948	70.708 ± 2.386	0.356	70.840 ± 8.128	76.593 ± 2.936	72.826 ± 2.643	71.339 ± 2.439	0.598
P-R interval (ms)	154.5 ± 7.5	151.313 ± 4.139	155.316 ± 4.858	152.458 ± 4.148	0.937	153.178 ± 13.884	148.117 ± 5.016	154.669 ± 4.514	155.211 ± 4.166	0.725
QT interval (ms)	365.5 ± 1.5	366.063 ± 7.484	381.421 ± 5.287	378.375 ± 4.547	0.26	358.495 ± 17.092	363.538 ± 6.175	381.625 ± 5.557	380.480 ± 5.129	0.092
QTC (ms)	397 ± 6.0	412.625 ± 6.297	420.895 ± 5.774	415.833 ± 3.822	0.452	388.105 ± 13.932	408.800 ± 5.033	420.570 ± 4.53	419.382 ± 4.181	0.066
QRS complex	87.5 ± 6.5	93.188 ± 3.17	91.632 ± 2.965	92.208 ± 1.797	0.915	89.189 ± 7.429	90.320 ± 2.684	90.519 ± 2.415	94.860 ± 2.229	0.507

* adjusted for age, sex, and education levels.
[a] unadjusted p values were calculated.

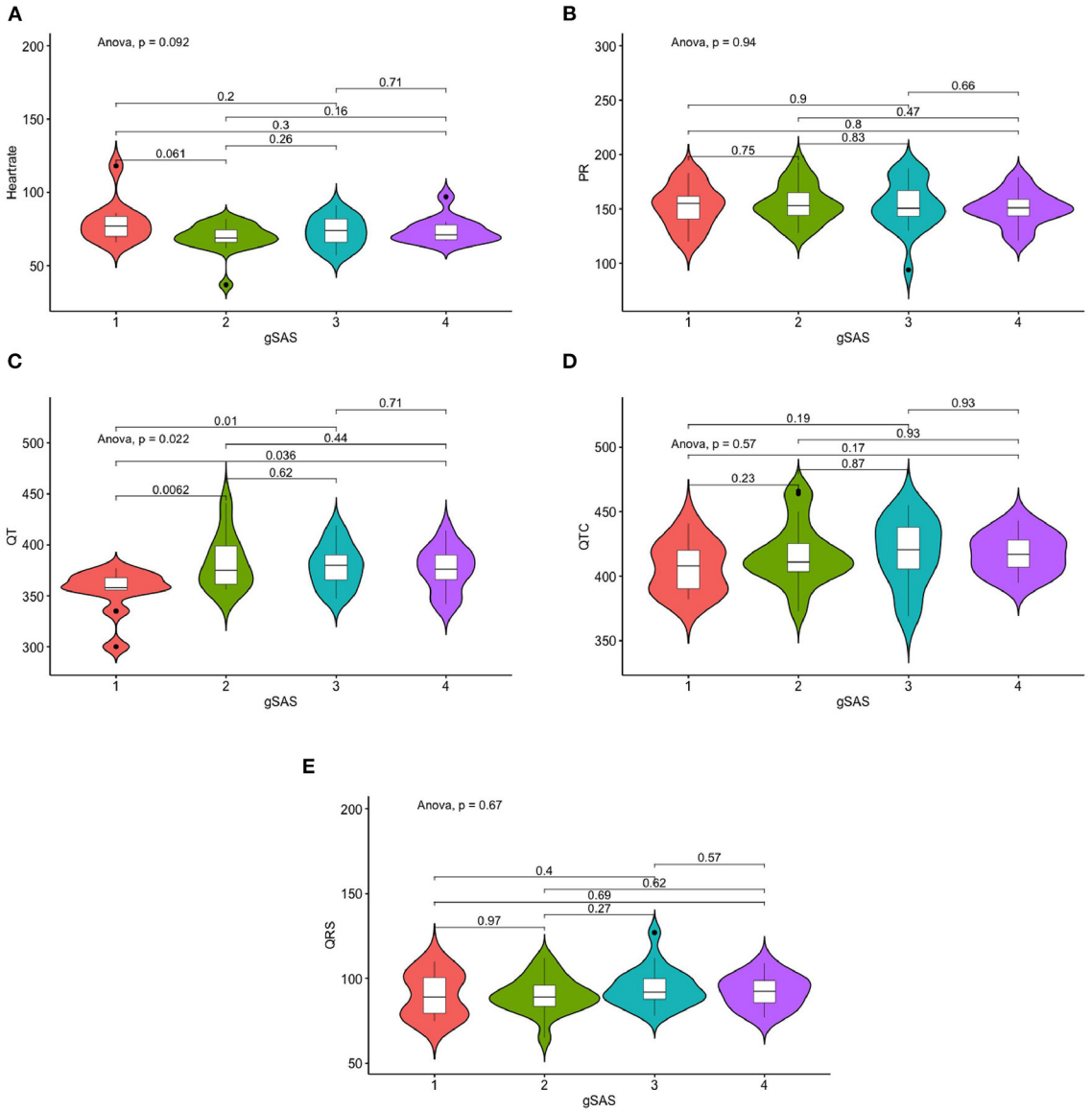

FIGURE 3
Differences in ECG measures of anxiety severity. **(A)** Differences in Heart rate of anxiety severity. **(B)** Differences in PR of depression severity. **(C)** Differences in QT of depression severity. **(D)** Differences in QTC of depression severity. **(E)** Differences in QRS measures of depression severity.

Correlations of depression and anxiety symptoms with ECG measurements

Associations between depression and ECG measurements

We conducted a one-way ANOVA on depression status and ECG indices (Table 2, Figure 1), and calculated Pearson correlation coefficients for continuous SDS scores and ECG indices (Figure 2). Correlations between depression status and all five ECG indices were not significant. After adjusting for age, sex, and education level, the correlations remained insignificant (Table 3).

Associations between anxiety and ECG measurements

Anxiety severity significantly differs in QT interval (p = 0.022), but not with other ECG indices (Table 2, Figure 3). Similarly, continuous SAS scores were significantly correlated with QT interval (r = 0.263, p = 0.04), but not with other ECG indices (Figure 1). Adjusting for age, sex, and education

level, attenuated the significance of this correlation (adjusted $p = 0.041$) (Table 4).

Associations between comorbid depression and anxiety and ECG measurements

Depression and anxiety levels were significantly positively correlated ($r = 0.717$, $p < 0.01$). When examining SDS and SAS scores simultaneously as continuous variables using multivariate regression analyses, it was found that SDS score was most strongly correlated with heart rate ($\beta = -0.215$, $p = 0.249$), while SAS score was most strongly correlated with QT interval ($\beta = 0.275$, $p = 0.136$). In addition, the comorbidity of anxiety and depression was significantly correlated with heart rate ($p = 0.039$) and QT interval ($p = 0.002$). Furthermore, disorder status only significantly differed with different QT intervals ($p = 0.021$).

Prediction of symptom status using ECG measurements

We tried to predict symptom status using the five ECG indices. Four symptom statuses were defined in this study: (1) depression severity: 1-normal, 2-mild, 3-moderate, 4-severe; (2) anxiety severity: 1-normal, 2-mild, 3-moderate, 4-severe; (3) comorbid severity: 1-no symptom/low severity of both anxiety and depression, 2-depression only, 3-anxiety only, 4-comorbid anxiety and depression; (4) status of comorbidity: 1-none comorbid, 2-comorbid depression and anxiety.

To predict the depression severity, anxiety severity and comorbid severity, we conducted logistic regression analyses. However, we could not predict these three symptom statuses based on the available ECG measurements.

To predict the status of comorbidity, we used logistic regression analyses (binary logistic regression; forward logistic regression). Results suggested that QT interval was the only significant predictor for the status of comorbidity ($p = 0.01$, $\beta = 0.058$, odds ratio [OR] = 1.059).

Discussion

Although a moderate to strong relationship between depression and anxiety symptoms and ECG features has been reported in previous literature, contradicting results generated from these studies are frustrating. Additionally, little has been done on predicting the severity of depression and anxiety. To our knowledge, this study is the first attempt to predict the severity of depression, anxiety, and their status of comorbidity using ECG indices.

Findings from the present study showed that continuous and categorical anxiety scores were significantly correlated with QT

TABLE 4 Association between anxiety severity and ECG measures.

ECG measures	Unadjusted mean					Adjusted mean*				
	SDS-1 mean ± sem	SDS-2 mean ± sem	SAS-3 mean ± sem	SAS-4 mean ± sem	P[a]	SAS-1 mean ± sem	SAS-2 mean ± sem	SAS-3 mean ± sem	SAS-4 mean ± sem	P*
Heart rate (bpm)	80 ± 4.749	69.211 ± 2.26	72.9 ± 2.259	74.167 ± 2.525	0.092	80.424 ± 3.412	68.997 ± 2.539	72.193 ± 2.427	75.331 ± 3.344	0.066
P-R interval (ms)	152.4 ± 6.277	154.842 ± 4.067	153.45 ± 5.096	150.417 ± 4.547	0.941	152.549 ± 6.188	153.999 ± 4.605	152.293 ± 4.402	153.556 ± 6.065	0.993
QT interval (ms)	354.6 ± 7.071	382.947 ± 6.109	379.05 ± 4.754	376.083 ± 6.381	0.022	355.793 ± 7.408	381.149 ± 5.513	377.762 ± 5.27	380.083 ± 7.261	0.041
QTC (ms)	406.7 ± 6.288	417.105 ± 5.491	418.4 ± 5.822	417.75 ± 4.462	0.572	409.087 ± 6.353	414.102 ± 4.729	415.466 ± 4.52	425.406 ± 6.227	0.325
QRS complex	90.3 ± 4.15	90.474 ± 2.463	94.5 ± 2.576	92.333 ± 2.762	0.665	89.885 ± 3.287	90.268 ± 2.447	93.772 ± 2.339	94.219 ± 3.222	0.596

*adjusted for age, sex, and education levels.
[a] unadjusted p-values were calculated.

interval. These findings are consistent with those of Lapidus et al. (28), who discovered that a high level of anxiety was associated with increased QT dispersion, which may predispose to cardiac arrhythmias (28). Surprisingly, the current study did not detect any evidence of a significant correlation between depression and ECG indices. However, because of the small sample size of our study, caution must be taken in interpreting our observations. Prior research also yielded heterogeneous findings (significant or non-significant) on the relationship between depression symptoms and ECG measurements (29, 30).

The simultaneous analyses of continuous SDS and SAS scores revealed significant associations of depression with heart rate, and anxiety and QT interval. Therefore, it seems reasonable to determine whether the comorbidity of anxiety and depression is significantly correlated with heart rate and QT interval. Additionally, disease status only differed significantly with different QT intervals. Noteworthy, we could not detect a statistically significant relationship between depression and ECG indices until taking anxiety into account. This agrees with prior research showing that anxiety, but not depression, negatively influenced parasympathetic modulation of heart rate, suggesting that anxiety may be more related to adverse cardiological outcomes (15). However, some research also suggests that the association between anxiety and heart disease may be responsible for the comorbidity of depression (31). This inconsistency in causality may be due to the specific ECG indices selected, as prior research also found that benign palpitation was significantly associated with anxiety, but not depression (32). Another factor to consider is the stage of disease, as aforementioned in the introduction. For example, one study has suggested that anxiety may play different roles in different stages of depression in individuals with inherited cardiac disorders (33).

Another important finding of our study is that QT interval was the only ECG index that can be used to predict the comorbidity of depression and anxiety. Likewise, the reliability of using ECG features obtained from wearable devices for diagnosing anxiety has been validated (34), and a dose-response relationship has been found between the severity of depression and the risk of coronary heart disease (35). In addition, a prior study used heart rate variability to effectively discriminate between depression and anxiety patients (10). Another study also predicted depressed patients with suicidal ideation based on ECG recordings (36). In summary, it is possible to predict the severity of depression and anxiety using ECG indices.

Limitations and future work

The present study has many limitations to acknowledge. First, despite the robust risk adjustment during statistical calculation, confounding effects as a result of unmeasured variables, such as baseline health status, lifestyle (e.g., diet habits, exercise habits), and current medication status, cannot be excluded. Future studies will be needed to further investigate these variables. In addition, it will be important for future studies to investigate how the other remaining ECG indices correlate with depression and anxiety symptoms. Second, there was a potential selection bias considering the small sample size of our study. Therefore, findings obtained based on this small sample may not be generalizable to other settings. However, as we aimed to investigate the association between ECG indices and earlier depression and anxiety symptoms in outpatients with first-episode depression, the sample used in this study was relatively representative. In the future, it is important to verify our results in longitudinal analyses with repeated measures in a large, high-risk population. Third, we only used SDS and SAS as depression and anxiety assessment tools, respectively. Due to the subjective nature of these two scales, recall bias may exist, and the evidence may be insufficient for establishing diagnoses. We believe that the correlation and prediction power would have been more statistically significant if more strict diagnoses were established. Fourth, although associations between ECG indices and depression and anxiety have been identified in this study, the causal mechanisms remain to be elucidated. Additionally, prospective studies are needed to clarify the pharmacological roles of depression and anxiety in the management of heart disease.

Conclusion

In conclusion, the present study demonstrated that QT interval was most strongly associated with and was the only significant predictor for the comorbidity of depression and anxiety. These findings have important implications for the prevention and intervention of depression and anxiety and highlight the need to consider psychological factors and established predictors when assessing a person's risk of heart disease. We believe that these data will have reference value for health care providers and hospital administrators.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Shanghai Pudong New Area Mental Health Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Full access to all of the data in the study and take responsibility for the integrity of the data, accuracy of the data analysis, obtained funding, administrative, technical, material support, and supervision: JX and XF. Concept, design, acquisition, analysis, interpretation of data, and critical revision of the manuscript for important intellectual content: JX, XF, and MT. Drafting of the manuscript and statistical analysis: MT. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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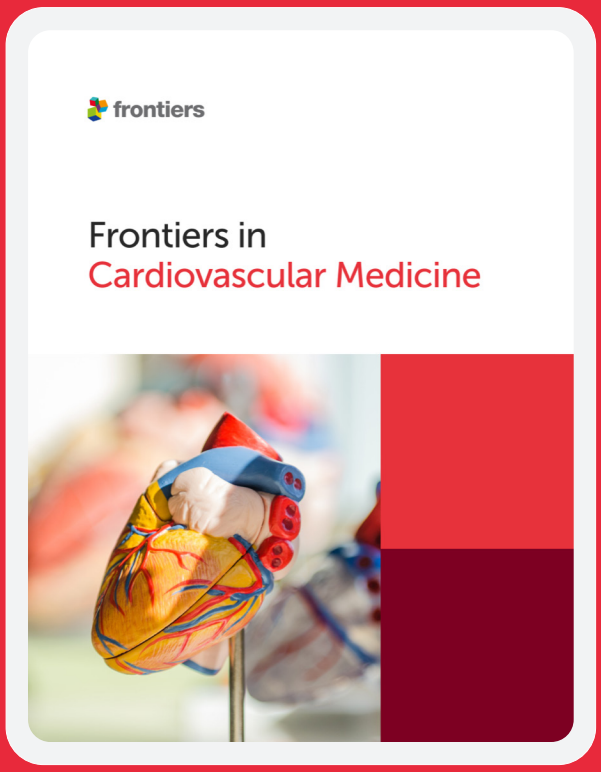

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