INSIGHTS IN HEART FAILURE AND TRANSPLANTATION: 2021

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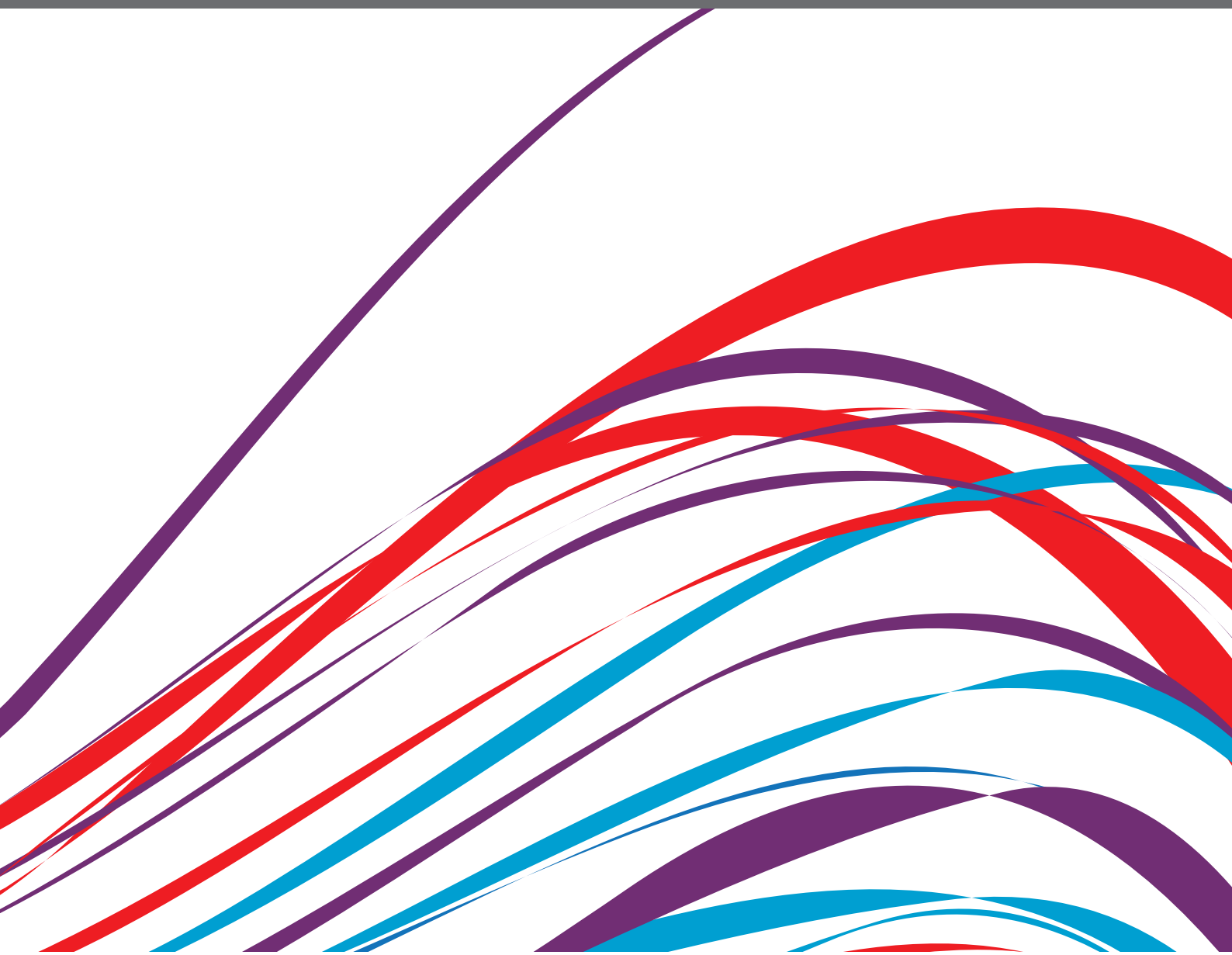

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INSIGHTS IN HEART FAILURE AND TRANSPLANTATION: 2021

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BRIEF RESEARCH REPORT
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Deep Neural Network to Accurately Predict Left Ventricular Systolic Function Under Mechanical Assistance

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Characterizing left ventricle (LV) systolic function in the presence of an LV assist device (LVAD) is extremely challenging. We developed a framework comprising a deep neural network (DNN) and a 0D model of the cardiovascular system to predict parameters of LV systolic function. DNN input data were systemic and pulmonary arterial pressure signals, and rotation speeds of the device. Output data were parameters of LV systolic function, including end-systolic maximal elastance ($E_{max,lv}$), a variable essential for adequate hemodynamic assessment of the LV. A 0D model of the cardiovascular system, including a wide range of LVAD settings and incorporating the whole spectrum of heart failure, was used to generate data for the training procedure of the DNN. The DNN predicted $E_{max,lv}$ with a mean relative error of 10.1%, and all other parameters of LV function with a mean relative error of <13%. The framework was then able to retrieve a number of LV physiological variables (i.e., pressures, volumes, and ejection fraction) with a mean relative error of <5%. Our method provides an innovative tool to assess LV hemodynamics under device assistance, which could be helpful for a better understanding of LV-LVAD interactions, and for therapeutic optimization.

Keywords: cardiovascular modeling, heart failure, deep neural network, left ventricular assist device, machine learning

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1. INTRODUCTION

Left Ventricular Assist Device (LVAD), a subset of mechanical circulatory support, assists the failing left ventricle (LV) by pumping blood from the LV into the ascending aorta. In recent years, LVAD has become a crucial therapeutic solution for patients with end-stage heart failure (1). Current indications for LVAD implantation include bridge to heart transplantation (2), and destination therapy, for patients not candidate for heart transplantation (3). LVAD may also be used as bridge to recovery, in patients in whom the LVAD can be removed after recovery of native myocardial function (4).

The assisted LV may retain a certain amount of residual native function. Therefore, complex and reciprocal interactions occur between the heart and the LVAD. The systemic blood flow, i.e., total cardiac output, represents the sum of the flows generated by the LVAD and the native LV, dependent on respective loading conditions (preload and afterload) and inherent function. The

latter corresponds to the rotational speed for the device (revolutions per minute, RPM) and residual systolic function (contractility or inotropy) of the native LV (5). Understanding these interactions is critical for appropriate settings of the LVAD and for estimating the possible recovery of native LV function. An essential step is therefore to appropriately evaluate LV systolic function under LVAD assistance (6).

Such evaluation is particularly challenging, owing to the unloading of the LV produced by the LVAD. Echocardiography and invasive cardiac catheterization are presently the only methods used for this purpose, and some authors have advocated specific protocols to optimize native LV function or to identify myocardial recovery (7–10) in patients assisted by LVAD. These methods, while clinically useful, provide either indirect (catheterization) or load-dependent indices of LV function, but unfortunately do not provide a direct, load-independent determination of LV contractility. The latter can indeed only be fully characterized by computing maximal systolic elastance ($E_{max,lv}$), which is the maximal slope of the end-systolic pressure volume relationship of the LV (11). Determining $E_{max,lv}$ requires the simultaneous measurement of LV pressure and LV volume. This is only feasible under experimental settings and is therefore not applicable to the clinical reality, indicating that novel strategies to assess LV inotropy are critically needed.

We recently proposed a method, based on a deep neural network (DNN), to predict $E_{max,lv}$ in failing, unassisted LV (12). In the present study, we aimed at evaluating whether such an approach could be used in the setting of LVAD support. To address this issue, we developed a framework using simple physiological signals (arterial pressure waveforms from the systemic and pulmonary arterial circulations) coupled to LVAD data (pump rotational speed ω_c) to predict $E_{max,lv}$ and other variables relevant to LV systolic function. The presence of the LVAD strongly affects the arterial pressure waveforms, it is therefore not possible to employ the same DNN considered in Bonnemain et al. (12) to recover the physiological variables of interest. In other words, the inherently different behavior of our cardiovascular system model (a 0D lumped model, see section 2.2) with and without LVAD requires us to train a new DNN on data specifically accounting for the presence of the device. One of the goals of this work, therefore, is to demonstrate that the approach presented in Bonnemain et al. (12) can be extended to patients with LVAD support by training the DNN on data adequately representing the pump settings considered in clinical settings.

2. METHODS

2.1. General Framework

Figure 1 displays a schematic representation of the framework (based on our recent publication (12)), used to evaluate (i) LV parameters of systolic function ($E_{max,lv}$ and other parameters of LV systolic function) and (ii) various physiological LV quantities (e.g., pressures, volumes), by employing a lumped parameter model of the cardiovascular system (see description below). Our framework makes use of a deep neural network (DNN) which infers, given systemic and pulmonary arterial pressure measurements and the RPM of the LVAD as inputs, an estimation of LV systolic parameters (comprising, in particular, $E_{max,lv}$). The DNN was trained with a lumped model of the cardiovascular system (13), modified to take into account the presence of a HeartMate III (HMIII) LVAD (Abbott Laboratories), one of the last third generation centrifugal-flow devices. In a second phase, the parameters of LV systolic function—which in general are unavailable in the daily practice—were provided to the lumped model to reconstruct various outputs such as LV pressures and volumes. It is worth noting that the network was trained on a dataset which is generated by the 0D model for a variety of heart failure cases and LVAD settings, therefore the first phase of the algorithm effectively consists in solving an inverse problem mapping the output of the 0D model to its underlying physical parameters.

2.2. Lumped Model of the Cardiovascular System and LVAD Modelization

The 0D model of the cardiovascular system is based on the mathematical description of the cardiovascular system presented by Ursino (13), which takes into account carotid baroregulation. It includes vascular compartments, heart ventricles with time-varying elastance, parasympathetic afferent and efferent pathways, and sympathetic efferent pathway. We modified it in order to model the presence of the HMIII LVAD.

The model comprises eight vascular compartments. The pulmonary circulation is represented by a serial arrangement of arterial, peripheral, and venous circulations. The systemic circulation begins with arteries and further subdivides into splanchnic and extrasplanchnic circulations, each having a peripheral and venous compartment in series. Each compartment i comprises at least a resistance (R_i) and a compliance (C_i) to account for viscous and elastic effects, respectively, and is further characterized by its unstressed volumes. Inertance (L_i) is considered only in large systemic and pulmonary arteries, i.e., blood acceleration is neglected in the rest of the vascular tree. Mass conservation (1), momentum conservation (2), and pressure-flow relationship (3) equations are applied to each compartment i, assuming that blood is an incompressible, isotropic, and Newtonian fluid:

$$\frac{dV_i}{dt}(t) = Q_{i,in}(t) - Q_{i,out}(t), \tag{1}$$

$$L_i \frac{dQ_{i,out}}{dt}(t) = P_{in}(t) - P_{out}(t) - R_i(t)Q_{i,out}(t), \tag{2}$$

$$V_i(t) = C_i P_{i,in}(t) + V_{i,0}, \tag{3}$$

where V_i is the volume of ith compartment, $V_{i,0}$ the unstressed volume of ith compartment (i.e., volume at zero pressure), $Q_{i,in}$ and $Q_{i,out}$ the inlet and outlet flow rates of ith compartment, $P_{i,in}$ and $P_{i,out}$ the inlet and outlet pressures of ith compartment.

The heart model comprises ventricles and atria as a four-compartment system, each of which is modeled by a serial arrangement of a compliance, a resistance, and an ideal valve, i.e., blood flows without viscous loss from inlet to outlet

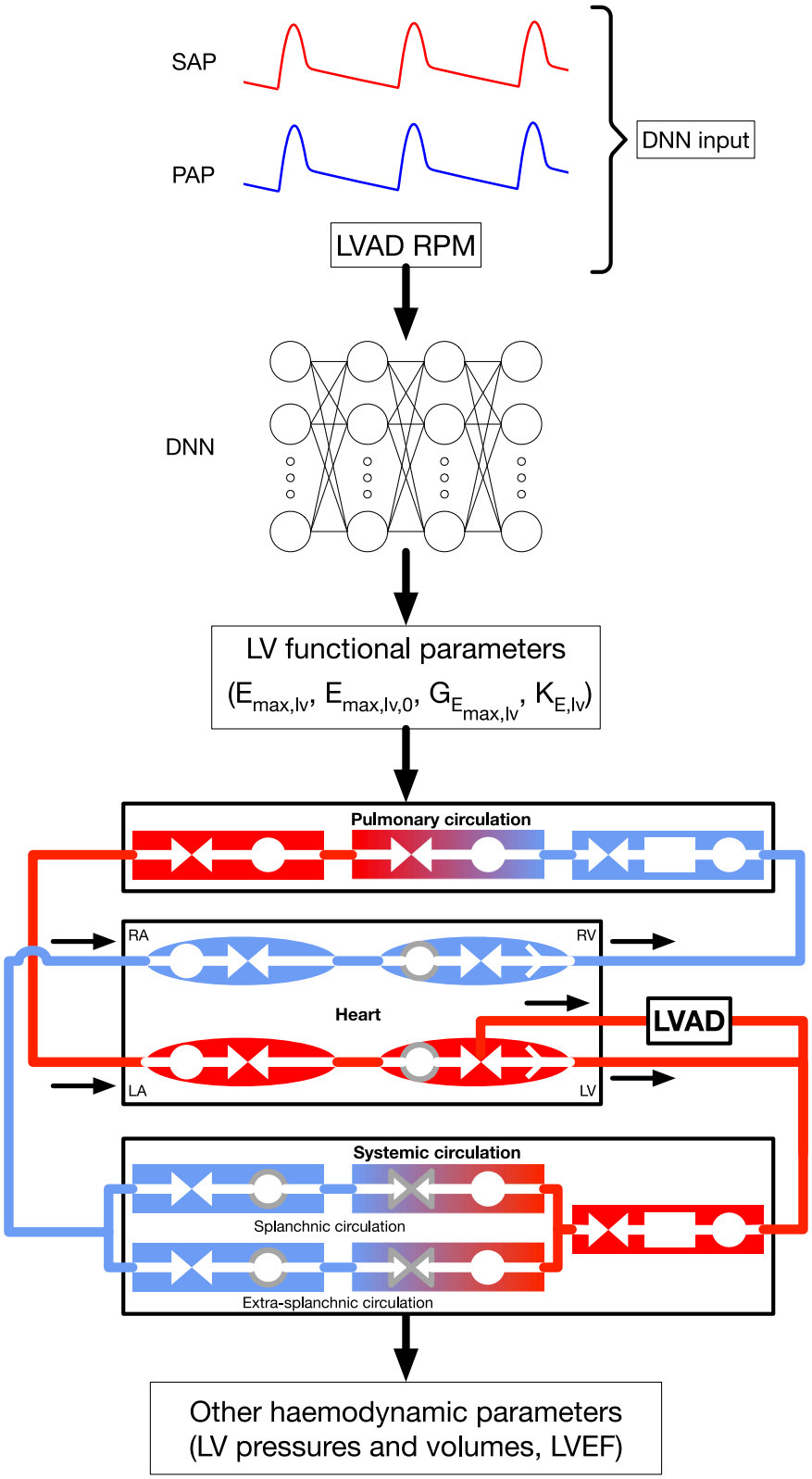

FIGURE 1 | General framework, modified from Bonnemain et al. (12) under CC-BY license. The DNN is fed with systemic and pulmonary arterial pressures, formulated in their frequency domain, as well as LVAD RPM, to predict parameters of LV systolic function. These parameters are integrated to the 0D model to retrieve

(Continued)

FIGURE 1 | the indicated additional hemodynamic parameters. Shapes and colors significance in the 0D model are: deoxygenated blood (blue elements); oxygenated blood (red elements:); compliance (circles); inertance (rectangles); resistance (facing triangles, double arrows); cardiac valves (single white arrows in heart chambers); elements affected by autoregulation (gray contour). RPM, Rotations per minute; SAP, systemic arterial pressure; PAP, pulmonary arterial pressure; DNN, deep neural network; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle. $E_{max,lv}$ [mmHg/ml]: end-systolic left ventricular elastance, $E_{max,lv,0}$ [mmHg/ml]: end-systolic left ventricular elastance in absence of baroregulation, $G_{E_{max,lv}}$ [mmHg/ml/(spikes/ml)]: maximum baroreceptor gain, $k_{E,lv}$ [1/ml]: steepness of end-diastolic pressure-volume curve.

compartments when pressure of the former exceeds pressure of the latter. Atria are passive elements, whereas contractility of ventricles is characterized by a time-varying elastance. Autoregulation occurs through the carotid baroreflex. The vagal afferent activity is modulated by the absolute systemic arterial pressure and its rate of change. Sympathetic and vagal efferent activities then modulate systemic peripheral resistances, systemic venous compliances, heart period, and ventricles resistances and compliances.

Different stages of left ventricle systolic failure severity were represented by modifying values of the following parameters: end-systolic elastance of the left ventricle with and without autoregulation, $E_{max,lv}$ and $E_{max,lv,0}$, respectively, the maximum baroreceptor gain $G_{E_{max,lv}}$, and $k_{E,lv}$, which describes the end-diastolic pressure-volume relationship for the left ventricle. Ranges for each parameters are shown in **Supplementary Table 1** and were validated with clinical data in Bonnemain et al. (14). All other parameters were not changed and can be found in the original paper (13). **Figure 2** shows different pressure-volume diagrams for different degrees of heart failure, with and without LVAD.

The LVAD is modeled as a pressure-controlled flow generator, based on pressure-flow curves interpolated from data available in the HMIII manual[1]. Specifically, the flow rate is a function of the pump differential pressure and the pump rotational speed, as shown in **Supplementary Figure 1**. The LVAD inflow and outflow cannulas are connected to the left ventricle and systemic arteries, respectively, as depicted at the bottom of **Figure 1**. The pump setting is characterized by a constant rotational speed, ω_c, and a pump speed modulation feature, namely the artificial pulse, which periodically modifies the pump speed from its preset value ω_c. More specifically, every 2 s the pump speed decreases by 2,000 RPM during 0.15 s and then increases by 4,000 RPM during the following 0.2 s. This aims at promoting pump washout (15) and thus preventing pump thrombosis (3, 5).

2.3. Deep Neural Networks

A DNN is a parametric machine learning algorithm used to capture complex nonlinear relationships between inputs and outputs, which needs to be trained on a large number data points. In contrast to other parametric models, DNNs do not require strong assumptions about the nature of the data distribution. The fundamental building block of a DNN is an artificial neuron, that is a simple function which takes a d-dimensional input $\mathbf{x} = (x_1, \ldots, x_d)$ and which outputs a scalar $a = g(w_0 + w_1x_1 + w_2x_2 + \ldots + w_dx_d)$, where the vector $\mathbf{w} = (w_0, \ldots, w_d) \in \mathbb{R}^{d+1}$ contains the parameters of the model, and g is the activation function, which is typically non-linear. Here, we focus on a simple and widely-used class of DNNs, namely multi-layer perceptrons (MLPs). A MLP is made of layers composed of artificial neurons in which each neuron receives input from all neurons in the previous layer; for this reason, this structure is commonly referred to as fully-connected. In matrix form, the output of the lth layer reads

$$\mathbf{a}^{(l)} = \mathbf{g}^{(l)}\left(W^{(l)}\mathbf{a}^{(l-1)} + \mathbf{b}^{(l)}\right), \tag{4}$$

where $W^{(l)}$ and $\mathbf{b}^{(l)}$ are the weight matrix (which collects all the parameters $\mathbf{w}$ of the neurons belonging to the layer) and the bias vector, respectively. We denote by L the total number of layers of the DNN. Layer 0 is the DNN input, and layer L is the output, whereas layers $0 < l < L$ are called hidden layers.

Each layer l in a MLP depends on the parameters contained in the weight matrix $W^{(l)}$ and in the bias vector $\mathbf{b}^{(l)}$. The process of calibration of these parameters corresponds to the training of the DNN. It is based on the use of a training dataset represented by a set of input-output pairs $\{\mathbf{x}^i, \mathbf{y}^i\}$. Let $\mathbf{f}(\mathbf{x}^i; \Theta) = \mathbf{a}^{(L)}$ when $\mathbf{a}^{(0)} = \mathbf{x}^i$, where $\Theta = \{W^{(1)}, \ldots, W^{(L)}, \mathbf{b}^{(1)}, \ldots, \mathbf{b}^{(L)}\}$ is the set of parameters of all layers. The fitting or training procedure consists in minimizing a loss function $\mathcal{L}_\Theta$ on the training set by means of an optimization algorithm (e.g., stochastic gradient descent). The goal is to find the weights Θ that yield good approximations $\mathbf{f}(\mathbf{x}^i; \Theta) \approx \mathbf{y}^i$. See (16, 17) for a detailed description of machine learning algorithms and deep neural networks.

2.4. Data Generation and Input/Output of the DNN

We generated a dataset by solving the 0D model N_s times for N_ω pump rotational speeds ω_c. Each of the $N_s \times N_\omega$ simulations was characterized by a pump setting (ω_c) and a set of four heart-failure-characterizing parameters (**Supplementary Table 1**), independently and randomly sampled with a uniform distribution. We selected $N_\omega = 21$ pump rotational speeds ω_c equally spaced in the range from 4,000 to 6,000 RPM, as these speeds encompass the usual pump setting in clinical conditions (18). For each rotational speed ω_c, $N_s = 10,000$ samples were generated, yielding a total of $N_\omega \times N_s = 210,000$ samples. Setting a large value for N_s allowed us to generate combinations of parameters that cover the whole range of left heart failure stages. The other 0D parameters are set to the values found in Ursino (13).

A simulation was performed over a time range $(0, T)$ with N interpolation equidistant points. We set the simulation time to $T = 30$ s, allowing signals to reach a steady state after initialization, with $N = 2,000$. The resulting output was a set

[1]https://www.heartmate.com/healthcare-provider/resource-center

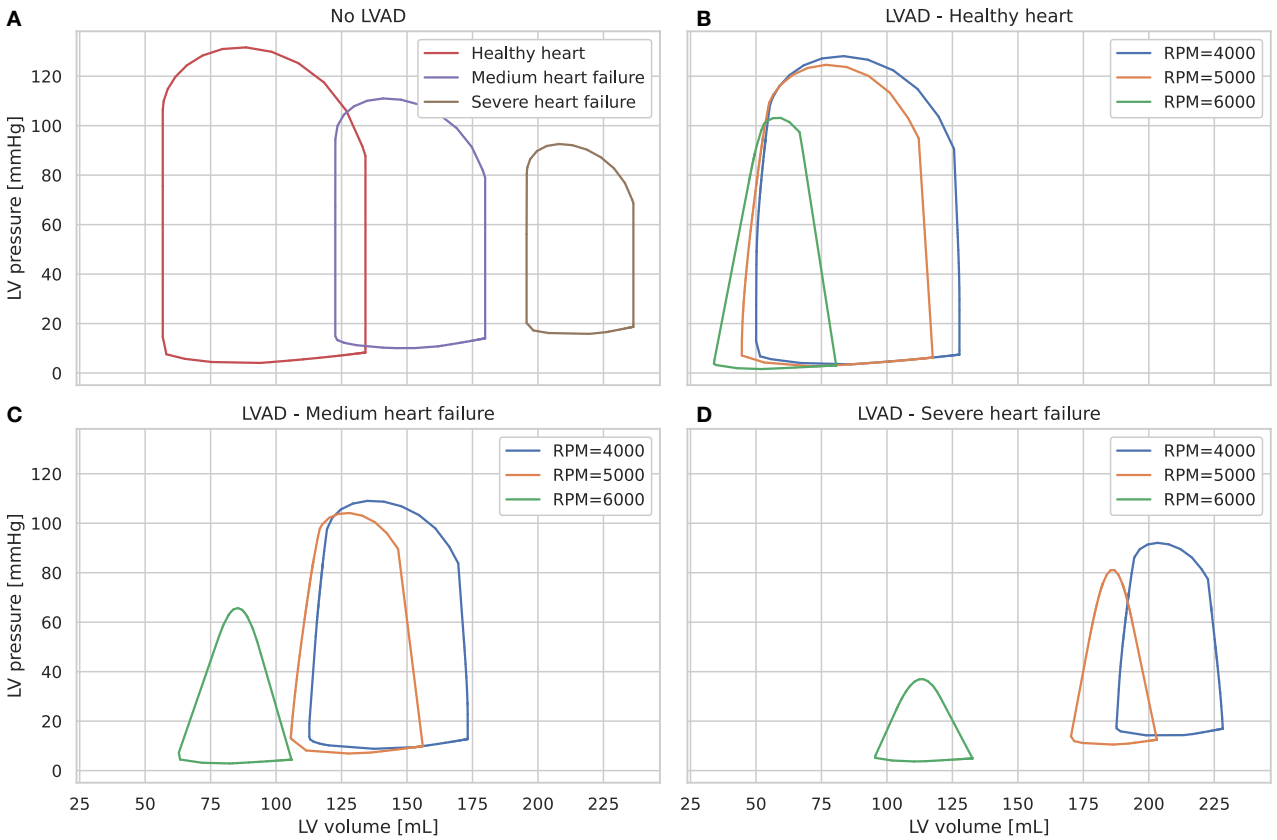

FIGURE 2 | Left ventricle pressure-volume diagrams for different stages of heart failure, without LVAD **(A)** and with LVAD for different pump speeds **(B–D)**.

of evenly-spaced time series. We note $u^{i,\mathrm{SAP}}(t_m)$ and $u^{i,\mathrm{PAP}}(t_m)$ the values of the systemic arterial pressure (SAP) and pulmonary arterial pressure (PAP), respectively, at time $t_m = mT/N, m \in \{0, 1, \ldots, N\}$, for the ith sample of the dataset. The pressure curves were represented in the frequency domain. That is, we computed the trigonometric Fourier coefficients $a_k^{i,X}$ and $b_k^{i,X}$ such that,

$$u^{i,X}(t_m) = \frac{a_0^{i,X}}{2} + \sum_{k=1}^{N/2} \left[a_k^{i,X} \cos(\omega_k t_m) + b_k^{i,X} \sin(\omega_k t_m) \right],$$

where N is even, $\omega_k = 2k\pi/T$ and X is either SAP or PAP (19).

We fixed the activation functions of the DNN and trained a model for various number of layers and neurons per layer. In addition to the Fourier coefficients of the signals, we provided the pump setting ω_c^i of ith sample as an additional predictor variable. To reduce the noise and to obtain better trainability thanks to a smaller input size, we choose a small number K and we only keep $(2K-1)$ Fourier coefficients of the signal $u^{i,X}$, which are stored in a vector $\mathbf{c}^{i,X} = (a_0^{i,X}, \ldots, a_{K-1}^{i,X}, b_1^{i,X}, \ldots, b_{K-1}^{i,X})$. An input-output pair is represented by the input vector $\mathbf{x}^i = (\mathbf{c}^{i,\mathrm{SAP}}, \mathbf{c}^{i,\mathrm{PAP}}, \omega_c^i)$, and the output vector $\mathbf{y}^i = (E_{max,lv}^i, E_{max,lv,0}^i, G_{E_{max,lv}}^i, k_{E,lv}^i)$.

2.5. Software Implementation

The 0D model has been implemented in the object-oriented and equation-based Modelica programming language, on the open-source OpenModelica framework. Pre- and post-processing procedures were implemented in the Python and Matlab languages. The DNN architecture was implemented with the Keras library within TensorFlow.

3. RESULTS

3.1. Fourier Coefficient Determination

We first aimed at determining the numbers of Fourier coefficients K required to accurately reconstruct the pressure signals. These are in turn given as input to the DNN. We provide in **Supplementary Figure 2** a reconstruction of a pressure signal with different values of K for a complex curve, as obtained with low RPM (4,000) and severe LV failure. Indeed, in these conditions, LV preload is little reduced, allowing the native LV to contract and eject through the aortic valve. Thus, ejection through the LVAD and the native aorta induced a complex signal (20). In addition, artificial pulse of the device adds a level of perturbation, that is moreover not synchronized with heart rate. Black curve on the top of the figure corresponds to the original signal, and colored curves reconstructions with different values

of K. We chose to restrict to $K = 50$. While limiting the size of the input data, this choice enables an accurate reconstruction of pressure curve signals.

3.2. DNN Architecture Evaluation

We used the rectified linear unit and sigmoid activation functions for the hidden and output layers, respectively. That is, $g^{(l)}(x) = \max(x, 0)$ for $l < L$ and $g^{(L)}(x) = e^x/(1 + e^x)$. For training, we used the typical mean squared error loss function $\mathcal{L}_\Theta = \frac{1}{|B|}\sum_{i\in B}\left[\mathbf{y}^i - \mathbf{f}(\mathbf{x}^i; \Theta)\right]^2$ that we minimized with Adam optimizer, with $B = 32$ being the batch size. Learning rate was set to 0.001. 5% of the samples in the dataset were kept for the test set, while 80% and 20% of the remaining samples were used in the training and validation sets, respectively.

We evaluated 28 different DNN architectures. For each architecture, the training and validation values of the loss and the mean absolute error were computed, as shown in **Supplementary Table 2**. We then selected the best performing and smallest architecture (in terms of number of layers and neurons), corresponding to architecture #2 in **Supplementary Table 2**.

3.3. DNN Performances

Table 1 shows performances of the DNN to predict the 4 output parameters of the test set (10, 500 samples). The data indicate accurate predictions for $E_{max,lv}$, $E_{max,lv,0}$, and $k_{E,lv}$ (mean relative error of predictions, respectively, 10.07, 7.58, and 0.93%). The predictive accuracy was slightly lower for $G_{E_{max,lv}}$ (mean relative error 12.43%), which is consistent with the sensitivity analysis performed in Bonnemain et al. (12), showing a lower sensitivity of the 0D model to this parameter. Graphical representation of data presented in **Table 1** is provided in **Figure 3**.

The DNN performance was further assessed by solving the 0D model with the 4 parameters (real and predicted) for each sample of the test set, using the following output measures: LV end-systolic pressure and volume, LV end-diastolic pressure and volume, LV ejection fraction, and pulmonary artery wedge pressure (a clinical surrogate of LV end-diastolic pressure). For each variable, the minimal, maximal, and mean values, as well as the standard deviation, were obtained using alternatively the exact and predicted values of the 4 parameters of LV systolic function, and the differences between obtained data were computed as the error, presented as mean ±SD, 95% confidence interval, and relative error. The results of this analysis are presented in **Table 2** which indicates values of relative error <5% for all the hemodynamic values evaluated.

TABLE 1 | Evaluation of the DNN performance on the test set, by comparing exact and predicted parameters of the output of the DNN.

	$E_{max,lv}$	$E_{max,lv,0}$	$G_{E_{max,lv}}$	$k_{E,lv}$
Exact				
Min	0.200	0.200	0.200	0.0110
Max	2.95	2.39	0.475	0.0140
Mean	1.58	1.30	0.338	0.0125
SD	0.791	0.632	0.0794	8.65e-4
Predicted				
Min	0.204	0.208	0.203	0.0111
Max	2.91	2.38	0.472	0.0140
Mean	1.56	1.27	0.342	0.0125
SD	0.782	0.627	0.0632	8.42e-4
Error				
Mean	0.111	0.0693	0.0386	1.17e-4
Min	2.05e-5	1.24e-6	2.12e-5	6.85e-9
Max	0.913	0.352	0.202	9.88e-4
SD	0.0887	0.0524	0.0319	9.56e-5
CI min	0.109	0.0683	0.0380	1.15e-4
CI max	0.112	0.0703	0.0392	1.18e-4
Relative error				
Mean	0.101	0.0758	0.124	9.33e-3

Error is computed as the difference between exact and predicted output in absolute value. Relative error is error divided by exact output. $E_{max,lv}$ [mmHg/ml], end-systolic left ventricular elastance; $E_{max,lv,0}$ [mmHg/ml], end-systolic left ventricular elastance in absence of baroregulation; $G_{E_{max,lv}}$ [mmHg/ml/(spikes/ml)], maximum baroreceptor gain; $k_{E,lv}$ [1/ml], steepness of end-diastolic pressure-volume curve.

4. DISCUSSION

LVAD has become a frequently used therapeutic option in end-stage heart failure. Although this type of mechanical circulatory support significantly improves clinical condition and outcome of patients (21), some issues deserve further exploration regarding the interactions between the LVAD and the residual function of the native LV (22). A better understanding of these interactions and of hemodynamic properties of the assisted LV would be important to optimize support strategies, detect early abnormal interactions between device and LV, and finally identify LV recovery to consider weaning of the LVAD (23).

Our present work provides a novel approach to help address such complex issues by implementing a DNN and by using a 0D model of the cardiovascular system, which incorporates the mathematical description of a last generation LVAD. We developed an automated framework to accurately recover LV hemodynamic parameters from data available in the clinical practice, namely systemic and pulmonary arterial pressures. These signals were represented in their frequency domain and were then given as input to the DNN. An appropriate selection of the number of Fourier coefficient allowed to retain only relevant physiological frequencies, control size of input, and clean possible noise. In addition to the pressure signals, the input of the DNN included information about the device setting (RPM).

Owing to this architecture, only one DNN has to be trained to include every possibility of the working range of the device. This makes our framework suitable for a fast and automated implementation. Our DNN proved excellent reliability, being able to predict $E_{max,lv}$ with a mean relative error of <10%. Furthermore, the 0D model allowed to precisely recover values of LVEF, ventricular volumes, and ventricular pressures, as indicated by the small relative error (<5%) between their actual and predicted values. Moreover, the average time to predict LV parameters from input signal was fast (<1 s) using a

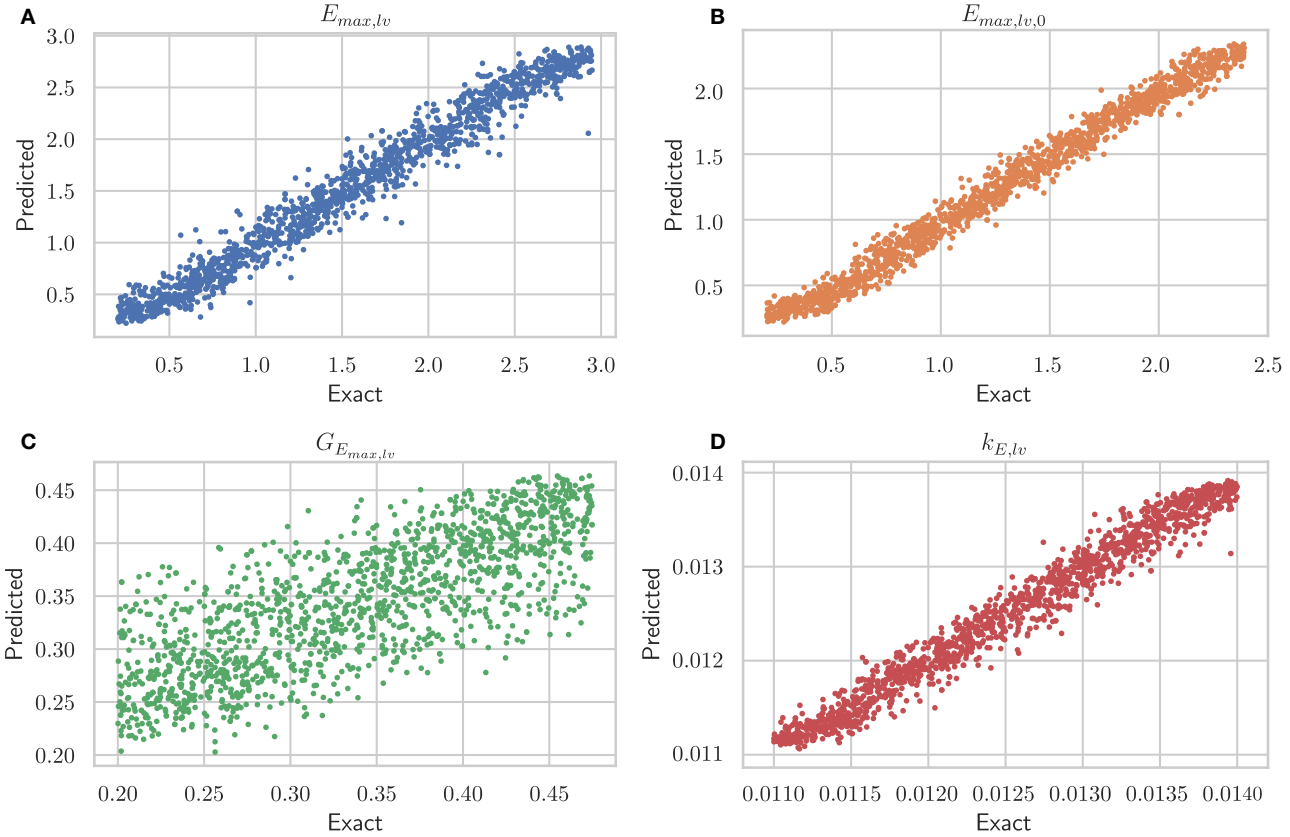

FIGURE 3 | Performance of architecture #2 (see **Supplementary Table 2**) on the test set. For each of the four parameters, the exact value is plotted against the predicted one. **(A)** $E_{max,lv}$ [mmHg/ml], end-systolic left ventricular elastance; **(B)** $E_{max,lv,0}$ [mmHg/ml], end-systolic left ventricular elastance in absence of baroregulation; **(C)** $G_{E_{max,lv}}$ [mmHg/ml/(spikes/ml)], maximum baroreceptor gain; **(D)** $k_{E,lv}$ [1/ml], slope of end-diastolic pressure-volume curve.

personal computer. Thus, real-time implementation could be easily considered.

The determination of $E_{max,lv}$ is challenging, requiring left-side heart chambers catheterization, a technique whose implementation is not realistic in the daily clinical practice. Non-invasive methods, including echocardiography and magnetic resonance imaging, coupled to measurement of arterial blood pressure have been proposed (24, 25), however their use is mainly restricted to the experimental setting. Furthermore, none of these techniques have so far been applied to assess $E_{max,lv}$ in patients assisted with a LVAD. It is noteworthy that a few preclinical studies have highlighted significant difficulties to determine $E_{max,lv}$ in the presence of a LVAD. In a study performed using an *in vitro* cardiac simulator under control and heart failure conditions, Jhune et al. (26) showed that acute LVAD support induced a "pseudo-improvement" of calculated ventricular elastance, highly dependent on the LVAD speed. In two experimental animal studies, a comparable dependence of ventricular elastance on LVAD pump speed has also been reported by Vandenberghe et al. (27) in a calf model, whereas Sugai et al. (28) did not find such dependence in a goat model.

In the present work, the determination of $E_{max,lv}$ remained accurate whatever the degree of residual LV function, LVAD setting, and loading conditions. Therefore, our method has the ability to determine $E_{max,lv}$ independently from all potential influences of the aforementioned parameters, thereby avoiding misleading information. The framework was able to generate large amounts of data encompassing the whole working range of the device and every stage of heart failure severity, thereby permitting to appropriately train the DNN and guarantee the accuracy of predictions. Therefore, the implementation of our framework allowed to leverage the power of DNN to predict key parameters whose determination would be otherwise extremely cumbersome. An important issue to emphasize here is that the value of $E_{max,lv}$ retrieved with our DNN cannot be calibrated with an effective measurement, which should require simultaneous recordings of intracardiac pressure and volume. Therefore, the absolute value of $E_{max,lv}$ as obtained from our framework, should be interpreted with caution, whereas variations of this value along time would provide invaluable information to identify rapidly changing hemodynamic condition such as can occur in the acute setting.

TABLE 2 | Results of 0D simulations using exact and predicted parameters of the test set.

	LVEF	LVEDV	LVESV	LVEDP	LVESP	PCWP
Exact						
Mean	53.0	141	67.8	3.66	113	7.43
Min	24.4	86.0	28.7	1.03	39.0	3.11
Max	71.1	220	166	12.0	135	16.7
SD	9.16	22.0	22.5	1.70	14.1	2.30
Predicted						
Mean	52.6	142	68.9	3.71	112	7.49
Min	24.3	85.6	29.2	1.05	39.2	3.15
Max	70.1	217	159	12.9	135	17.3
SD	9.30	22.6	23.3	1.75	14.5	2.34
Error						
Mean	1.04	1.62	2.15	0.112	0.881	0.107
Min	1.17e-4	8.11e-5	5.83e-7	9.44e-7	5.53e-6	2.14e-5
Max	8.36	16.8	17.5	1.27	20.4	1.09
SD	1.04	1.52	2.15	0.127	1.39	0.109
CI min	1.02	1.59	2.11	0.109	0.855	0.105
CI max	1.06	1.65	2.19	0.114	0.908	0.109
Relative error						
Mean	0.0204	0.0111	0.0317	0.0295	8.82e-3	0.0138

The error on the retrieved haemodynamic parameters is expressed as absolute or relative. LVEF [%], left ventricular ejection fraction; LVEDP [mmHg], left ventricular end-diastolic pressure; LVESP [ml], left ventricular end-systolic pressure; LVEDV [ml], left ventricular end-diastolic volume; LVESV [ml], left ventricular end-systolic volume; PCWP [mmHg], pulmonary capillary wedge pressure.

The implementation of our tool could be notably useful in the post-operative phase of LVAD implantation. Indeed, in this context, LVAD RPM must be constantly adjusted to find the optimal settings of the device: although too high RPMs may lead to suction events promoting a reduction of pump flow, too low RPMs may cause inadequately low LVAD flow with systemic hypoperfusion, as well as left ventricle insufficient unloading and pulmonary oedema. These disturbances are likely to be influenced by the residual left ventricular systolic function, whose real time evaluation using our method would therefore be extremely helpful for hemodynamic optimization (29–31). Owing to the rapidity of the framework to make predictions on low-performance devices (e.g., standard personal computer), its direct implementation in the monitoring system of the patient might be straightforwardly considered. Arterial signals could be analyzed to make real-time predictions of LV parameters. Moreover, further development may include automatized algorithm to optimally set RPM in function of the predictions. This concept could be already implemented in the catheterism laboratory when performing ramp test during routine follow-up to optimize LVAD outflow or evaluate LV function recovery.

Some limitation of our work has to be acknowledged. Firstly, our framework was exclusively trained and run using numeric data. Obviously a next step will be to assess the performance of this framework using clinical data of pulmonary and systemic arterial pressure. Although this could be relatively challenging owing to the noise included in the signals under clinical acquisition, this limitation could be overcome by reducing the number of Fourier coefficients. Secondly, the 0D model used to train the DNN did not include possible alterations in left sided valve dysfunction such as mitral valve regurgitation, or right ventricle dysfunction, which may be both associated with LVAD implementation. Future refinements of our model should therefore take into account such possibilities.

5. CONCLUSION

In summary, we developed a novel method to assess systolic function of the mechanically assisted left ventricle, based on a DNN trained with data obtained from a 0D model of the cardiovascular system taking into account the presence of a LVAD. This DNN is fed with simple pressure signals (systemic and pulmonary) and with the rotation speed of the device, allowing to predict end-systolic elastance and other parameters of left ventricular function with excellent accuracy. Our method could represent a useful tool to optimize LV-LVAD interactions early after implantation as well as during chronic therapy, and to evaluate the possible functional recovery of the left ventricle.

DATA AVAILABILITY STATEMENT

The code used to support the findings of this study has been deposited in the following repository: https://github.com/matthiaszeller/VAD-0D-DNN.

AUTHOR CONTRIBUTIONS

JB: design and implementation of the work, data acquisition and interpretation, and manuscript drafting. MZ: implementation of the work, data acquisition and interpretation, and manuscript drafting. LP: data interpretation and manuscript drafting. SD: design of the work, data interpretation, final manuscript drafting, and financial support. LL: data interpretation, final manuscript drafting, and financial support. All authors critically reviewed and approved the final 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.2021.752088/full#supplementary-material

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ORIGINAL RESEARCH
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A Model for the Prediction of Mortality and Hospitalization in Chinese Heart Failure Patients

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Background: Although many risk prediction models have been released internationally, the application of these models in the Chinese population still has some limitations.

Aims: The purpose of the study was to establish a heart failure (HF) prognosis model suitable for the Chinese population.

Methods: According to the inclusion criteria, we included patients with chronic heart failure (CHF) who were admitted to the Department of Cardiac Rehabilitation of Tongji Hospital from March 2007 to December 2018, recorded each patient's condition and followed up on the patient's re-admission and death. All data sets were randomly divided into derivation and validation cohorts in a ratio of 7/3. Least absolute shrinkage and selection operator regression and Cox regression were used to screen independent predictors; a nomogram chart scoring model was constructed and validated.

Results: A total of 547 patients were recruited in this cohort, and the median follow-up time was 519 days. The independent predictors screened out by the derivation cohort included age, atrial fibrillation (AF), percutaneous coronary intervention (PCI), diabetes mellitus (DM), peak oxygen uptake (peak VO_2), heart rate at the 8th minute after the cardiopulmonary exercise peaked (HR8min), C-reaction protein(CRP), and uric acid (UA). The C indexes values of the derivation and the validation cohorts were 0.69 and 0.62, respectively, and the calibration curves indicate that the model's predictions were in good agreement with the actual observations.

Conclusions: We have developed and validated a multiple Cox regression model to predict long-term mortality and readmission risk of Chinese patients with CHF.

Registration Number: ChicTR-TRC-00000235.

Keywords: risk prediction, mortality, hospitalization, heart failure, Chinese population

INTRODUCTION

Heart failure (HF) is a serious manifestation of the late stage of various heart diseases. Its morbidity has an increasing trend, and the mortality and rehospitalization rates remain high, posing a huge economic burden for health care systems (1–3). According to recent studies, the 1-year mortality rate of patients with chronic heart failure (CHF) is 6.4%,

and the combined death or HF hospitalization rate within 1 year is 14.5% (4). Therefore, stratifying patients according to the risk of future results (re-admission and death), and optimizing treatment strategies for patients with different needs would be beneficial to all healthcare systems and patients.

The 2019 American College of Cardiology (ACC) Expert Consensus on HF proposes that the assessment of risk-increasing factors can help guide decision-making for preventive intervention (5). Many risk prediction models have been released internationally (6–10). The 2017 A systems Biology Study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF) research plan included 2,516 HF patients from 69 centers in 11 international centers. It concluded that the strongest predictors of mortality are age, urea nitrogen, N-terminal B-type natriuretic peptide, hemoglobin, and beta blockers. The predictors of hospitalization rate are age, hospitalization history for HF, edema, systolic blood pressure, and estimated glomerular filtration rate (6). In 2019, the Korean Acute Heart Failure registry used 12 predictors to establish a risk score that predicts the risk of HF-specific readmission or death at 30 days after discharge (7). The 2020 Prospective Comparison of angiotensin receptor neprilysin inhibitor (ARNI) with angiotensin-converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) model can accurately predict the morbidity and mortality of ambulatory patients with CHF with reduced ejection fraction at 1 and 2 years (8). It can be seen from the above that the current existing forecasting models have the following advantages: Indicators are easily available and not focusing on a single risk factor. However, the application of these models in the Chinese population still has some limitations. Most of these models use static indicators, which are not sufficient to reflect the overall condition of the patients (6–8, 10, 11). Further, most studies have a short follow-up time and cannot judge the long-term prognosis (7, 10, 11). As there are regional differences in the mortality and rehospitalization rates of patients with CHF and scarce data from the Chinese population, the applicability of the international HF risk prediction model to the Chinese population is controversial (4, 12). Therefore, it is necessary to establish a new HF risk prediction model suitable for the Chinese population.

In this study, we selected individuals with CHF in China as the target population for modeling and conducted relevant cardiopulmonary exercise tests (CPETs) to monitor the respiratory and circulatory parameters of patients under exercise to obtain comprehensive indicators of cardiopulmonary function. According to the literature, CPET parameters are predictors of the prognosis of HF, especially the level of peak oxygen uptake (peak VO_2) (13–15). Of note, our follow-up time is long (the longest follow-up time is as long as 12 years) which is helpful to assess the long-term prognosis of patients with CHF. Our research combines the experimental indicators of cardiopulmonary exercise to propose a long-term prognosis and readmission model for CHF in the Chinese population, which provides a basis for the treatment of clinical CHF and reveals potential targets for interventions to improve prognosis.

METHODS

Data Sources and Processing

This study follows the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) report (16). The clinical data of the study were from 2,136 patients with CHF in the Outpatient or Cardiac Rehabilitation Department in Shanghai Tongji Hospital Affiliated to Tongji University from March 1, 2007 to December 31, 2018. The available information includes demographics, medical history, CPET indicators, echocardiography, laboratory testing, and drugs. Other data extracted include the number of hospital admissions, length of stay, and New York Heart Association (NYHA) classification at admission. Inclusion criteria include CHF diagnosed in accordance with the "Chinese Heart Failure Diagnosis and Treatment Guidelines 2018" with a medical history of more than 3 months; age $\geq$18 years; NYHA heart function level 1–3; and ability to cooperate to complete the CPET. Exclusion criteria include chronic obstructive pulmonary disease, pulmonary heart disease or pulmonary vascular disease; acute myocardial infarction; second or third degree atrioventricular block; acute pericarditis, rheumatic heart disease; thrombophlebitis or intracardiac thrombosis; severe supraventricular or ventricular arrhythmia; and uncontrolled hypertension. According to the criteria of acceptance, 1,589 patients were excluded, and 547 patients with HF were finally included (**Figure 1**). The study was conducted in accordance with the Declaration of Helsinki as revised in 2013 and was approved by the Ethics Committee of Tongji Hospital Affiliated to Tongji University [LL(H)-08-04]. Informed consent was taken from all the patients. Before analysis, the patient's records/information were anonymized and de-identified.

Potential Predictive Variables

Potential predictors include the following characteristics of the patient: demographic characteristics (e.g., gender, age, height, weight, and body mass index), basic heart disease

Abbreviations: ACC, American College of Cardiology; ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; AHA, American Heart Association; ANOVA, analysis of variance; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor; BIOSTAT-CHF, Biology Study to Tailored Treatment in Chronic Heart Failure; BNP, B-type natriuretic peptide; CHF, chronic heart failure; CPETs, cardiopulmonary exercise tests; CRP, C-reactive protein; DCM, dilated cardiomyopathy; DM, diabetes mellitus; HBP, high blood pressure; HF, heart failure; HF-ACTION, Heart Failure: A Controlled Trial Investigating Outcomes of Exercise TraiNing; HFmrEF, heart failure with a moderately reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR8min, heart rate at the 8th minute after the cardiopulmonary exercise peaked; HRAT, heart rate at anaerobic threshold; IHD, ischemic heart disease; IQR, interquartile ranges; KM, Kaplan-Meier; LASSO, least absolute shrinkage and selection operator; LVEF, left ventricular ejection fraction; MECKI, The Metabolic Exercise test data combined with Cardiac and Kidney Indexes; MI, myocardial infarction; NYHA, New York Heart Association; PARADIGM-HF, Global Mortality and Morbidity in Heart Failure; PCI, percutaneous coronary intervention; Peak DBP, peak diastolic blood pressure; Peak MBP, peak average blood pressure; Peak VO_2, peak oxygen uptake; $PETCO_2$, end-tidal CO_2 pressure; TnI, troponin I; TRIPOD, transparent reporting of a multivariable prediction model for individual prognosis or diagnosis; UA, uric acid; VE/VCO_2, ventilation/carbon dioxide production; VO_2 AT, oxygen consumption at anaerobic threshold; WT, weight.

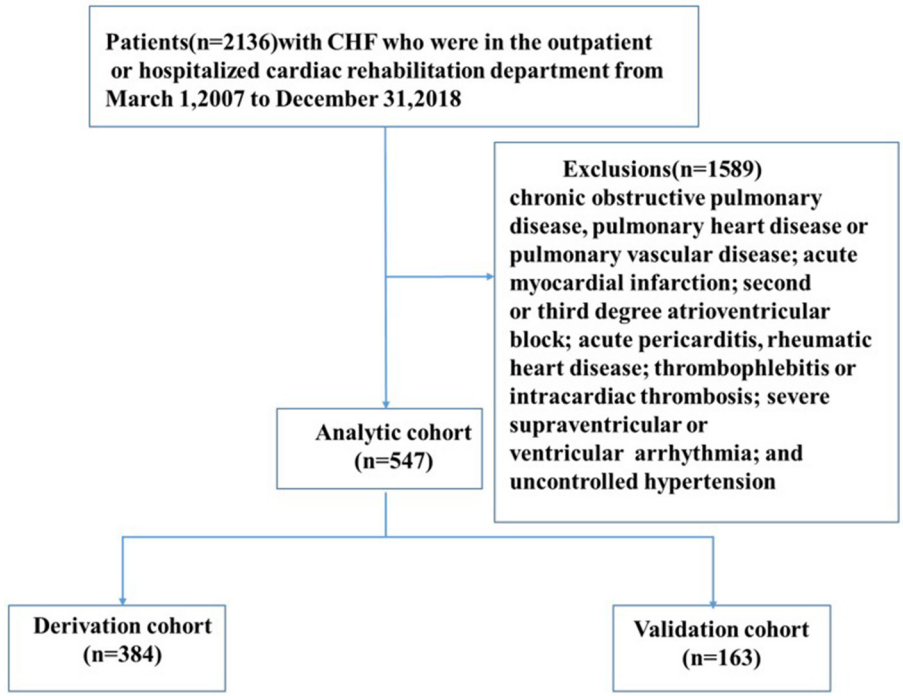

FIGURE 1 | Study flow. CHF, chronic heart failure.

history (e.g., coronary heart disease, dilated heart disease, and hypertension), other related medical history (e.g., diabetes, hyperlipidemia, and stroke), CPET indicators [e.g., peak VO_2, end-tidal CO_2 pressure ($PETCO_2$)], cardiac ultrasonography [e.g., left ventricular ejection fraction (LVEF)], laboratory tests (e.g., blood lipids, and blood potassium), and medications for HF treatment [e.g., angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), angiotensin receptor neprilysin inhibitors (ARNI), β-blockers].

Study Design

A total of 90 variables were included in the study as potential prognostic factors. Patients with readmission or death records mainly for HF during the follow- up were defined as the readmitted or died group. Patients who did not have a re-admission or death record during the follow up were defined as the not readmitted, alive group. This is an open-label design trial. In order to reduce bias, examiners, researchers collecting data on outcome indicators, data managers, and statisticians do not know the patient's name.

Outcomes

Readers should refer to the definitions of key clinical data elements and cardiovascular endpoint events issued by the ACC/American Heart Association (AHA) in conjunction with the US Food and Drug Administration and the Cardiovascular Trial Standard Data Collection Program. The endpoint of this study was the composite endpoint of all-cause death and all-cause admission. The data from the electronic medical records and our follow-up results were used to measure this result.

Follow-Up

Starting from December 2018, a telephone follow-up or electronic medical record review was conducted every 6 months to collect information on hospitalization or death in the past period, until the patient's first readmission or death or the study was terminated by the follow-up on June 30, 2020. The time of hospitalization or death was recorded by the follow-up staff. A wrong telephone number, lack of response, and refusal to follow up were considered as being lost to follow up.

Statistical Analysis

We used R language [R software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria)] and SPSS software (version 20.0; IBM Corp, Armonk, NY, USA) for statistical analysis. The measurement data were tested for normal distribution. Normally distributed measurement data were expressed as mean ± standard deviation. The comparison between two groups was done using an independent sample *t*-test and the comparison between multiple groups using one-way analysis of variance (ANOVA). The least significant difference test was used for multiple comparisons between groups. Non-normal distribution measurement data were expressed as medians and interquartile ranges (IQR) and compared by the non-parametric Mann-Whitney *U*-test. Categorical data were expressed as frequency (percentage), and χ^2-test was used for comparison between groups. In addition, variables with missing

values <20% were subjected to multiple imputation using the R language mice package. $P < 0.05$ indicates that the difference is statistically significant.

Modeling and Validation

Through random sampling, the entire data set was divided into derivation and validation cohorts in a ratio of 7:3. Least absolute shrinkage and selection operator (LASSO) regression and Cox multivariate analysis were used to screen independent risk factors that could affect the prognosis of CHF, and a nomogram was used to establish a risk prediction model. The C-index values were calculated for the derivation and validation groups. The degree of discrimination was determined and a calibration curve drawn to evaluate the degree of calibration. Finally, the patients were classified into high (greater than the mean risk score) and low risk (no greater than the mean risk score) categories according to the score, and the Kaplan-Meier (KM) curve was drawn for survival analysis (17).

RESULTS

Study Population and Cohort Characteristics

A total of 547 patients with HF were screened; 18.3% were women; the median age was 63 years; the median follow-up time was 519 days and the loss to follow up rate was 10.79%; The incidence of composite endpoints (all-cause death and all-cause admission) in 1/3/5/10 years were 40.95%, 56.86%, 60.15%, and 63.44%, respectively. Compared with the not readmitted and alive group, the readmitted or died group

TABLE 1 | The characteristics of death or readmission stratification in patients with CHF.

Characteristic	Overall ($n = 547$)	Not readmitted, alive ($n = 196$)	Readmitted or died ($n = 351$)	χ^2/Z	p
Time (median [IQR])	519.00 [193.50, 1444.50]	1609.50 [752.75, 2644.25]	262.00 [127.50, 632.50]	**−14.470**	**0.000**
Female, *n* (%)	100 (18.3)	43 (21.9)	57 (16.2)	2.735	0.098
Age (median [IQR])	63.00 [56.00, 69.00]	60.50 [55.00, 68.00]	64.00 [57.00, 70.00]	**−3.021**	**0.003**
Smoke, *n* (%)	329 (60.1)	119 (60.7)	210 (59.8)	0.041	0.839
Alcohol, *n* (%)	91 (16.6)	32 (16.3)	59 (16.8)	0.021	0.884
IHD, *n* (%)	333 (60.9)	105 (53.6)	228 (65.0)	**6.846**	**0.009**
DCM, *n* (%)	171 (31.3)	71 (36.2)	100 (28.5)	3.501	0.061
AF, *n* (%)	81 (14.8)	20 (10.2)	61 (17.4)	**5.132**	**0.023**
MI, *n* (%)	205 (37.5)	47 (24.0)	158 (45.0)	**23.749**	**0.000**
PCI, *n* (%)	225 (41.1)	55 (28.1)	170 (48.4)	**21.556**	**0.000**
HBP, *n* (%)	386 (70.6)	146 (74.5)	240 (68.4)	2.263	0.132
DM, *n* (%)	158 (28.9)	40 (20.4)	118 (33.6)	**10.684**	**0.001**
Height (median [IQR])	168.31 [166.00, 172.00]	168.31 [165.00, 172.00]	168.31 [166.50, 172.00]	−0.005	0.996
WT (median [IQR])	71.97 [65.00, 76.25]	71.97 [65.00, 80.00]	71.97 [65.00, 76.00]	−0.066	0.947
VO_2 AT (median [IQR])	10.72 [9.10, 12.20]	10.80 [9.50, 12.83]	10.70 [9.00, 12.00]	**−2.525**	**0.012**
Peak VO_2 (median [IQR])	14.66 [12.35, 16.90]	14.80 [12.60, 17.70]	14.40 [12.30, 16.15]	**−2.998**	**0.003**
HRAT (median [IQR])	94.00 [85.00, 100.50]	94.50 [86.00, 106.00]	93.00 [84.00, 99.00]	**−3.146**	**0.002**
HR8min (median [IQR])	81.00 [81.00, 81.00]	81.00 [81.00, 81.00]	81.00 [81.00, 81.00]	−0.905	0.366
Peak DBP (median [IQR])	81.00 [72.00, 90.00]	81.00 [75.00, 90.00]	81.00 [72.00, 90.00]	−1.380	0.168
Peak MBP (median [IQR])	105.00 [93.83, 114.33]	107.00 [96.00, 115.42]	105.00 [93.33, 113.67]	**−2.091**	**0.037**
VE/VCO_2 (median [IQR])	34.90 [30.65, 39.10]	34.00 [29.26, 38.12]	35.75 [31.50, 40.15]	**−3.088**	**0.002**
LVEF (median [IQR])	0.45 [0.36, 0.52]	0.45 [0.38, 0.50]	0.45 [0.36, 0.52]	−0.040	0.968
LVEF group				3.004	0.223
LVEF <0.4, *n* (%)	170 (31.1)	57 (29.1)	113 (32.2)		
LVEF 0.4–0.49, *n* (%)	222 (40.6)	89 (45.4)	133 (37.9)		
LVEF ≥0.5, *n* (%)	155 (28.3)	50 (25.5)	105 (29.9)		
CRP (median [IQR])	6.40 [3.00, 6.40]	6.40 [3.00, 6.40]	6.40 [3.00, 6.40]	−0.562	0.574
BNP (median [IQR])	702.00 [702.00, 702.00]	702.00 [702.00, 702.00]	702.00 [702.00, 702.00]	−0.750	0.453
TnI (median [IQR])	0.05 [0.01, 0.39]	0.08 [0.01, 0.39]	0.05 [0.01, 0.39]	**−1.988**	**0.047**
UA (median [IQR])	432.00 [355.00, 464.00]	432.00 [368.75, 456.00]	432.00 [353.00, 469.50]	−0.244	0.807

Significant values of P < 0.05 is indicated in bold.

AF, atrial fibrillation; BNP, B-type natriuretic peptide; CRP, C-reactive protein; DCM, dilated cardiomyopathy; DM, diabetes mellitus; HBP, high blood pressure; HR8min, heart rate at the 8th minute after the cardiopulmonary exercise peaked; HRAT, heart rate at anaerobic threshold; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; Peak DBP, peak diastolic blood pressure; Peak MBP, peak average blood pressure; Peak VO_2, peak oxygen uptake; TnI, troponin I; UA, uric acid; VE/VCO_2, ventilation/carbon dioxide production; VO_2AT, oxygen consumption at anaerobic threshold; WT, weight.

TABLE 2 | Analysis of risk events indicators in chronic heart failure patients.

Indicators	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.03 (1.02–1.04)	**0.000**	1.03 (1.01–1.04)	**0.000**
AF	1.80 (1.30–2.49)	**0.000**	1.60 (1.12–2.29)	**0.009**
MI	1.73 (1.34–2.24)	**0.000**	1.26 (0.72–2.20)	0.417
PCI	1.70 (1.31–2.20)	**0.000**	1.81 (1.02–3.18)	**0.041**
DM	1.56 (1.18–2.05)	**0.002**	1.41 (1.06–1.88)	**0.020**
Height	1.01 (0.99–1.03)	0.175	1.01 (1.00–1.03)	0.124
Peak VO_2	0.93 (0.90–0.97)	**0.000**	0.95 (0.91–0.99)	**0.012**
HR8min	1.05 (1.02–1.08)	**0.004**	1.06 (1.03–1.10)	**0.000**
Peak DBP	0.99 (0.98–1.00)	**0.008**	1.00 (0.98–1.02)	0.696
Peak MBP	0.99 (0.98–1.00)	**0.010**	0.99 (0.98–1.01)	0.538
CRP	1.03 (1.01–1.05)	**0.000**	1.04 (1.02–1.05)	**0.000**
BNP	1.00 (1.00–1.00)	**0.003**	1.00 (1.00–1.00)	0.108
TnI	0.93 (0.83–1.05)	0.243	0.92 (0.81–1.04)	0.187
UA	1.00 (1.00–1.00)	**0.016**	1.00 (1.00–1.00)	**0.005**

Significant values of P < 0.05 is indicated in bold.

AF, atrial fibrillation; BNP, b-type natriuretic peptide; CRP, c-reactive protein; DM, diabetes mellitus; HR8min, heart rate at the 8th minute after the cardiopulmonary exercise peaked; MI, myocardial infarction; PCI, percutaneous coronary intervention; Peak DBP, peak diastolic blood pressure; Peak MBP, peak average blood pressure; Peak VO_2, peak oxygen uptake; TnI, troponin I; UA, uric acid.

had the following characteristics: (i) older subjects; (ii) a high proportion of patients with a history of ischemic heart disease (IHD) (65%), atrial fibrillation (AF) (17.4%), myocardial infarction (MI) (45%), percutaneous coronary intervention (PCI) (48.4%), and diabetes mellitus (DM) (33.6%) ($P < 0.05$); (iii) lower oxygen consumption at anaerobic threshold (VO_2 AT), peak VO_2, heart rate at anaerobic threshold (HRAT), and peak average blood pressure (Peak MBP); (iv) higher ventilation/carbon dioxide production (VE/VCO_2) slope; (v) lower levels of biochemical indicator, troponin I (TnI) (**Table 1**).

Risk Model Development and Validation

Using computer-generated random numbers, the majority (70%) of the cohort were randomly assigned to the derivation cohort ($n = 384$), and the remaining 30% were assigned to the validation cohort ($n = 163$). There was no significant difference in the characteristics between the derivation and validation groups (**Supplementary Table 1**). After 90 variables entered LASSO regression screening, 14 variables [age, AF, MI, PCI, DM, height, peak VO_2, heart rate at the 8th minute after the cardiopulmonary exercise peaked (HR8min), peak diastolic blood pressure (peak DBP), peak MBP, c-reactive protein (CRP), b-type natriuretic peptide (BNP), TnI, uric acid (UA)] were obtained (**Supplementary Figures 1A,B**), and eight variables were retained after univariate analysis, multivariable analysis, and stepwise regression (**Table 2**; **Supplementary Table 2**).

In univariate regression analysis, 12 variables were significantly related to the prognosis of heart failure (the composite endpoint of death and rehospitalization). In the multivariate Cox regression analysis, the regression coefficients of the indicators in **Table 3**, and construct the prognostic risk proportion model [the calculation formula is h(t,x) = h0 (t)exp(0.025Age+0.560AF+0.803PCI+0.423DM−0.056Peak VO2+0.056HR8min+0.039 CRP+0.002UA)] according to the multivariate Cox regression coefficients of the eight indicators (18). Factors—age, AF, PCI, DM, peak VO_2, HR8min, CRP, and UA—that were independently associated with a higher likelihood of readmission or death were construct a risk scoring model, which was expressed in the form of a nomogram (**Tables 2**, **3**; **Figure 2**; **Supplementary Figure 2**).

TABLE 3 | The selected variables for model construction.

Factors	Coefficient	HR (95%CI)	*P*
Age	0.025	1.03 (1.01–1.04)	0.000
AF	0.560	1.75 (1.24–2.47)	0.001
PCI	0.803	2.23 (1.68–2.96)	0.000
DM	0.423	1.53 (1.16–2.02)	0.003
Peak VO_2	–0.056	0.95 (0.91–0.98)	0.005
HR8min	0.056	1.06 (1.02–1.09)	0.001
CRP	0.039	1.04 (1.03–1.05)	0.000
UA	0.002	1.00 (1.00–1.00)	0.000

AF, atrial fibrillation; CRP, c-reactive protein; DM, diabetes mellitus; HR8min, heart rate at the 8th minute after the cardiopulmonary exercise peaked; PCI, percutaneous coronary intervention; Peak VO_2, peak oxygen uptake; UA, uric acid.

The AUC of the prediction model is shown in **Supplementary Figure 3**. To evaluate the effectiveness of risk prediction for the composite endpoint of heart failure death and readmission. The sensitivity, specificity, positive predictive value, and negative predictive value of the training group's prediction model are shown in **Supplementary Table 3**.

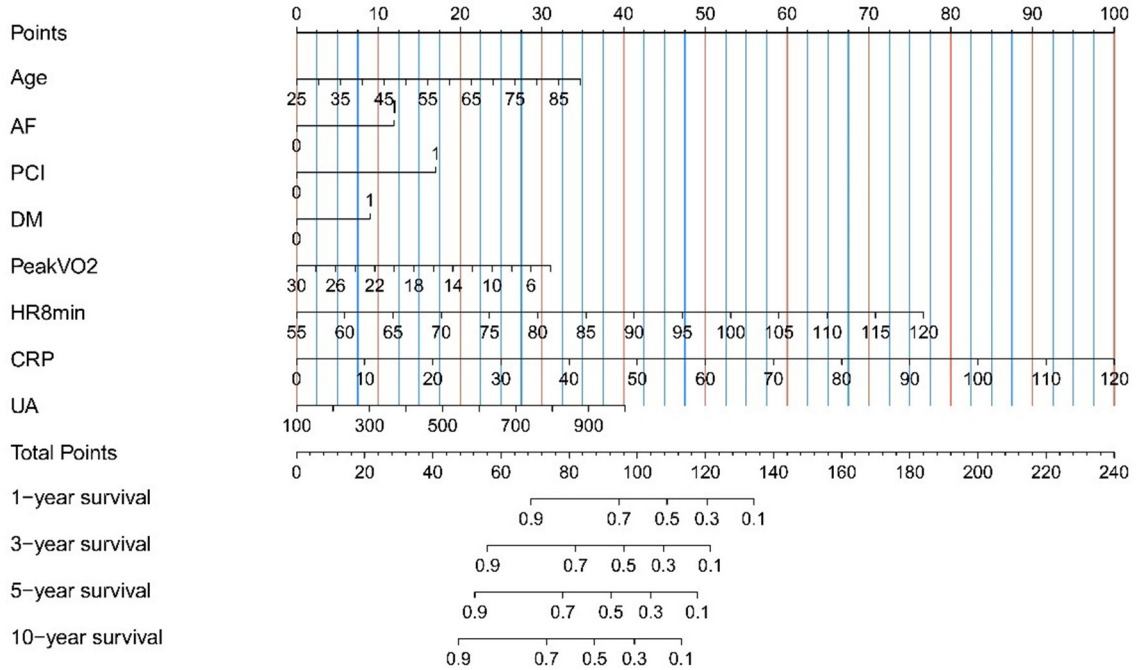

FIGURE 2 | Nomogram for the prediction of mortality and hospitalization in Chinese heart failure patients. Instructions for use of nomogram: draw a vertical line, and then add up the points corresponding to each feature, and then draw the vertical line according to the total points until it intersects each survival axis to determine the survival probability of 1, 3, 5, and 10 years. For binary variables, 0 = no, 1 = yes. AF, atrial fibrillation; CRP, c-reactive protein; DM, diabetes mellitus; HR8min, heart rate at the 8th minute after the cardiopulmonary exercise peaked; PCI, percutaneous coronary intervention; Peak VO_2, peak oxygen uptake; UA, uric acid.

In the derivation and validation cohorts, the calculated model discrimination C-index values were 0.69 (95%CI 0.65–0.72) and 0.62 (95%CI 0.57–0.67), respectively, and the model's discrimination ability was moderate. The calibration chart shows that the occurrence of end-point events at 1 year/3 years/5 years/10 years was in good agreement with the actual observations (**Supplementary Figure 4**).

Based on the score calculated by the nomogram, the derivation cohort was divided into two groups, high- and low- risk groups, and KM curve survival analysis was performed. The results of the LogRank method showed that the KM curves of the high-risk and low-risk groups were significantly different in the three cohorts (derivation group, validation group, and the whole group). In the derivation group, the risk of rehospitalization or death at 1 year/3 years/5 years/10 years was 69.5, 87.8, 92.7, and 100% for the high-risk group and 32.5,61.9, 75.8, and 95.7% for the low-risk group, respectively (**Figure 3**; **Supplementary Figure 5**).

DISCUSSION

In this study, we selected simple parameters based on clinical conditions, laboratory indicators, cardiopulmonary exercise tests, and other measurements, and developed a new prediction model based on the Chinese HF population, which can assess the risk of readmission or death of patients with CHF. The C index values of the derivation cohort and validation cohorts were 0.69 (95%CI 0.65–0.72) and 0.62 (95%CI 0.57–0.67), respectively, which indicate moderate levels of predictive ability. Our C-index values are high among those from previously published HF risk prediction models (19). Moreover, the calibration curve at 1 year/3 years/5 years/10 years showed good consistency. Compared with the traditional HF risk prediction model, our model has some advantages for CHF patients in China: (i) it adds relevant CPET indicators; (ii) has a long follow-up time, and (iii) the target population is based on the Chinese population. This model can comprehensively assess the long-term prognosis of patients with HF and provide data for the Chinese population for inclusion in the world's CHF prognosis assessment.

In our cohort study, it was observed that patients with CHF who were hospitalized or who died were older, had more complications, and had poorer exercise endurance. The indicators included in the model were age, AF, PCI, DM, peak VO_2, HR8min, CRP, and UA. As a protective factor, peak VO_2 has been used as a tool to assess the severity of the disease, judge the short-term and long-term prognosis of patients with HF, and select patients for heart transplantation (20, 21). Lewis and Zlotoff (22) summarized the application of risk stratification based on cardiopulmonary exercise experiments in the management of advanced HF. They showed that exercise response patterns are predictive: Peak oxygen consumption can predict the lifespan of ordinary people, and CPET can effectively divide patients into high-risk and low-risk categories of HF events (22). Of note, as the peak VO_2 index can be improved by exercise (23), this model evaluation encourages high-risk

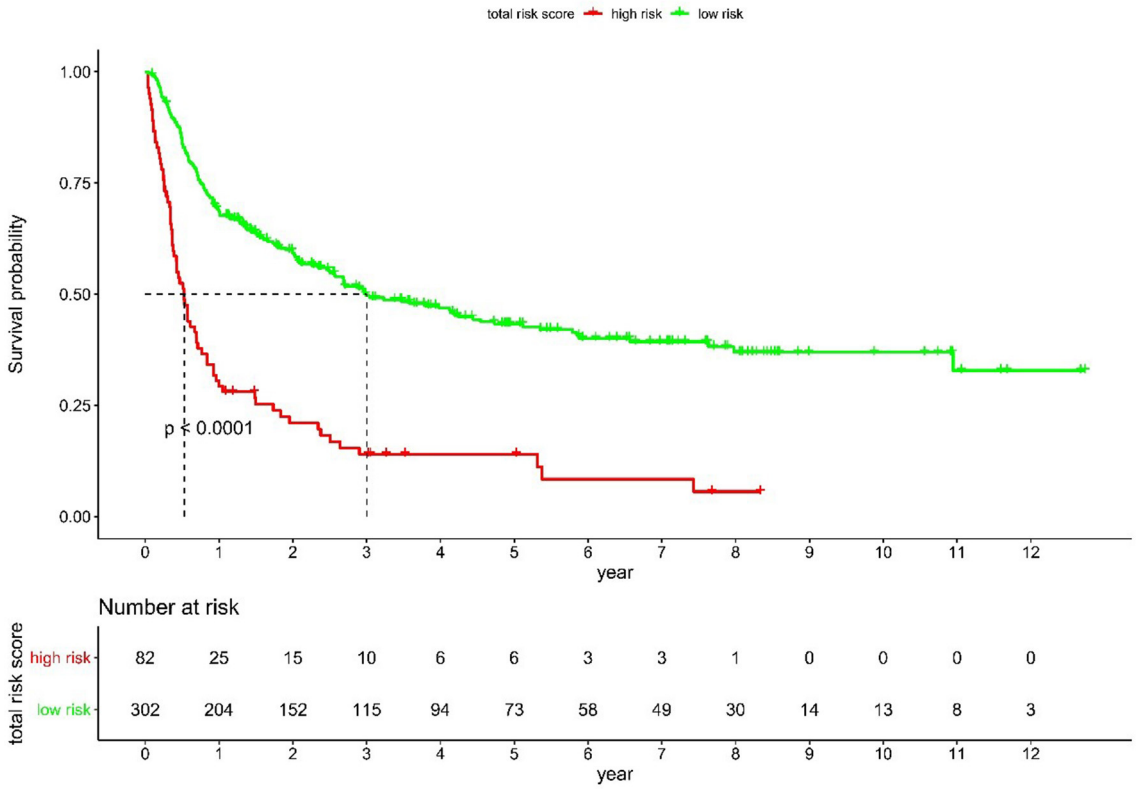

FIGURE 3 | Kaplan–Meier cumulative event rates in the derivation cohort.

HF patients to undergo exercise-based cardiac rehabilitation. Therefore, we believe that during continuous exercise, with the improvement of exercise endurance, the risk score may continue to improve, and finally improve the long-term prognosis.

In addition, we noted that the risk factors that affect the prognosis also include heart rate (specific time), CRP, and UA, which is consistent with the risk factors mentioned in the current study (24–30). Heart rate is a determinant of myocardial oxygen demand, coronary blood flow, and myocardial function, and is the key to adapting cardiac output to metabolic demands. An elevated heart rate can predict adverse outcomes in patients with CHF, which may be related to neurohormonal activation (24). Inflammation plays a key role in the etiology and progression of atherosclerosis. Studies have shown that in patients undergoing PCI for the first ST elevation myocardial infarction, there is a clear relationship between the in-hospital CRP plasma concentration and the development of HF after infarction (25). Uric acid can affect cardiovascular disease through platelet aggregation and endothelial inflammation activation. The change in serum uric acid levels in the hospital can predict adverse outcomes in patients with HF (26, 31).

There are other combined CPET HF risk scores, whose predictive accuracy is variable, depending on population selection, treatment, event selection, and follow-up time (32–35). The 2012 Heart Failure: A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION) predictive risk score model is the first risk predictive model for HF patients caused by systolic insufficiency. It analyzes multiple candidate variables, including demographics, medical history, laboratory values, CPET exercise parameters, quality of life, and the level of depression (32). The HF-ACTION represents heart failure with reduced ejection fraction (HFrEF) patients, and its score contains indicators that are easily available. However, the limitation is that patients with preserved systolic function are excluded, and the representativeness of people from outside the United States are limited. Our study included patients with heart failure with a moderately reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF), and included the Chinese population for modeling, which has good applicability to the Chinese population. At the same time, the indicators we included are easily available clinically. In 2013, the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score combined CPET indicators with established clinical, laboratory and echocardiography parameters, and finally included six indicators of hemoglobin, Na+, modification of diet in renal disease, LVEF, peak VO_2, and VE/VCO_2 slope (33). These continuous variables define the MECKI score, identify the risk of cardiovascular death and heart transplantation, and have been validated in different settings (34). However, it is mainly used for white people, and its applicability to the Chinese

population is unknown. In 2020, Pugliese et al. identified five independent predictors including peak oxygen consumption, which can determine the increased risk of adverse events in patients with HF with preserved ejection fraction (35). However, the sample size of that study is small, the follow-up time is short, and its applicability in Chinese population needs to be investigated.

Although there are many HF risk prediction models in the world, a model based on Chinese population data is an unmet need. On the one hand, our current model highlights the importance of CPET in risk scoring, helps optimize the risk stratification and management of HF patients, and supports cardiac rehabilitation programs. On the other hand, the indicators included in our model are simple and easy to obtain, which helps its vigorous promotion in primary hospitals.

Our study has the following limitations: First, as all the patients are from Shanghai Tongji Hospital, this is a single-center study with regional limitations and an insufficient sample size. Our future research will include people from other parts of China and expand the sample size of the research. Second, the included population comprises people who are around 60 years old, which may limit the generality of our model. However, compared with younger patients, older patients tend to have a higher risk of death and readmission. Third, there is currently a lack of external verification. At the same time, there is also a lack of comparison data with other international forecasting models in the same Chinese cohort. In the future, we will promote this model, conduct external verification, compare it with other international models in the same Chinese cohort, and continue to improve the model to provide a theoretical basis for treatment decisions for Chinese HF patients. Finally, the loss to follow-up rate in this study exceeded 5%. The main reasons include patients' lack of attention to the study, poor compliance, and insufficient communication skills of the follow-up staff. Moreover, due to the long follow-up time (the longest follow-up time is up to 12 years), the patient's telephone number and place of residence have changed, resulting in a high rate of loss to follow-up. In the future follow-up, we will strengthen patient education, increase doctor-patient contact, and conduct communication training for follow-up personnel, so as to reduce the rate of loss to follow-up as much as possible.

CONCLUSIONS

In this study, a scoring model for CHF in China was constructed based on CPET indicators. This model can evaluate the long-term risk of death or rehospitalization due to CHF and provide decision-making basis for clinicians, patients, and their families.

Clinical Perspectives

Clinicians use this model to assess the prognosis of patients with heart failure and identify high-risk patients, so as to better guide the implementation of treatment plans.

Translational Outlook

Although there are many models for evaluating the mortality and hospitalization risk of patients with heart failure, this study combines the experimental indicators of cardiopulmonary exercise to propose a long-term prognosis and readmission model for chronic heart failure in the Chinese population, laying the foundation for more accurate risk stratification in the future.

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 Tongji Hospital Affiliated to Tongji University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BZ and TS prepared the manuscript and all the authors participated in the clinical and related research. All authors gave final approval and agreed to be accountable for the integrity and accuracy of all aspects of the work.

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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.2021.761605/full#supplementary-material

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SYSTEMATIC REVIEW
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Vagal Neuromodulation in Chronic Heart Failure With Reduced Ejection Fraction: A Systematic Review and Meta-Analysis

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Objectives: The aim of this study was to evaluate the effects of invasive vagal nerve stimulation (VNS) in patients with chronic heart failure (HF) and reduced ejection fraction (HFrEF).

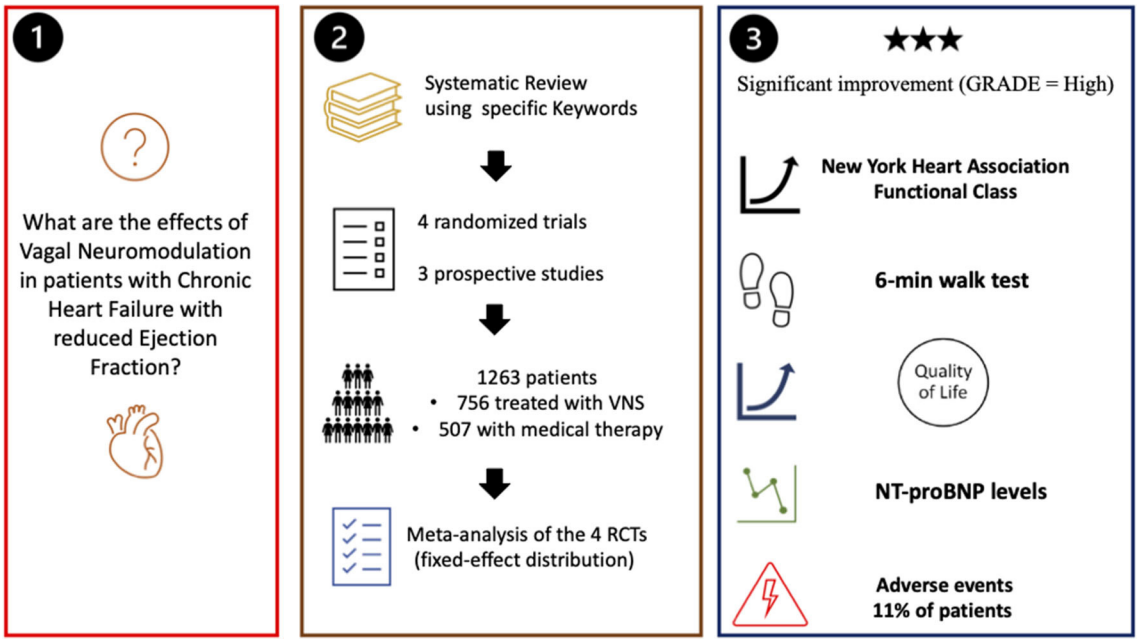
Background: Heart failure is characterized by autonomic nervous system imbalance and electrical events that can lead to sudden death. The effects of parasympathetic (vagal) stimulation in patients with HF are not well-established.

Methods: From May 1994 to July 2020, a systematic review was performed using PubMed, Embase, and Cochrane Library for clinical trials, comparing VNS with medical therapy for the management of chronic HFrEF (EF $\leq$ 40%). A meta-analysis of several outcomes and adverse effects was completed, and GRADE was used to assess the level of evidence.

Results: Four randomized controlled trials (RCT) and three prospective studies, totalizing 1,263 patients were identified; 756 treated with VNS and 507 with medical therapy. RCT data were included in the meta-analysis (fixed-effect distribution). Adverse effects related to VNS were observed in only 11% of patients. VNS was associated with significant improvement (GRADE = High) in the New York Heart Association (NYHA) functional class (OR, 2.72, 95% CI: 2.07–3.57, $p < 0.0001$), quality of life (MD −14.18, 95% CI: −18.09 to −10.28, $p < 0.0001$), a 6-min walk test (MD, 55.46, 95% CI: 39.11–71.81, $p < 0.0001$) and NT-proBNP levels (MD −144.25, 95% CI: −238.31 to −50.18, $p = 0.003$). There was no difference in mortality (OR, 1.24; 95% CI: 0.82–1.89, $p = 0.43$).

Conclusions: A high grade of evidence demonstrated that vagal nerve stimulation improves NYHA functional class, a 6-min walk test, quality of life, and NT-proBNP levels in patients with chronic HFrEF, with no differences in mortality.

Keywords: chronic heart failure, vagal nerve stimulation, reduced ejection fraction, NYHA class, 6 min walk distance (6 MWD)



Graphical Abstract | Summary of the study.

INTRODUCTION

The autonomic nervous system (ANS) is responsible for the homeostatic balance of the human body, notably on the cardiac and gastrointestinal systems. ANS has two main components: the sympathetic and parasympathetic systems. In the heart, parasympathetic system activation decreases the frequency, contractility, conductance, and O_2 consumption, leading to a drop in cardiac output with relaxation and rest of the heart (1). The vagus nerve (10th cranial pair) is responsible for most of the parasympathetic innervation, including all major thoracic organs (2).

Autonomic nervous system imbalances have been observed in a diverse range of diseases and health problems and, in most cases, are associated with increased sympathetic and decreased parasympathetic tone (3), such as in heart failure (4), inflammatory bowel diseases (5), and chronic pain syndrome (6). Thus, the idea of using vagal stimulation to increase parasympathetic activity to treat some of these diseases was first introduced by James Corning in the late nineteenth century (7). Currently, vagal stimulation is approved by the US Food and Drug Administration (FDA) for treatment of epilepsy (8) and treatment-resistant depression (8), and recently, it has been also approved to treat episodic cluster headaches (9).

The imbalance of the ANS and the heart failure (HF) creates a vicious cycle; the excess of sympathetic activity and the withdrawal of vagal activity clearly contribute to the progression of ventricular remodeling and worsening of heart failure, and *vice versa*, the progression of HF could augment the imbalance between sympathetic and vagal activity (10). The enhanced sympathetic activity can be regulated by drugs of beta-adrenergic blockade or inhibitors of the renin–angiotensin–aldosterone system, and reduced parasympathetic activity can be maintained by physical training, for example. However, the pace of new drug therapies has declined significantly. Several relatively new and experimental non-pharmacological interventions, which target specific aspects of autonomic imbalance (cervical vagus nerve stimulation, renal denervation, spinal cord stimulation, and carotid sinus nerve stimulation), are being actively investigated nowadays. All in all, autonomic neuromodulation was the key target in HF treatment, and device therapy to achieve autonomic modulation has garnered significant interest.

Although heart failure is associated with ANS imbalance, the beneficial effects of deep or transcutaneous vagal stimulation in these patients remain unclear despite some randomized controlled trials (RCT) that have been conducted (11). Moreover, all studies using invasive vagal nerve stimulation (VNS) for heart failure involved patients with reduced ejection fraction, which is the most common and serious presentation of HF. Therefore, the aim of the present study was to perform a systematic review and meta-analysis on the effects of invasive VNS in patients with chronic heart failure and reduced ejection fraction (HFrEF).

METHODS

This systematic review and meta-analysis being reported according to Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) (12) guidelines and remain in accordance with specific regulations for non-randomized studies. A protocol for this systematic review was developed *a priori* and registered in PROSPERO under the number CRD42021232377.

TABLE 1 | Search strategy.

Source	MeSH terms	Date	Results
MEDLINE	(Vagus Nerve Stimulation OR Vagal Nerve Stimulation OR VNS OR Baroreflex Activation) AND (Heart Failure OR Cardiac Failure OR CHF OR Chronic Heart Failure OR Congestive Heart Failure)	From May 1994 to July 11th, 2020	762
EMBASE	(Vagus Nerve Stimulation OR Vagal Nerve Stimulation OR VNS OR Baroreflex Activation) AND (Heart Failure OR Cardiac Failure OR CHF OR Chronic Heart Failure OR Congestive Heart Failure)	From May 1994 to July 11th, 2020	1494
Cochrane library of trials	(Vagus Nerve Stimulation OR Vagal Nerve Stimulation OR VNS OR Baroreflex Activation) AND (Heart Failure OR Cardiac Failure OR CHF OR Chronic Heart Failure OR Congestive Heart Failure)	From May 1994 to July 11th, 2020	122

Data Sources and Search Strategies

Initially, a search was conducted for similar meta-analyses on the cardiac effects of vagal stimulation for the treatment of heart failure. This initial search was carried out on MEDLINE (PubMed) and Embase; one meta-analysis published only as an abstract was found (13). The same search was then performed in the aforementioned platforms and the Cochrane Library, using the MeSH terms ("Vagus Nerve Stimulation" OR "Vagal Nerve Stimulation" OR "VNS" OR "Baroreflex Activation") AND ("Heart Failure" OR "Cardiac Failure" OR "CHF" OR "Chronic Heart Failure" OR "Congestive Heart Failure"), to search for clinical trials (randomized or not) conducted in humans between May 1994 and July 2020 (**Table 1**).

Study Selection

Studies were selected according to any of the following criteria: (1) measurements of the effects of vagal stimulation in patients with chronic heart failure and reduced left ventricular ejection fraction (LVEF $\leq$ 40%) on (a) heart rate; (b) ejection fraction (reflecting left ventricular function); (c) left ventricular end-systolic and end-diastolic volume (LVESV and LVEDV); (d) six-minute walking test (6-min WT); (e) quality of life (QoL); (f) changes in NYHA (New York Heart Association) functional class; and (g) NT pro-B-type natriuretic peptide (NT-proBNP) levels; (2) clear description ofVNS; (3) other interventions, if present, well-discriminated and described; (4) monitoring of results; and (5) clear description of adverse effects.

The key exclusion criteria of the studies were: persistent or permanent atrial fibrillation, cardiac resynchronization (CRT) for <1 year or a QRS of >130 ms without CRT, type I diabetes, type II diabetes for >5 years, sleep disordered breathing that had been treated for <6 months, a surgically correctable cause of HF, recent HF hospitalization or myocardial infarction (30 or 90 days, respectively), or an indication for dialysis, cardiac surgery in the preceding 6 months, and severe liver or renal failure.

TABLE 2 | Risk of bias of the included randomized controlled trials.

	Zannad	Abraham	Gold	Zile
Adequate sequence generation?	+	+	+	+
Allocation concealment?	+	+	+	+
Blinding of participants and personnel (performance bias)?	+	−	−	−
Blinding of outcome assessment (detection bias)?	+	+	+	+
Incomplete outcome data assessed?	+	+	−	+
Free of selective reporting?	+	+	+	+

+, Yes; −, No.

One trial (14) recruited patients with CRT but persistent NYHA functional class III, and another one also included patients with atrial fibrillation (15).

In most studies, effectiveness endpoints were the change from the baseline to 6 months in 6-min walk distance, Minnesota Living with HF Questionnaire quality-of-life (QOL) score, NYHA functional class, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Only one study (14) evaluated death from any cause or first event for worsening HF.

The initial list of articles generated was initially filtered for clinical trials, and then duplicates were removed. The selected titles had the abstracts analyzed. All these steps were done by three researchers (LBS, FMS, and EAF) using the above-described criteria. Disagreements between investigators were solved by a discussion with a senior researcher (FMS). Finally, all studies selected were read by all the authors to confirm eligibility, and results were tabulated according to the specific description of the selected studies and reviewed for further statistical analysis.

Assessment of Study Quality

Individual study quality was assessed by three reviewers (SLMC, FMS, and LBS) using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0) across five domains (randomization, intended intervention, missing data, outcome, measurement, and reported results) (16) (**Table 2**). The quality of evidence was rated by the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) process (17). Confidence in the estimate of the primary outcome was based on five domains, the risk of bias, inconsistency, indirectness, imprecision, and other considerations, and was categorized into four levels, from very low (⊕⊖⊖⊖) to high (⊕⊕⊕⊕) (**Table 3**). Any differences were resolved by discussion until consensus was reached.

Statistical Analysis

This meta-analysis was carried out with the software Review Manager (RevMan), version 5.4 (The Cochrane Collaboration, 2020). A funnel plot was used to assess for publication bias. A fixed effects model with inverse variance weighting was used to account for heterogeneity across studies, which was measured using the Cochrane I^2 statistic: <25–50% = mild, 50–75% = moderate, and >75% = severe heterogeneity. Adjusted odds

TABLE 3 | Summary of findings.

Vagal nerve stimulation plus usual care compared to usual care for heart failure with reduced ejection fraction

Patient or population: heart failure with reduced ejection fraction

Setting: chronically stable patients enrolled in multiple centers in USA, Europe and Canada

Intervention: vagal nerve stimulation plus usual care

Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with vagal nerve stimulation plus usual care				
Mortality Follow up: median 6 months	81 per 1,000	**96 per 1,000** (66–138)	**OR 1.2** (0.80–1.82)	1,206 (4 RCTs)	⊕⊕⊕⊕ HIGH	VNS has no effect on mortality.
NYHA functional class Follow up: median 6 months	304 per 1,000	**543 per 1,000** (474–609)	**OR 2.72** (2.07–3.57)	969 (4 RCTs)	⊕⊕⊕⊕ HIGH	There was an improvement of at least one NYHA functional class in VNS group.
Quality of life Follow up: median 6 months	The mean quality of life was **44.3**	MD **14.18 lower** (18.09 lower to 10.28 lower)	-	450 (3 RCTs)	⊕⊕⊕⊕ HIGH	Quality of life, assessed by the MLwHFQ (lesser is better), showed a consistent improvement in all RCTs.
6-min WT Follow up: median 6 months	The mean 6-min WT was **303.6** meters	MD **55.46 meters higher** (39.11 higher to 71.81 higher)	-	728 (3 RCTs)	⊕⊕⊕⊕ HIGH	6-min walking test distance significantly increased in all trials in VNS groups.
NT-proBNP (pg/ml) Follow up: median 6 months	The median NT-proBNP (pg/ml) was **970.5** pg/ml	MD **144.25 pg/ml lower** (238.31 lower to 50.18 lower)	-	445 (3 RCTs)	⊕⊕⊕⊕ HIGH	NP-proBNP levels (a biomarker of heart failure) decreased in most trials analyzed.

**The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*
CI, Confidence interval; OR, Odds ratio; MD, Mean difference; NYHA, New York Heart Association; 6-min WT, 6-min walking test; MLwHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal-pro-brain natriuretic peptide.
GRADE Working Group grades of evidence.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

ratios (ORs) and mean differences (MD) with 95% CIs were pooled to evaluate prognosis.

Data were separated into two distinct groups for comparisons: VNS and no VNS (control) and compared by fixed-effect distribution tests. The variability of the results between the studies (τ^2) was considered the same for the two groups, and differences between the groups were considered statistically significant if $p < 0.05$; all tests were two-tailed.

RESULTS

Study Characteristics and Quality Assessment

The initial search of articles by the MeSH terms used on the EMBASE, MEDLINE (PubMed), and Cochrane Library platforms returned 2,378 articles, which were filtered as "controlled clinical trial" OR "randomized clinical trial," with 238 articles remaining. A total of 102 duplicates were removed, and the selection by titles excluded another 92 articles. Of the 44 remaining papers, 36 were removed after reading the abstracts. During the complete analysis of the manuscripts, another study was eliminated. Of the seven articles selected, three were prospective studies (4, 18, 19) and four were RCT (14, 15, 20, 21). Only data from the RCTs were included in the meta-analysis (**Figure 1**). The Egger's test and funnel plot showed no evidence of publication bias.

The four RCTs enrolled a total of 1,107 patients, of which 641 were treated with VNS: mean age was 62.1 years, 82.5% were male, and all patients were NYHA class $\geq$ II. The median follow-up was 6 months (range: 6–16 months). The methodology used was similar between the studies. There were no significant differences in the populations included and baseline characteristics of VNS and control groups (**Tables 4**, **5**).

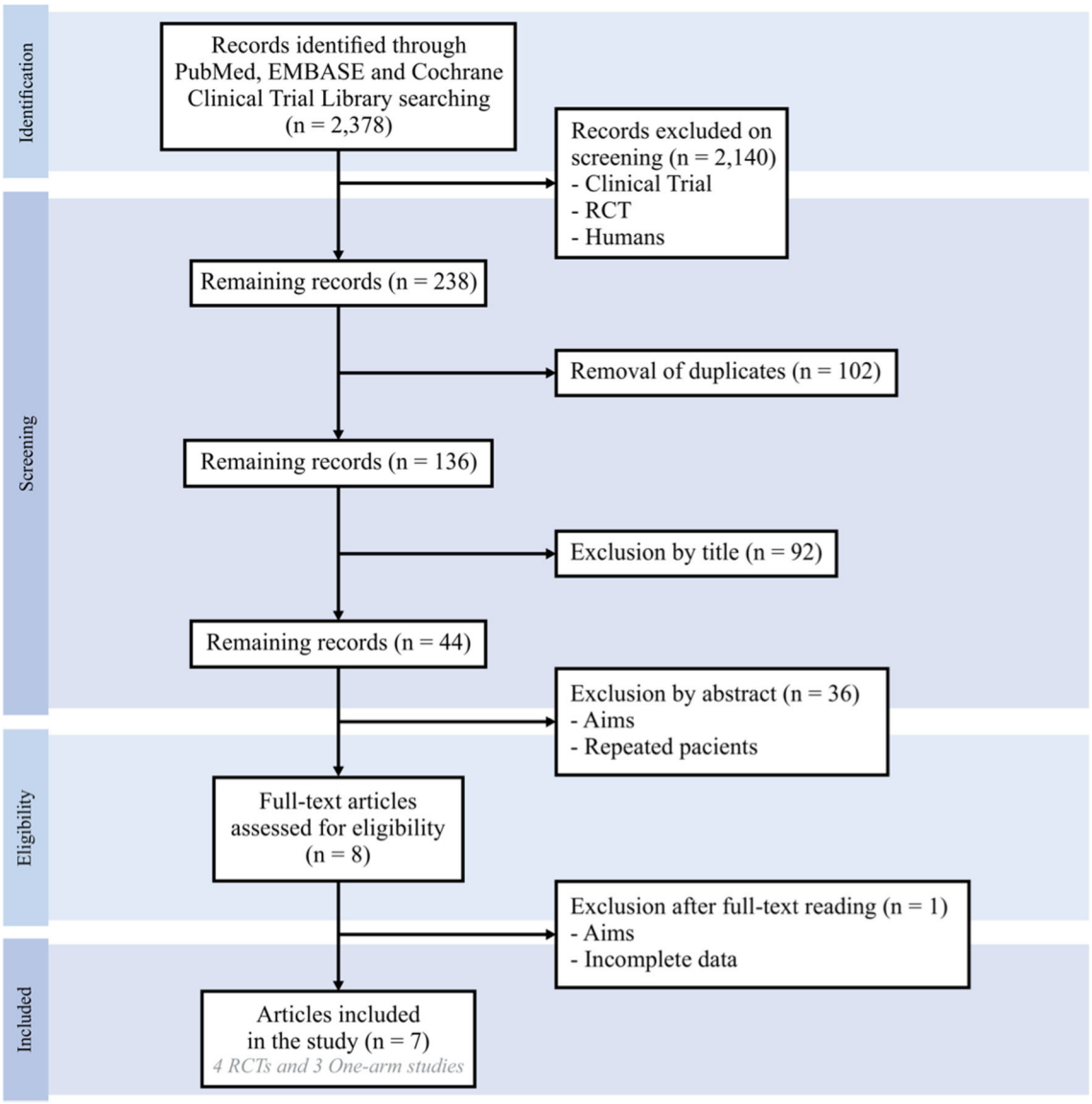


FIGURE 1 | A study flowchart.

Outcomes

Mortality

No differences in mortality between VNS and control groups (OR, 1.24; 95% CI, 0.82–1.89, $p = 0.43$) were detected (**Figure 2**).

Left Ventricular End-Systolic and Diastolic Volumes, Heart Rate, and Left Ventricular Ejection Fraction

LVESV was evaluated in only two of the RCTs and by using different methodologies. There were no differences between groups. In contrast, two prospective studies have shown a decrease in LVESV after VNS (18, 19) when compared to baseline measurements. No study depicted a statistically significant difference in LVEDV after treatment. Only two prospective studies evaluated HR after VNS and found a significant HR decrease [FIM, HR = 87 ± 13 (before) vs. 83 ± 12 (after 6 months), $p = 0.01$, and CARDIOFIT, HR = 85 ± 14 (before) vs. 76 ± 11 (after 1 year), $p = 0.003$]. All trials evaluated LVEF at the baseline, but only the prospective studies and 1 RCT (21) assessed it after 6 months. There was a significant improvement in LVEF in two prospective studies (4, 19), but not in the others.

NYHA Criteria

All trials evaluated NYHA criteria. A significant improvement of at least one point in the NYHA class could be observed in patients undergoing VNS for all studies analyzed. In the meta-analysis (**Figure 3**), the VNS group showed better class scores when compared to controls (OR, 2.72; 95% CI, 2.07–3.57; $p < 0.0001$).

TABLE 4 | Initial data of the randomized controlled trials.

	Zannad et al. (21)		Abraham et al. (20)		Gold et al. (14)		Zile et al. (15)	
	VNS	**Control**	**BAT**	**Control**	**VNS**	**Control**	**BAT**	**Control**
Initial size	63	32	76	70	436	271	130	134
Finally analyzed	59	28	71	69	391	244	120	125
Men (%)	89	81	87.3	84.1	77.8	80.8	82	78
Age (mean ± SD)	59.8 ± 12.2	59.3 ± 10.1	64 ± 11	66 ± 12	61.7 ± 10.5	60.9 ± 11.2	62 ± 11	63 ± 10
Main outcomes	LVESD		NYHA class, 6-min WT, QoL		Death or worsening of HF		NT-proBNP, 6-min WT, QoL	
Other outcomes	LVESV, LVEF, peak VO_2, NT-proBNP		NT-proBNP, echo parameters		NYHA class, 6-min WT, QoL		NYHA class, death or HF hospitalization	
Follow-up	6 months		6 months		16 months		6 months	
NYHA II/III, *n*	7/52	7/21	1/70	0/69	0/436	0/271	9/121	7/127
QoL	44.4 ± 22.2	42.4 ± 25.1	51 ± 21	43 ± 22	51.6 ± 20.7	52.2 ± 21.8	53 ± 24	52 ± 24
6-min WT (m)	-	-	297 ± 79	308 ± 85	304 ± 111	317 ± 178	316 ± 68	294 ± 73
Heart rate	68.2 ± 13.2	71.3 ± 12.9	73 ± 11	75 ± 12	72.5 ± 12.2	71.4 ± 11.5	75 ± 10	75 ± 11
LVEF (%)	30.5 ± 6.0	30.8 ± 4.2	24 ± 7	25 ± 7	23.9 ± 6.7	25.2 ± 7.3	27 ± 7	28 ± 6
LVESD/LVEDD (cm)	4.9/5.9	5.2/6.0	-	-	-	-	-	-
NT-proBNP (pg/ml)	870 (370–1,843)	882 (488–1,926)	1,422 (455–4,599)	1,172 (548–2,558)	-	-	731 (475–1,021)	765 (479–1,052)
Mortality, *n* (%)	1 (1.6)	2 (6.3)	5 (6.6)	5 (7.1)	62 (14.2)	28 (10.3)	2 (1.5)	3 (2.2)
AERP, *n* (%)	9 (14.3)	4 (12.5)	10 (14.1)	-	37 (9.4)	-	4 (3.2)	-

VNS, vagus nerve stimulation; BAT, baroreflex activation therapy; NYHA, New York Heart Association functional class; QoL, quality of life; 6-min WT: 6 min walking test (meters); LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVEDD, left ventricular end diastolic diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; HF, heart failure; AERP, adverse effects related to the procedure.

TABLE 5 | Prospective studies before and after vagus nerve stimulation.

	Schwartz et al. (18) (*n* = 8)		De Ferrari et al. (4) (*n* = 32)		Gronda (19) (*n* = 11)	
	Baseline	**6-months**	**Baseline**	**6-months**	**Baseline**	**6-months**
Men	100%		94%		82.7%	
Age	54		56 ± 11		67 ± 9	
Main outcomes	All AERP		All AERP		MSNA, QOL, functional capacity	
Other outcomes	NYHA class, QoL, 6-min WT, LVEF, LVESV, LVEDV		NYHA class, QoL, 6-min WT, LVEF, LVESV, LVEDV		BNP, LVEF	
NYHA I/II/III/IV, n	0/1/7/0	1/3/4/0*	0/15/15/2	10/14/5/0**	0/0/11/0	8/2/1/0**
QoL	52 ± 14	31 ± 18‡	49 ± 17	32 ± 19**	33.4 ± 29.8	−10.6 ± 3.8*
6-min WT (m)	405 ± 43	446 ± 96*	411 ± 76	471 ± 111**	304.4 ± 49.6	+51.1 ± 25.6*
Heart rate	87 ± 13	83 ± 12*	82 ± 13	76 ± 13‡	72.3 ± 8.3	−0.5 ± 1.8
LVEF (%)	24 ± 5	26 ± 10	22.3 ± 6.9	28.7 ± 6.4**	32.0 ± 7.3	+3.6 ± 1.4‡
LVESV (ml)	208 ± 71	198 ± 83*	103 ± 35 ml/m^2	89 ± 38 ml/m^{2*}	116.9 ± 40.9	−11.3 ± 5.6*
LVEDV (ml)	273 ± 81	250 ± 82	132 ± 42 ml/m^2	125 ± 46 ml/m^2	168.6 ± 43.5	−8.7 ± 7.5
BNP, pg/ml	-	-	-	-	314.4 ± 306.9	+33.1 ± 112.3
MSNA (bursts/min)	-	-	-	-	45.1 ± 7.7	−13.8 ± 5.4**
Mortality, *n* (%)	0		3 (9.4)		0	
AERP, *n* (%)	1 (12.5)		5 (15.6)		1 (9.1)	

NYHA, New York Heart Association functional class; QoL, quality of life; 6-min WT: 6 min walking test (meters); LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVEDV, left ventricular end diastolic volume; MSNA, muscle sympathetic nerve activity; BNP, brain natriuretic peptide; HF, heart failure; AERP, adverse effects related to the procedure. Continuous data is presented as mean ± SD, except for Gronda, which is presented as mean ± SE.

$^*p < 0.05$.

$^‡p < 0.005$.

$^{**}p < 0.001$.

Quality of Life

Comparison between the quality of life (QoL) before and after treatment showed an improvement in its scores in all four randomized clinical trials and prospective studies (**Tables 4**, **5**). Three of the randomized studies used the Minnesota Living with Heart Failure Questionnaire (MLwHFQ) (15, 20, 21), and one

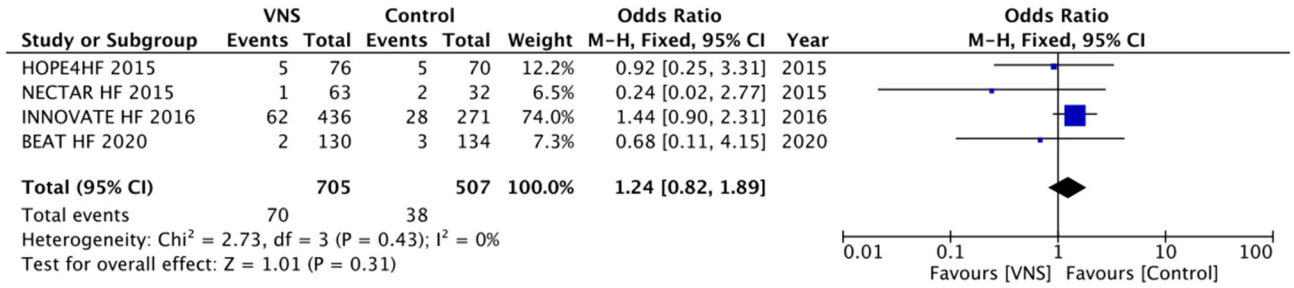


FIGURE 2 | All-cause mortality during follow-up between vagal nerve stimulation and control groups for management of chronic heart failure with reduced ejection fraction. VNS, vagus nerve stimulation.

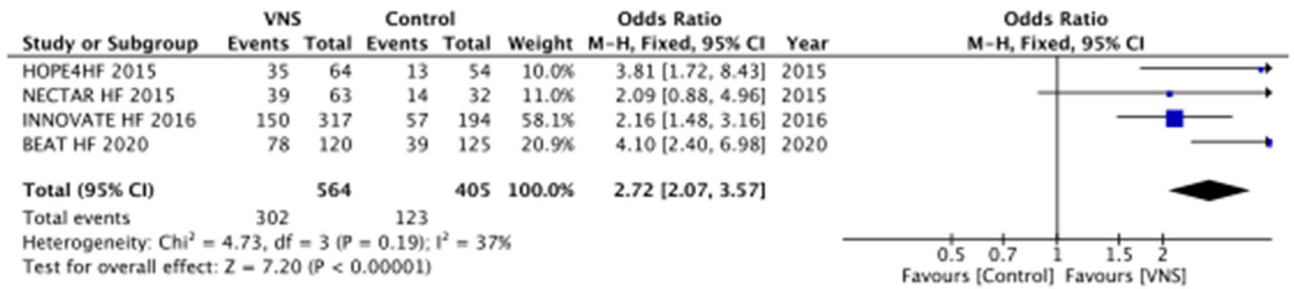


FIGURE 3 | Improvement of at least one New York Heart Association functional class during follow-up between VNS and control groups for management of chronic heart failure with reduced ejection fraction. VNS, vagus nerve stimulation.

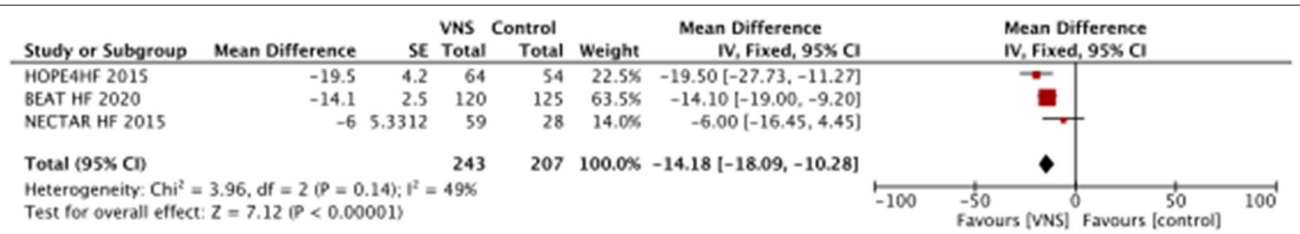


FIGURE 4 | Improvement of quality of life during follow-up between VNS and control groups for management of chronic heart failure with reduced ejection fraction. VNS, vagus nerve stimulation.

used the Kansas City Cardiomyopathy Questionnaire (KCCQ) (14). There was a significant improvement in QoL favoring VNS in all randomized studies (MD −14.18; 95% CI, −18.09 to −10.28; $p < 0.0001$) (**Figure 4**).

6-min Walking Test Distance

Six trials measured this parameter. In the three RCTs, there was a significant increase in the distance achieved after VNS compared to control (MD, 55.46 m; 95% CI, 39.11–71.81; $p < 0.0001$) (**Figure 5**). In the other three prospective studies, there was also a significant improvement in the 6-min WT distance, ranging from 41 to 60 m.

NT-proBNP

NT-proBNP levels were evaluated in three RCTs. There was an important decrease in levels in VNS groups when compared to controls (MD, −144.25; 95% CI, −238.31 to −50.18; $p = 0.003$) (**Figure 6**).

Adverse Events Related to the Procedure

Only one prospective study reported 10 AERP, including three deaths. In the RCTs, a total of 130 AERP occurred, with 70 deaths (6%). Therefore, freedom from AERP was seen in 89.3% of patients implanted with the VNS device.

DISCUSSION

This systematic review and meta-analysis showed an overall beneficial effect of the use of invasive VNS in patients with chronic heart failure and reduced ejection fraction. Altogether, the seven clinical trials included demonstrated a significant

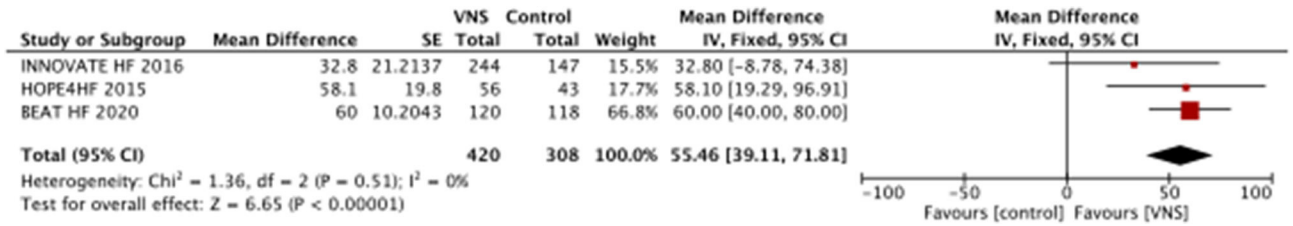


FIGURE 5 | Improvement of the 6-min walking test during follow-up between VNS and control groups for management of chronic heart failure with reduced ejection fraction. VNS, vagus nerve stimulation.

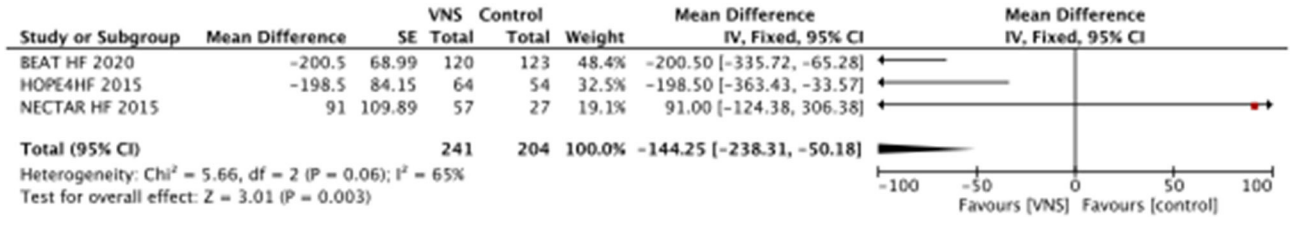


FIGURE 6 | Improvement of NT-proBNP levels during follow-up between VNS and control groups for management of chronic heart failure with reduced ejection fraction. VNS, vagus nerve stimulation.

improvement in the functional NYHA class, QoL, 6-min WT, and NT-proBNP levels, with some adverse effects but no impact on mortality.

No differences in mortality were noted in any of the studies analyzed. This was not surprising as none of the studies were designed to detect differences in mortality, which would require a much larger number of patients since death rates with optimal medical therapy are around 3.8% according to a large clinical trial (22). The annual mortality rate is also higher in symptomatic patients, and some predictors of poor prognosis and increased mortality include systolic blood pressure <115 mmHg, serum creatinine >2.7 mg/dL, serum urea over 15 mmol/L, NT-proBNP exceeding 986 pg/ml, and LVEF under 45% (23). All patients involved in this meta-analysis presented LVEF < 40% and NYHA class II or III, but they were also in full medical therapy, and differences in mortality in this setting were not expected, considering the small sample sizes.

A few cardiac parameters were assessed by the three RCTs. No significant improvement (two RCTs) or a trend to positive results (11) was observed in LVESV. This was similar to the results of an animal study where VNS effectively improved left ventricular function and remodeling (24). The three prospective studies analyzed corroborated this finding (4, 18, 19), with significant differences noted in LVESV before and after VNS. No differences were observed in LVEDV before and after VNS in any of the included studies. In two prospective studies, VNS leads to a decreased HR at 6 and 12 months after the procedure (4, 18). The NECTAR HF (21) study analyzed heart rate variability to assess the autonomic status (25) and found no differences before and after VNS, but patients were on beta blockers, which could have affected the measurements. Two prospective studies (4, 19) showed significant improvement on LVEF after VNS, but this was not analyzed by the RCTs. LVEF could fluctuate in repeated measurements or recover after treatment (26), blunting the borders between proposed categories of HF and should not be used as a surrogate marker of left ventricular systolic function.

New York Heart Association functional class and QoL improved after VNS in all studies (4, 14, 18–22). These positive effects demonstrate that most patients became less symptomatic and more capable of day-to-day activities after VNS treatment. A 6-min walking test was performed in six of the seven studies analyzed with a significant increase in walking distance in patients treated by VNS (4, 14, 15, 18–20). These findings align with the improvement in NYHA class and QoL observed, pointing that those patients became physically fitter after vagal stimulation.

An important finding of this meta-analysis was the significant decrease in NT-proBNP levels in patients with HFrEF treated with VNS, given the correlation between this biomarker and clinical outcomes in patients with heart failure. Indeed, NT-proBNP levels independently predict event-free survival in patients with systolic heart failure (27). Also, the NT-proBNP level is an objective measure, reinforcing the beneficial effects of VNS.

Adverse events definitions were different between studies. In the RCTs, they were defined as: (1) death and/or (2) hospitalization due to worsening heart failure, whereas, in the prospective studies, they were defined as any serious adverse event. Thus, the CARDIOFIT study (4) presented a high number of adverse events, but most of them did not meet the criteria used by the other studies, and 19 of the 26 events reported were not related to the procedure. In this systematic review and metanalysis, the overall rate of adverse effects related to the procedure was 10.7%. Importantly, mortality rates were similar between VNS and control. Some of the adverse events were

related to the implantation of the vagal device, which has been previously described (3, 28).

Transcutaneous auricular VNS (ta-VNS) is a viable and non-invasive alternative with fewer side effects than invasive electrode implantation (29). A previous study identified that low-level transcutaneous electrical stimulation of the auricular branch of the vagus nerve was an effective modality for non-invasive autonomic neuromodulation in the beagle dog post-myocardial infarction mode (30), and it could activate the afferent and efferent vagal nerve and modulate intrinsic cardiac autonomic nervous system to achieve cardioprotective effect (31). Moreover, low-level transcutaneous electrical stimulation of the auricular branch of vagus nerve treatment was tolerated and convenient for ambulatory patients and, especially, for patients who could not have pharmacological therapies. It was feasible that non-invasive VNS may be useful for a large population of patients with HF (32). We are conducting a trial, registered in Brazilian Registry of Clinical Trials (ReBEC) under the number RBR-77wqymk (https://ensaiosclinicos.gov.br/rg/RBR-77wqymk) to investigate the effects of ta-VNS on patients with heart failure by comparing heart rate variability, NYHA functional class, 6-min walk test, and quality of life before and after 4 weeks of ta-VNS, five times a week.

The use of ta-VNS has been investigated in patients with paroxysmal atrial fibrillation (33, 34) without HF with promising results. The use of ta-VNS suppressed the arrhythmia and significantly decreased systemic levels of pro-inflammatory cytokines (tumor necrosis factor alpha and C-reactive protein). Therefore, future studies should evaluate ta-VNS as a mode for vagal stimulation in patients with chronic heart failure and reduced ejection fraction (HFrEF).

There were some limitations in the present systematic review and meta-analysis: (1) small number of studies included, which demonstrate the paucity of RCTs to evaluate the effects of vagal stimulation in this specific population, (2) heterogeneity in the objectives or primary outcomes of each study, and (3) no evidence regarding the etiology of the HF in most of the studies, something we know that may elicit different prognosis.

CONCLUSIONS

In patients with chronic heart failure and reduced ejection fraction, the use of invasive vagal stimulation was associated with improvement of NYHA functional class, quality of life, 6-min walking test distance, and NT-proBNP levels, with a high grade of evidence. VNS was associated with some adverse events but had no impact on mortality. However, these results are limited to a small number of studies using variable outcomes. Thus, larger investigations using standardized methods and important outcomes are required. Also, non-invasive transcutaneous auricular vagal nerve stimulation (ta-VNS) is a viable alternative that may improve outcomes with less adverse events but needs further investigation.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

LS and FS designed the study, conducted the research, and wrote the article. SC, EM, and GS contributed to the revision of the article for important content. LS, FS, PC, MS, and EF prepared the figures and helped to analyze and interpret the data. All authors have read and approved the final version of the article.

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Malnutrition and Frailty Are Critical Determinants of 6-Month Outcome in Hospitalized Elderly Patients With Heart Failure Harboring Surgically Untreated Functional Mitral Regurgitation

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Background: Hospitalized patients with acute decompensated heart failure (ADHF) frequently exhibit aggravating mitral regurgitation (MR). Those patients do not always undergo surgical mitral valve repair, but particularly in the elderly, they are often treated by conservative medical therapy. This study was aimed to investigate factors affecting 6-month outcomes in hospitalized patients with heart failure (HF) harboring surgically untreated MR.

Methods: We screened the presence of MR in hospitalized patients with HF between September 2017 and May 2020 in the Yamaguchi Prefectural Grand Medical (YPGM) center. At the time of discharge of these patients, individuals with surgically unoperated MR, including primary and secondary origin, were consequently recruited to this single-center prospective cohort study. The patients with severe MR who undergo surgical mitral valve treatment were not included in this study. The primary endpoint was all-cause readmission or all-cause death and the secondary endpoint was HF-related endpoint at 6 months after discharge. The Cox proportional hazard regression analyses were employed to assess the predictors for the composite endpoint.

Results: Overall, 489 patients with ADHF were admitted to the YPGM center. Of those, 146 patients (30% of total patients with HF) (median age 83.5 years, 69 men) were identified as harboring grade II MR or greater. Consequently, all the recruited patients were diagnosed as functional MR. During a median follow-up of 186.0 days, a total of 55 patients (38%) reached the primary or secondary endpoints (HF death and readmission in 31 patients, other in 24 patients). As a result of multivariate analysis, geriatric nutritional risk index [hazard ratio (HR) = 0.932; 95% CI = 0.887–0.979, $p = 0.005$], age (HR = 1.058; 95% CI = 1.006–1.112, $p = 0.027$), and left ventricular ejection fraction

(HR = 0.971; 95% CI = 0.945–0.997, $p = 0.030$) were independent predictors of all-cause death or all-cause admission. Body mass index (HR = 0.793; 95% CI = 0.614–0.890, $p = 0.001$) and ischemic heart disease etiology (HR = 2.732; 95% CI = 1.056–7.067, $p = 0.038$) were also independent predictors of the HF-related endpoints.

Conclusion: Malnutrition and underweight were substantial predictors of adverse outcomes in elderly patients with HF harboring surgically untreated moderate-to-severe functional MR.

Keywords: functional mitral regurgitation (FMR), heart failure, older people, body mass index, malnutrition, frailty

INTRODUCTION

Heart failure (HF) is becoming a common disease in our aging society. Hospitalized patients often exhibit significant mitral regurgitation (MR), an aggravating factor of HF (1). Although the severity of MR is known to be associated with poor prognosis, surgical repair of MR is not always chosen in clinical settings. In this case, guideline-based recommendations do not decide this choice, but patient–individual-related factors, including comorbidities, physical, and social activity, restrict directions for treatment.

When mitral valve degeneration is the primary cause of MR, surgical mitral valve repair is the most curative treatment, if cardiac contractility is preserved (2). However, secondary MR, also called functional MR (FMR), is more common in the acute exacerbation of HF. In this regard, recent advances in transcatheter edge-to-edge repair (TEER) technology (3) have been drawing attention to treating FMR associated with left ventricular dysfunction and remodeling. Because of its less invasiveness, TEER may apply to elderly patients with HF complicated by moderate-to-severe MR. However, it is also reported that the therapeutic effect of TEER is limited without adequate standard pharmacotherapy (4). Currently, dissemination of the procedure is not yet sufficient.

In addition, elderly patients with HF often were categorized as HF with preserved ejection fraction (HFpEF) (5, 6). In this regard, atrial hamstringing FMR associated with left atrial enlargement has also come to the fore as a cause of FMR associated with HFpEF (2). There are currently few data available for a recommendation of surgical repair in patients with atrial hamstringing FMR. Furthermore, older patients with HF harboring MR often have multiple comorbidities, physical frailty, and cognitive impairment that increase the risk of surgical intervention (7–10). Therefore, currently, conservative medical therapy often becomes the only remaining choice.

In the clinical settings, once the cardiac overload on admission has been removed by pharmacotherapy, patients with HF harboring moderate-to-severe MR become a less symptomatic chronic state at the time of discharge. We believe that it is essential to help such patients avoiding symptomatic deterioration in daily life. In this regard, the heart team must make a holistic decision to predict the optimal patient outcome and reflect an outpatient care during the follow-up period. Assessing physical and nutritional status for cardiac rehabilitation (CR) is also essential for the multidisciplinary treatment of HF (11).

In this study, we investigate the predictive factors in hospitalized patients with HF harboring moderate-to-severe MR.

METHODS

Study Population

From September 1, 2017 to May 31, 2020 at the Yamaguchi Prefectural Grand Medical (YPGM) center, patients who were admitted to the emergency room due to acute decompensated HF (ADHF) and have grade II MR or greater and received CR were employed in this cohort study. For entry of this study, at least two expert cardiologists reviewed echocardiography. They decided whether the patient was eligible for the investigation by assessing that HF aggravation was associated with exacerbation of MR. Indication for surgical repair of MR was discussed in the heart team conference and patients eligible for surgical repair underwent mitral repairment ($n = 4$). Eligibility for surgery was determined by at least five expert cardiology physicians and two expert cardiac surgeons. Patients who did not choose surgical repair despite the expert opinion or were diagnosed as ineligible for surgical repair were included in this cohort study according to the Japanese Circulation Society/Japanese Heart Failure Society guidelines (12). The following patients were excluded from this entry due to the complicated nature of disease pathophysiology. Exclusion criteria were: (i) patients who undergo maintenance dialysis due to end-stage renal failure, (ii) patients classified as clinical scenario 4 or 5 (13), or (iii) patients who lost follow-up.

This study was performed in accordance with the Declaration of Helsinki and approved by the local institutional board at the YPGM center (ID: 2017–2019). All the patients received a written informed consent before registration.

Echocardiography Study

Transthoracic echocardiography was performed on admission and 2 weeks after entry in a stable condition. First, the nature of MR was classified as primary or secondary MR and presence or absence of ischemic heart disease (IHD). Second, the severity of MR was divided into five levels by semiquantitative assessment, i.e., grade 0: none to trace MR, grade 1: mild MR, grade 2: moderate MR, grade 3: moderate-to-severe MR, and grade 4: severe MR. Quantitative assessments of MR severity were obtained by evaluating the effective

regurgitant orifice area (EROA), the tethering height, and the vena contracta of the MR. Left ventricular ejection fraction (LVEF), estimated by Simpson's biplane formula, left ventricular end-diastolic dimension (LVDd), left ventricular end-systolic dimension (LVDs), left atrial dimension (LAD), E/A ratio, E/e' ratio, tricuspid annular plane systolic excursion (TAPSE), transtricuspid pressure gradient (TRPG), and left atrial volume index (LAVI) were also obtained. Patients were categorized into three groups by LVEF, namely, HF with reduced LVEF (HFrEF) (LVEF $<$ 40%), HF with mid-range LVEF (HFmrEF) (LVEF 40–49%), and HFpEF (LVEF $\geq$ 50%) (14).

Clinical Data Collection

The clinical characteristics of the patients were collected from medical records including age, sex, body mass index (BMI), the New York Heart Association (NYHA) on admission, length of hospital stay (days), prior hospitalization, living alone, use of nursing care insurance, cognitive function assessed by the Montreal Cognitive Assessment-Japanese version (MoCA-J) (15), past histories of orthopedic disease, stroke, chronic kidney disease, diabetes, and atrial fibrillation. The biochemical laboratory data were also obtained from medical records including brain natriuretic peptide (BNP) on admission, serum albumin (Alb), serum hemoglobin, serum creatinine, and C-reactive protein (CRP). The geriatric nutritional risk index (GNRI) was calculated by the formula of [1.489 $\times$ Alb (g/l) + 41.7 $\times$ body weight (kg)/ideal body weight (kg)] (16). The estimated glomerular filtration rate (eGFR) at discharge was calculated from the above variables. Details of pharmacotherapy of HF were confirmed at the time of discharge including angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB), β-blocker, tolvaptan, loop diuretics, and mineralocorticoid receptor antagonists (MRAs). Systolic blood pressure (SBP) and mean blood pressure (MBP) were measured at discharge.

Physical Function

The effectiveness of CR was evaluated 5 days before the discharge. These include the short physical performance battery (SPPB) test (17), a handgrip test by a grip strength meter (T.K.K.5401 GRIP-D; Takei, Tokyo, Japan), and the quadriceps isometric strength (QIS) test by a handheld dynamometer (MT-100 mobile; Sakai Med, Tokyo, Japan) (18). Exercise tolerance was assessed by the 6-minute walk test (6MWT) (19). The activity of daily living was assessed by calculating the Barthel Index (BI) (20). Frailty was assessed by the Kihon Checklist (KCL), defined by the Ministry of Health, Labor, and Welfare, Japan (21–23). The KCL consists of 25 questionaries; a higher KCL score indicates a higher risk of frailty, those with the range from 0 to 3 points as the non-frailty group, those with the range from 4 to 7 points as a prefrailty group, and those scores of $\geq$8 points were defined as the frailty group. Sarcopenia was also assessed by the diagnostic criteria of the Asia Working Group for Sarcopenia (24). Weaker grip strength ($<$26 kg for men, $<$18 kg for women), slower gait speed ($<$0.8 m/s), and lower skeletal muscle mass index (SMI) measured by bioimpedance

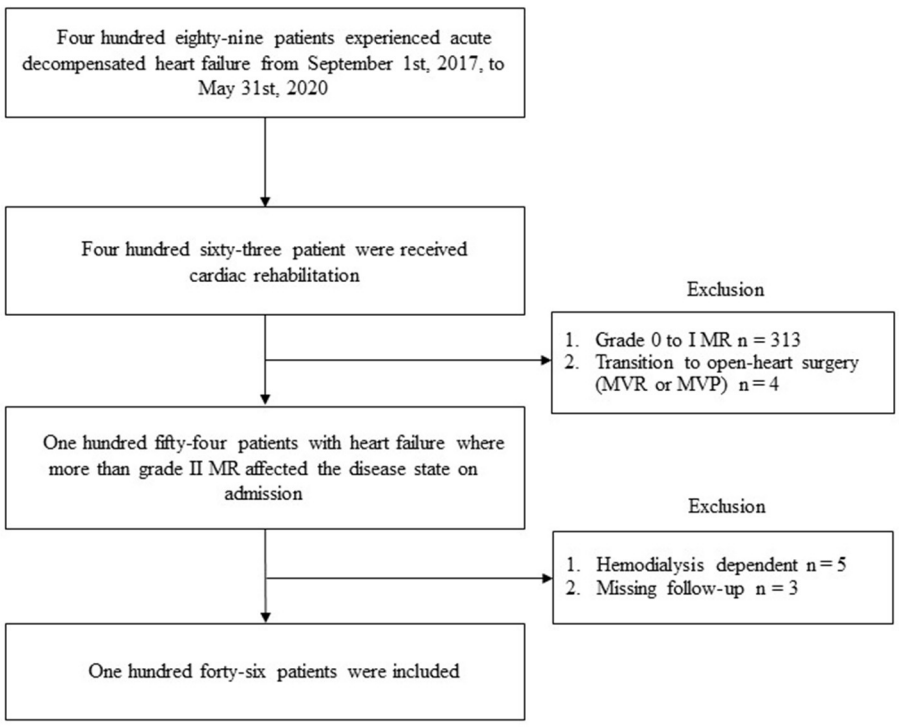

FIGURE 1 | The flowchart of the study in patients with heart failure harboring moderate-to-severe MR in the Yamaguchi Prefectural Grand Medical center. MR, mitral regurgitation; MVR, mitral valve replacement; MVP, mitral valvuloplasty.

TABLE 1 | Baseline clinical characteristics of 146 patients with ADHF harboring FMR.

	Value
Demographics	
Age, years	83.5 (72.3–88.0)
Male sex	69 (47)
BMI, kg/m^2	20.2 (17.9–22.7)
NYHA class III/IV (on admission)	47/99 (32/68)
Living alone	35 (24)
Nursing care insurance	59 (40)
Length of hospital stay, day	20.0 (15.0–27.0)
Follow-up period, day	180.0 (109.8–180.0)
Prior hospitalization	72 (49)
Return to home	114 (78)
SBP, mmHg (at discharge)	114.4 ± 18.3
MBP, mmHg (at discharge)	83.6 ± 12.0
Cognitive function	
MoCA-J, points	18.5 (14.3–24.0)
Co-morbidities	
Orthopedic disease	51 (35)
Stroke	23 (16)
Hypertension	80 (55)
CKD	32 (22)
DM	42 (29)
Atrial fibrillation	61 (42)
IHD	47 (32)
Transthoracic echocardiography (two weeks after admission)	
MR	
Zero	11 (8)
I	26 (18)
II	67 (46)
III	40 (27)
IV	2 (1)
MR grade (continuous variable)	2 (1–3)
LVEF, %	45.0 (32.0–60.5)
HFrEF	65 (45)
HFpEF	58 (40)
HFmrEF	19 (13)
LVDd, mm	52.0 ± 8.8
LVDs, mm	38.5 (30.0–47.3)
LAD, mm	45.0 (40.0–50.0)
LAVI	58.0 (45.5–81.0)
E/e' ratio	16.0 (13.0–22.0)
E/A ratio	0.99 (0.65–1.46)
TRPG, mmHg	28.0 (23.1–35.0)
TAPSE, mm	16.1 ± 4.2
Tethering height, mm	9.0 ± 3.0
Vena contracta, mm	3.8 (3.0–5.0)
EROA, cm^2	0.12 (0.07–0.18)
Laboratory data	
Serum albumin, g/dl	3.4 ± 0.5
Serum creatinine, mg/dl	1.03 (0.82–1.29)
eGFR, mL/min/1.73 m^2	48.0 (36.0–63.0)
Serum hemoglobin, g/dl	11.5 (10.1–13.2)
BNP, pg/ml (on admission)	574.0 (299.5–967.3)
Nutritional status (at discharge)	
Geriatric nutrition risk index, points	89.2 ± 10.6
Medication (at discharge)	
ACE-I /ARB	102 (70)
Loop diuretics	111 (76)
β-blocker	102 (70)
MRAs	50 (34)
Tolvaptan	46 (32)
Physical function (at discharge)	
SPPB, points	8 (5–10)
6MWT, m	279.0 (195.5–350.0)
QIS, Nm/kg	0.66 (0.50–0.78)
Handgrip strength, kg	13.3 (8.5–19.8)
Sarcopenia	73 (50)
KCL, points	11.0 (7.0–14.0)
BI, points	85.0 (70.0–90.0)

Values were shown as mean ± SD, median [interquartile range (IQR): 25th to 75th percentiles], n (%).

*ADHF, acute decompensated heart failure; FMR, functional mitral regurgitation; BMI, body mass index; NYHA, New York Heart Association; SBP, systolic blood pressure; MBP, mean blood pressure; MoCA-J, Montreal Cognitive Assessment-Japanese version; CKD, chronic kidney disease; DM, diabetes mellitus; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LAD, left atrial dimension; LAVI, left atrial volume index; TRPG, transtricuspid pressure gradient; TAPSE, tricuspid annular plane systolic excursion; EROA, effective regurgitant orifice area; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; GNRI, geriatric nutritional risk index; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; MRAs, mineralocorticoid receptor antagonists; SPPB, short physical performance battery; 6MWT: six minute walking test; QIS, quadriceps isometric strength; KCL, Kihon Checklist (see **Supplementary File 1**); and BI, Barthel Index.*

analysis <7.0 kg/m^2 for men and <5.7 kg/m^2 for women were regarded as sarcopenia. Bioimpedance analysis was performed using a bioelectrical impedance analyzer (Inbody S10; Inbody Japan, Tokyo, Japan).

Bioimpedance analysis was not applicable for patients implanted with implantable cardioverter defibrillator (ICD) or pacemaker (26/146 patients, 18%). Moreover, the 6MWT was inappropriate for patients who could not walk more than 100 m (20/146 patients, 14%).

Follow-Up and Endpoint for the Analysis

The primary endpoint was defined as the composite endpoints consisting of all-cause death or all-cause admission and the secondary endpoint was defined as HF death or HF admission. Six months after discharge from the hospital, patient status was surveyed by postcard to determine whether they had experienced any events.

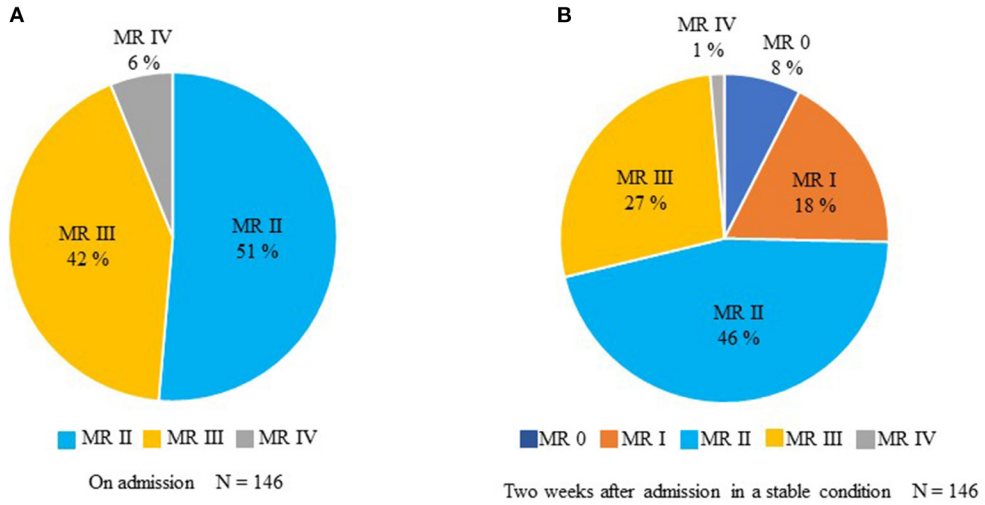

FIGURE 2 | The temporal change in MR from admission to 2 weeks after entry in a stable condition. **(A)** Assessment of MR on admission. **(B)** Evaluation of MR 2 weeks after entry.

Statistical Analysis

Statistical analysis was performed by using the EZR on R commander (version 1.37) (25). Categorical baseline variables were expressed as number and percentage or continuous variables were expressed as mean ± SD or median [interquartile range (IQR): 25th to 75th percentiles]. The primary endpoints were all-cause mortality and all-cause readmission and secondary endpoints were HF-related death and HF-related readmission. The severity of MR significantly contributed to prognosis of the patient that was tested by the log-rank test and compared by the Kaplan–Meier curve before the multivariate Cox proportional hazard regression analysis.

Next, predictors of survival and readmission were identified by the univariate and multivariate Cox proportional hazard regression analyses. Independent variables for multiple modeling were selected from predictive factors with $p < 0.20$ using the univariate analysis and previously reported predictive factors (1, 26–29). A stepwise variable reduction method was used for the multivariate Cox proportional hazard regression modeling.

Results were summarized as hazard ratio (HR), 95% CI, and p-value. When the predictors of continuous variables were identified by the multivariate analysis, a receiver operating characteristic (ROC) analysis was employed to determine the optimal cut-off value acting as independent predictive factors, followed by the sensitivity, the specificity, and the area under the curve (AUC). Event-free ratios were estimated by the Kaplan–Meier method and compared by the log-rank test. A $p < 0.05$ was considered as statistically significant.

RESULTS

Baseline Clinical Characteristics

Overall, 489 patients with ADHF were admitted to the YPGM center. Of those, 146 patients (**Figure 1**) (30% of total patients with HF) (median age 83.5 years, 69 men) were identified as individuals harboring grade II MR or greater and enrolled in this study. Baseline clinical characteristics are shown in **Table 1**. All the patients expressed exacerbating symptoms of HF regarded as NYHA III/IV on admission. One in four patients lived alone and 40% of patients had been receiving nursing care insurance. The average length of hospitalization was 20 days. A total of 114 patients could return home at discharge and the rest had to be transferred to other CR hospitals due to insufficient physical and social activity recovery.

None of the patients with primary MR was included and all the recruited patients were diagnosed as secondary MR, i.e., FMR. **Figure 2** shows the change of MR severity from admission to 2 weeks after admission; 108 (74%) patients have remained more than grade II MR. The rest of 38 patients (26%) of included patients exhibited clinically insignificant MR grades 2 weeks after admission. Concerning the left ventricular function, 45% of patients with HF revealed reduced EF (<40%), 13% of patients with HF showed mid-range EF (40–49%), and 40% of patients with HF exhibited preserved EF (≥50%).

Figures 3A,B show the 6-month outcomes of patients with MR of grade III or greater and those with MR of less than grade III. **Figures 3C,D** show the 6-month outcomes of MR patients with grade II or greater and MR patients with less than grade II. In both the cases, severity of MR was not a statistically significant factor.

The mean GNRI score was 89.2 ± 10.6, indicating that most patients had an intermediate or higher risk of protein–energy malnutrition. The median (IQR) MoCA-J was 18.5 (14.3–24.0), indicating that all the patients had mild-to-moderate cognitive impairment. Moreover, most patients had multiple comorbidities including orthopedic disease, stroke, hypertension, chronic kidney disease, diabetes, and atrial fibrillation. A total of 47 (32%) patients had IHD.

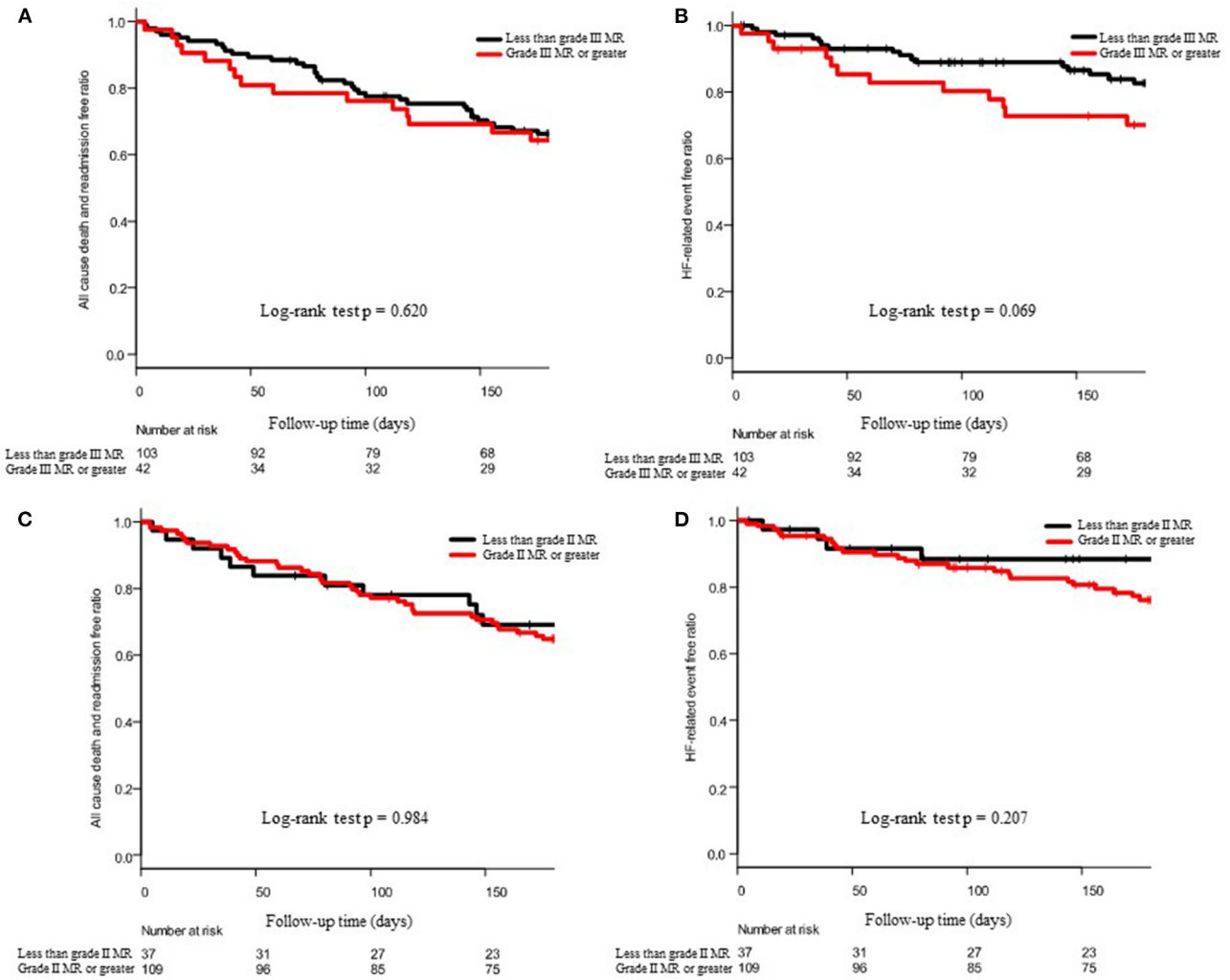

FIGURE 3 | Effect of the severity of MR on 6-month outcomes. **(A,C)** show the Kaplan–Meier curve of all-cause death and admission and **(B,D)** show the Kaplan–Meier curve of HF-related death and admission. In **(A,B)**, patient groups were divided into the grade III MR or greater and less than grade III, and in **(C,D)**, patients were divided into the grade II MR or greater and less than grade II. The *p*-values of the log-rank test were described at the bottom of each panel.

All the patients were treated by guideline-based standard pharmacotherapy except for angiotensin receptor-neprilysin inhibitor (ARNI) and sodium-glucose cotransporter 2 (SGLT2) inhibitor. These drugs had not yet been approved as HF treatment at the time of analysis in Japan. The mean SPPB was 8 (5–10), indicating that most patients had lower levels of lower limb muscle strength accompanying prefrail or frail physical activity. The higher KCL score and the lower BI score also support that most patients with HF harboring FMR had significant frailty and limited daily living activities.

Overall Outcome

A total of 12 patients died during a median follow-up of 186.0 days (109.8–186.0) (HF in 8 patients, sepsis in 1 patient, acute peritonitis in 1 patient, multiple organ failure in 1 patient, and aspiration pneumonia in 1 patient). A total of 43 patients were readmitted to the hospital (worsening HF in 23 patients, aortic dissection in 1 patient, cerebral thromboembolism in 1 patient, pneumonia in 2 patient, orthopedic disease in 5 patients, cancer in 1 patient, and others in 10 patients); consequently, 31 patients (21%) reached HF-related endpoints. Although two patients with HF were harboring severe aortic stenosis (AS) in addition to FMR in this study, the presence of AS did not affect the primary and secondary endpoints.

Predictive Factors of Primary and Secondary Composite Endpoints

Tables 2, **3** show the univariate and multivariate Cox proportional hazard regression analyses for the primary and secondary endpoints, respectively.

For the all-cause death and admissions, BMI, EROA, BNP, GNRI, and use of tolvaptan were significant determinants of the all-cause death and admissions in the univariate analysis,

TABLE 2 | The univariate and multivariate Cox proportional hazard regression analyses to predict composite endpoint after discharge of patients with ADHF harboring FMR.

Variables	Univariate			Multivariate		
	HR	95%CI	*p*-value	HR	95%CI	*p*-value
Age	1.489	0.862–2.572	0.154	1.058	1.006–1.112	0.027
Male sex	1.149	0.670–1.969	0.614			
BMI	0.430	0.243–0.760	0.004			
SBP	0.990	0.976–1.005	0.206			
IHD	1.524	0.892–2.603	0.123			
Grade 0 MR (reference)						
Grade III MR or greater	1.117	0.633–1.972	0.702			
LVEF	0.582	0.335–1.010	0.054	0.971	0.945–0.997	0.030
EROA	2.131	1.121–4.051	0.021			
BNP	1.881	1.075–3.291	0.027			
GNRI	0.511	0.292–0.895	0.019	0.932	0.887–0.979	0.005
Tolvaptan	2.334	1.359–4.007	0.002			
SPPB	0.740	0.424–1.291	0.289			

The multivariate Cox proportional hazard regression analysis results were shown using a stepwise variable reduction method described in the Method section. The remaining univariate analysis variables, the p-value larger than 0.20, were listed in ***Supplementary File 2****.*

HR, hazard ratio; ADHF, acute decompensated heart failure; FMR, functional mitral regurgitation; BMI, body mass index; SBP, systolic blood pressure; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; EROA, effective regurgitant orifice area; BNP, brain natriuretic peptide; GNRI, geriatric nutritional risk index; SPPB, short physical performance battery.

TABLE 3 | The univariate and multivariate Cox proportional hazard regression analyses to predict HF-related endpoint after discharge of patients with ADHF harboring FMR.

Variables	Univariate			Multivariate		
	HR	95%CI	*p*-value	HR	95%CI	*p*-value
Age	1.590	0.765–3.304	0.214			
Male sex	0.784	0.378–1.628	0.514			
BMI	0.487	0.231–1.027	0.059	0.793	0.614–0.890	0.001
SBP	1.001	0.982–1.021	0.893			
Readmission	2.261	1.058–4.832	0.035			
IHD	1.797	0.897–3.599	0.098	2.732	1.056–7.067	0.038
Grade 0 MR (reference)						
Grade III MR or greater	1.748	0.869–3.517	0.117			
LVEF	0.600	0.289–1.248	0.172			
EROA	1.275	0.532–3.058	0.586			
BNP	2.336	1.093–4.994	0.029			
GNRI	0.432	0.201–0.926	0.031			
Tolvaptan	2.965	1.445–6.083	0.003			
KCL	2.647	1.238–5.658	0.012			
SPPB	0.515	0.236–1.125	0.096			

The multivariate Cox proportional hazard regression analysis results were shown using a stepwise variable reduction method described in the Method section. The remaining univariate analysis variables, the p-value larger than 0.20, were listed in ***Supplementary File 3****.*

HR, hazard ratio; ADHF, acute decompensated heart failure; FMR, functional mitral regurgitation; BMI, body mass index; SBP, systolic blood pressure; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; EROA, effective regurgitant orifice area; BNP, brain natriuretic peptide; GNRI, geriatric nutritional risk index; KCL, Kihon Checklist; SPPB, short physical performance battery.

as shown in **Table 2**. The multivariate Cox proportional hazard regression analysis revealed that GNRI, age, and LVEF were independent determinants of the all-cause death and admissions, as shown in **Table 2**. In the ROC analysis, when the cut-off value of the GNRI was set to 86.6, the sensitivity, specificity, and the AUC were 65, 57%, and 0.625 (95% CI = 0.530–0.721), respectively (**Figure 4A**). The Kaplan–Meier curve revealed a significantly higher incidence of the primary endpoints in patients with the GNRI < 86.6 than in GNRI ≥ 86.6 (**Figure 4B**).

For the HF-related endpoints, readmission, BNP, GNRI, use of tolvaptan, and the KCL score were significant determinants of the HF-related endpoints in the univariate analysis. The multivariate Cox proportional hazard regression analysis revealed that etiology of BMI and IHD were independent determinants of the HF-related endpoints. In the ROC analysis, when the cut-off value of BMI was set to 20.3, the sensitivity, specificity, and the AUC were 58, 72%, and 0.675 (95% CI = 0.586–0.765), respectively (**Figure 5A**). The Kaplan–Meier curve revealed a significantly higher incidence of HF-related endpoint in patients with BMI < 20.3 kg/m^2 than those with BMI ≥ 20.3 kg/m^2 (**Figure 5B**).

DISCUSSION

In this prospective observational cohort study of patients with ADHF harboring moderate-to-severe FMR, we found that a lower nutrition index and underweight were substantial predictors of 6-month all-cause mortality and HF-related composite outcomes. In addition, higher age and lower LVEF were associated with a worse outcome of all-cause death and admission and etiology of IHD was also associated with a worse outcome of HF-related death and admissions. Interestingly, severity of MR was not significantly associated with the primary and secondary outcomes. To the best of our knowledge, this is the first report describing that nutritional status is more important than the severity of MR *per se* in elderly patients with ADHF harboring moderate-to-severe FMR.

We initially intended to include all the moderate-to-severe etiologies of MR in elderly patients ADHF in this study. Consequently, all the patients were categorized as secondary MR at enrollment, underscoring that FMR plays a crucial role in the onset of ADHF. Of the 146 patients with FMR, 109 (74%) of patients with HF had more than grade II MR 2 weeks after admission, whereas 26% of patients with HF showed a transition to less than grade II MR 2 weeks after admission. These are typical characteristics of secondary MR in ADHF, as previously reported (26). Indeed, these secondary MR contains two categories of etiology, approximately half of the patients showed ventricular FMR with reduced EF (26, 29, 30) and the remaining half of the patients revealed atrial hamstringing FMR associated with atrial

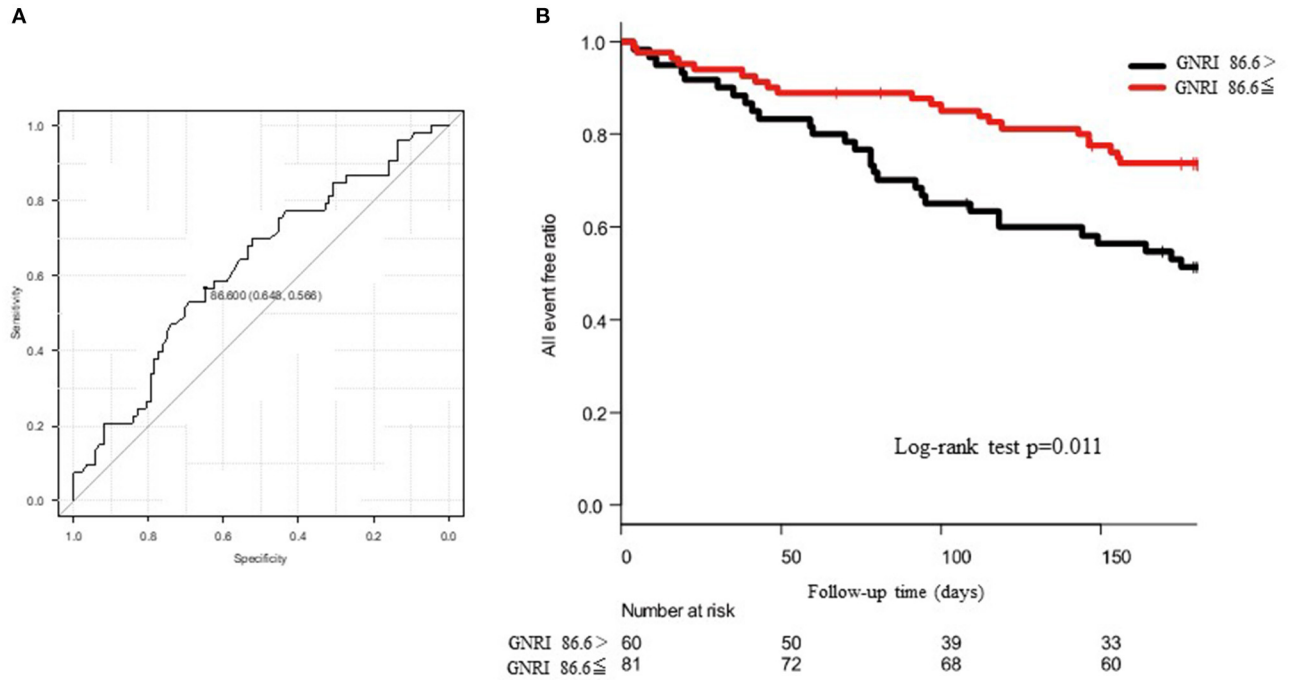

FIGURE 4 | (A) shows the receiver operating characteristic (ROC) curve to predict the cut-off value of composite endpoints using the geriatric nutritional risk index (GNRI). The area under the curve (AUC) was 0.625 and 95% CI was from 0.530 to 0.721. When the cut-off value of GNRI was set to 86.6, the sensitivity and the specificity became 65 and 57%, respectively. **(B)** shows the Kaplan–Meier curve to evaluate the cumulative incidences of composite endpoints. The log-rank test revealed a *p*-value of 0.011.

fibrillation and preserved or mid-range ejection fraction (26, 31–34). A higher incidence of atrial fibrillation in the latter category is consistent with such etiological origin.

It is noteworthy that severity of MR was not associated with primary and secondary outcomes in this study. This result is different from previous studies that reported that mild-to-severe secondary MR affected all-cause mortality and HF readmission (35). It is plausible that a relatively small number of analyzed patients, use of older-aged groups, short follow-up period, and predominance of female patients (53% of the patients) in this study may be associated with the difference from the previous studies. Indeed, the mean age of this study was more than 10 years older than those of earlier reports (35–37). The percentage of female patients was more prominent than those in previous reports (35–37). It has been reported that women have a 26% higher relative risk than men to be frail and have lower body weight in HF (38). Therefore, the characteristics of female patients with HF may override MR-related outcomes. In addition, in the previous studies, nutritional variables and physical and social parameters associated with CR were not used in the univariate and multivariate Cox proportional hazard regression analyses to predict composite endpoints after discharge of patients with ADHF. Therefore, it is plausible that the difference of used statistical variables affected our results. In this regard, further analysis may be needed to determine which is more important for predicting patient outcome in elderly patients, the severity of functional MR or malnutrition, and associated frailty.

It is of note that lower GNRI was significantly associated with poor primary endpoints. Several studies have reported that lower GNRI is associated with a substantially higher number of cardiac death or HF admission than higher GNRI (39, 40), of which the cut-off value is 92 (41). In this study, the cut-off value of GNRI predicting the poor outcome of the primary endpoint was 86.6, which was further lower than those previously reported. This value may reflect the higher age of the analyzed population, multiple comorbidities, and significant cognitive impairment in this study. It has been reported that malnutrition was also associated with hospitalization of HF-unrelated events including orthopedic accidents, infection, and other non-cardiac diseases. The present data were consistent with previous studies (42, 43). Additionally, the therapeutic effect of minimally invasive treatment for patients with severe AS, namely transcatheter aortic valve implantation (TAVI), was affected by the low GNRI score (44). Likewise, when minimally invasive therapy (TEER) for mitral regurgitation is considered in the future, the low GNRI score may also be a poor prognostic factor, as was the case in this study.

It is well-known that higher patients with BMI have better prognoses than those of lower patients with BMI (7). Although our result is compatible with previous findings, the coexistence of sarcopenia, frailty, and lower GNRI value underscores the importance of nutritional status in elderly patients with HF

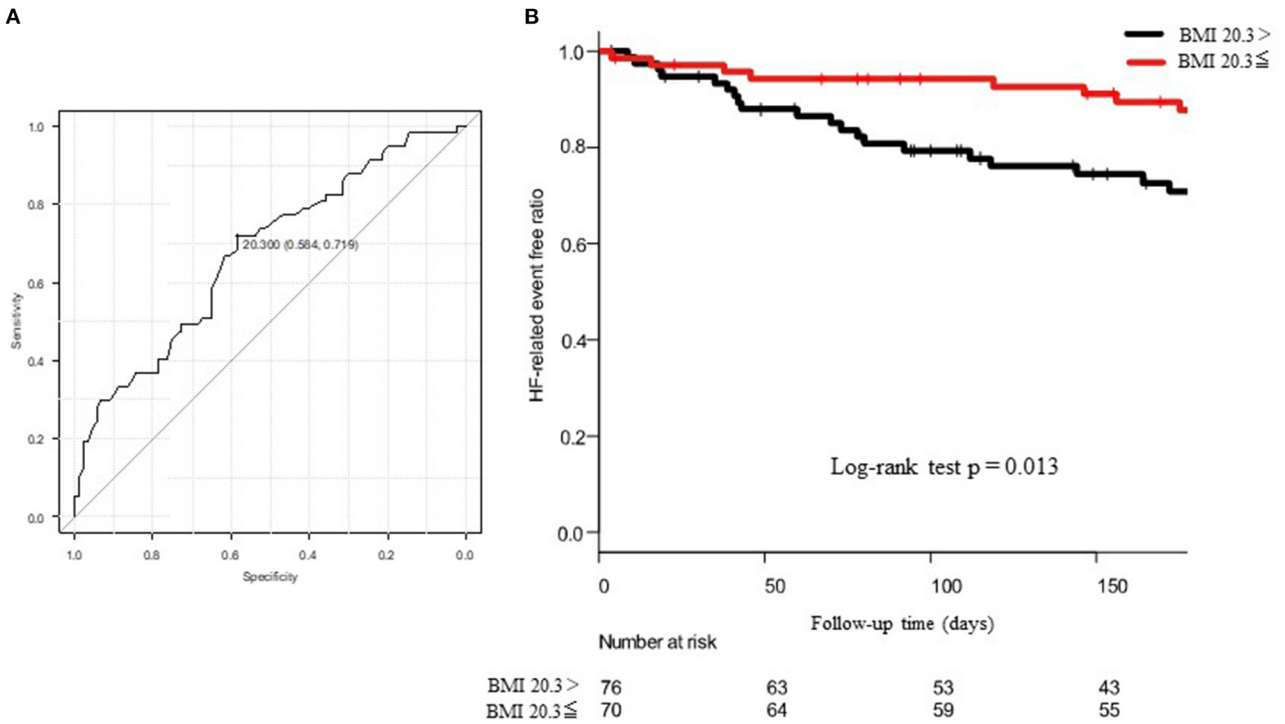

FIGURE 5 | (A) shows the ROC curve to predict the cut-off value of HF-related endpoints using the body mass index (BMI). The AUC was 0.675 and 95% CI was from 0.586 to 0.765. When the cut-off value of BMI was set to 20.3, the sensitivity and the specificity became 58 and 72%, respectively. **(B)** shows the Kaplan–Meier curve to evaluate the cumulative incidences of HF-related endpoints. The log-rank test revealed a *p*-value of 0.013.

harboring moderate-to-severe MR (7, 45). Moreover, the cut-off value of BMI that predicts poor outcome was 20.3 in this study, nearly the same value as previously reported (27, 46, 47). In this regard, we may seek potential therapeutic intervention targeting body weight in elderly patients with HF harboring FMR in future studies.

Concerning multiple CR parameters, why were SPPB, 6MWT, QIS, handgrip strength test, sarcopenia indexes, and BI not effective as predictive indicators in this study? For example, the SPPB has been previously reported as a good outcome predictor in elderly patients with HF (48, 49). A relatively shorter follow-up period of this study may be associated with this difference. Moreover, we only provided a CR program during hospital admission, but not in the outpatient clinic, although we instructed every patient to perform CR at home. Further study will be needed how to provide an optimal CR program in elderly patients with HF harboring FMR.

Limitations

This study has several limitations. First, we intended to include primary and secondary MR patients with surgically unoperated status before starting this study; however, an analysis was consequently performed only on inpatients with secondary MR. Because all the hospitalized patients with ADHF with severe primary MR, which was a tiny number, received surgical treatment, we did not enroll those patients. However, the number of surgically untreated primary patients with MR may increase in a superaged society; further study may be required. Second, this study was a prospective single-center study with relatively short-term enrollment and a small sample size. Further studies with larger samples and multicenter enrollment need to be considered. Third, this cohort was exclusively Japanese, not including other races such as African American, White, Pacific, or others.

CONCLUSION

In conclusion, we found that a lower nutrition index and underweight were substantial 6-month outcome predictors in the hospitalized elderly patients with ADHF harboring with moderate-to-severe FMR.

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 local institutional board at Yamaguchi

Prefectural Grand Medical Center (ID: 2017-019). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MM was the primary investigator for this study, collating data, and as well as the overall writing of the project. YI and TY were the project supervisor, they reviewed all documents as well as helping analyze the data, and figures and tables. KM, HN, TU, FN, and SO reviewed the manuscript and offered insights based on their own experiences. MS performed the statistical analysis. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.764528/full#supplementary-material

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Not Baseline Atrial Fibrillation but New-Onset Atrial Fibrillation and the Loss of Left Atrial Function Are Essential for Predicting Poor Outcomes in Non-ischemic Cardiomyopathy

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Aims: The clinical impact of the type of atrial fibrillation (AF) has not been completely elucidated in non-ischemic cardiomyopathy (NICM). Although the structure and function of the left atrium (LA) provide prognostic information in patients with heart failure, the relationship of the AF type with LA structure and function in NICM is unclear.

Methods: Consecutive patients with NICM who underwent cardiac magnetic resonance were evaluated and followed. Multivariable Cox regression models were used to estimate hazard ratios (HRs) for major adverse cardiovascular events (MACE) related to the AF type, such as paroxysmal AF, chronic AF, and new-onset AF (NOAF).

Results: Among 625 patients with NICM (mean age, 64.4 ± 14.2 years; women, 39.7%), 133 had a history of AF at baseline; of these, 60 had paroxysmal AF. Each baseline AF type was associated with higher LA volume and lower LA emptying fraction but not with an increased incidence of MACE ($p = 0.245$). New-onset AF developed in 5.9% of patients with sinus rhythm over a median follow-up period of 609 days, and maximum LA volume was a strong and independent predictor [$p < 0.001$, area under the ROC curve (AUC): 0.795]. Maximum LA volume was superior to LA emptying fraction and B-type natriuretic peptide (AUC: 0.683 and 0.680, respectively). The use of β-blocker and the age of the patient were associated with the incidence of NOAF (HR: 0.37, 95% CI: 0.16–0.84 and HR: 1.05, 95% CI: 1.01–1.09, respectively). Kaplan–Meier analysis showed that patients with NOAF had a higher incidence of MACE than those with sinus rhythm or baseline AF ($p = 0.002$). NOAF and LA emptying fraction were independent predictors of MACE (HR: 2.28, 95% CI: 1.20–3.97 and HR: 0.98, 95% CI: 0.96–0.99, respectively) after adjusting for age, sex, body mass index, and diagnosis.

Conclusions: Paroxysmal and chronic AF in patients with NICM were not associated with an increased incidence of MACE despite their association with LA volume and

function. NOAF was independently associated with poor prognosis. Higher maximum LA volume predicted the onset and lower LA emptying fraction was independently associated with poor prognosis.

Keywords: left atrium, new-onset atrial fibrillation, clinical outcomes, non-ischemic cardiomyopathy, magnetic resonance imaging

INTRODUCTION

Atrial fibrillation (AF) results in atrial enlargement and is a major arrhythmia associated with heart failure (HF). Hypertension, diabetes, obesity, smoking, and coronary artery disease have been scored as risk factors for AF development (1). AF is classified as paroxysmal or chronic (persistent or permanent) depending on the duration, and among these types, newly developed AF events are attracting attention. A recent study reported that new-onset AF (NOAF) was associated with poor prognosis in acute coronary syndrome (2). Additionally, among patients with HF, NOAF had a significant prognostic impact (3). However, previous studies reported conflicting findings regarding whether baseline AF is an independent predictor of poor prognosis in patients with HF (4). Although NOAF was found to have a significant association with cardiovascular (CV) events in a broad cohort of patients with HF, the clinical impact of NOAF remains unclear in a subcohort of patients with HF, particularly in non-ischemic cardiomyopathy (NICM). NICM, which leads to a decline in cardiac function, results in HF and severe arrhythmic events (5, 6). The relationship of these outcomes with AF types has not been fully elucidated in NICM, and although several factors have been reported, novel predictive factors for the onset of AF need to be explored to prevent the onset of NOAF.

Left atrial (LA) enlargement is a strong predictor of cardiovascular events in the general population and patients with AF or HF (7, 8). A detailed assessment of the structure and function of LA using echocardiography or cardiac magnetic resonance (CMR) provides prognostic information about incident AF, HF onset, and stroke (9, 10). However, the relationship of AF type with LA structure and function in NICM has not been completely examined. In this study, we evaluated the clinical impact of baseline AF and NOAF in patients across a broad spectrum of NICM who underwent CMR examination. We performed a detailed CMR analysis to assess the relationship between LA volume/function and AF type and attempted to elucidate its prognostic potential.

METHODS

Study Protocol

This was a single-center study in which consecutive patients with cardiomyopathy referred for cardiac magnetic resonance (CMR) were enrolled between February 2008 and December 2018 at Kindai Hospital (Osakasayama, Japan). The referral reason for CMR was to diagnose or evaluate the cardiomyopathy initially, and the patients were in a stable condition. Patients with significant coronary artery disease (significant stenosis of $\geq$50% of a major coronary artery and history of myocardial infarction) were ruled out by coronary angiography, computed tomography, or CMR (11). NICM was then defined as cardiomyopathy excluding significant primary valve disease, congenital heart disease, acute myocarditis, arrhythmogenic right ventricular cardiomyopathy, and postchemotherapeutic left ventricular dysfunction (12).

The further etiological diagnosis was made based on the following criteria: left ventricular non-compaction (LVNC); the ratio of non-compacted to compacted myocardium in end-diastole of >2.3 by CMR (13); dilated cardiomyopathy (DCM); LV dysfunction and dilatation in the absence of coronary artery disease and specific heart muscle diseases (14); hypertrophic cardiomyopathy (HCM); LV hypertrophy of $\geq$15 mm and asymmetric/focal hypertrophy in the absence of another disease that could account for the hypertrophy (15); cardiac sarcoidosis (CS); fulfilling the guidelines published in 2016 by the Japanese Circulation Society or the characteristic manifestations and positive findings of echocardiography, ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET), or CMR with or without extra CS after exclusion from other known cardiac diseases (16); cardiac amyloidosis (CA); and histological confirmation of amyloidosis by tissue biopsies. The workup at the initial diagnosis included an electrocardiogram (ECG) and echocardiography. The LA diameter and degree of mitral regurgitation (MR) were also assessed. MR was considered to be significant if at least grades 2 of 4 were obtained. The plasma B-type natriuretic peptide (BNP) and serum creatinine levels were measured for clinical purposes. The estimated glomerular filtration rate (eGFR) was calculated using an equation specific to the Japanese population: eGFR = 194 $\times$ (serum creatinine) – 1.094 $\times$ (age) – 0.287 ($\times$ 0.739 for woman).

Paroxysmal AF (PAF) was defined as self-terminating or being cardioverted within 7 days of onset. Chronic AF (CAF), including persistent or permanent AF, lasted >7 days. NOAF was defined if AF was diagnosed or documented during follow-up by the attending physicians among patients without baseline AF (no history of AF and no AF in the baseline ECG).

CMR Image Acquisition and Analysis

Cardiac magnetic resonance was performed using a 1.5 T scanner (Intera 1.5T; Philips Medical Systems, the Netherlands), according to a standardized protocol. Cine images were acquired with a steady-state free-precession breath-hold sequence (SSFP) in contiguous short-axis slices (10 mm, no gap) from the atrioventricular ring to the apex. Image analysis was performed using commercially available workstations (Aze Virtual Place; Aze, Japan). Endocardial and epicardial contours on short-axis SSFP images were manually delineated on end-diastolic and end-systolic short-axis slices in LV. The summation disk method

was used to calculate end-diastolic volume, end-systolic volume, ejection fraction (EF), and masses (17).

To assess LA volume and function, the endocardial borders in two- and four-chamber cine images were contoured carefully, excluding the pulmonary veins and LA appendage. LA volume was calculated based on the biplane area–length method, i.e., LA volume $= (0.848 \times \text{area}_{4-\text{ch}} \times \text{area}_{2-\text{ch}})/[(\text{length}_{2-\text{ch}} + \text{length}_{4-\text{ch}})/2]$, based on a previous study (18). Maximum LA volume (Vmax: LA volume at end-systole, immediately before mitral valve opening), minimum LA volume (Vmin: LA volume at end-diastole, immediately before mitral valve closure), and preatrial contraction volume (VpreA: LA volume at the onset of the P-wave on ECG) were defined, and LA emptying fraction [(Vmax–Vmin)/Vmax × 100%], LA passive emptying fraction [(Vmax–VpreA)/Vmax × 100%], and LA active emptying fraction [(VpreA–Vmin)/VpreA × 100%] were calculated (**Supplementary Figure 1**).

Clinical Follow-Up

Long-term clinical follow-up, through 2,500 days from CMR testing, was accomplished through a patient-completed questionnaire, telephone interviews, or *via* chart reviews. The following events were recorded: combined major adverse cardiac events (MACE), such as CV mortality, hospitalization for worsening HF, and severe arrhythmia; and all-cause mortality, including the cause of death. CV death was defined as sudden death and death attributed to CV causes, such as fatal myocardial infarction, pump failure, stroke, and severe arrhythmia. Hospitalization for worsening HF was defined as an unexpected presentation to an acute-care facility requiring hospitalization with exacerbation of HF. Severe arrhythmia was defined as sustained ventricular tachycardia/fibrillation, including appropriate implantable cardioverter-defibrillator discharge. All events were based on the clinical diagnosis; however, to validate these events, the medical records were reviewed by us or the physician in charge. They were reviewed independently by two cardiologists (MY and TK), and disagreements were forwarded to a senior cardiologist (YI) for further review.

Statistical Analysis

The student's *t*-test was performed for comparisons among groups as part of the univariate analysis for continuous variables. Pearson χ^2 or Fisher's exact test was used to assessing differences in categorical variables using JMP version 14.0 software (SAS Institute, Cary, NC, USA). Furthermore, multiple logistic regression analysis was used to explore the relationship of CMR parameters and BNP level with NOAF. The cutoff levels for NOAF and the sensitivities and specificities of the cutoff levels were calculated using receiver operating characteristic (ROC) curve analysis. Event-free survival curves were analyzed using the Kaplan–Meier method, and the curves were compared using the log-rank test. Univariate and multivariate analyses of the clinical outcomes were evaluated using Cox's proportional hazard model, and hazard ratios (HRs) and 95% CIs were calculated. For incident AF (NOAF), the forward stepwise selection was performed to identify crucial independent variables other than LA Vmax, LA emptying fraction, or log BNP level. For MACE and all-cause mortality, to explore the independent associations between the two variables, NOAF and LV emptying fraction, by univariate analysis, the following covariates were included in the models: age, sex, body mass index, etiological diagnosis, LV EF, and log BNP level after considering collinearity. A value $p < 0.05$ was considered statistically significant. All results were expressed as the mean ± standard deviation.

Ethical Statement

The study was approved by the Ethics Committee of Kindai University Faculty of Medicine and was conducted according to the principles of the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all the participants after an explanation of the study's purpose and protocol.

RESULTS

Study Population and CMR Findings

In total, 718 consecutive patients with eligible NICM were identified among those with CMR from February 2008 to December 2018. After the exclusion of patients with repeated CMR and poor images, 625 patients with NICM (cohort 1) were enrolled into the analysis, among whom 133 (21.3%) had prevalent AF at baseline. Of these, 73 and 60 patients had CAF and PAF, respectively (**Supplementary Figure 2**). **Table 1** presents the baseline clinical characteristics of cohort 1. The mean age was 64.4 ± 14.2 years, and 39.7% were women. In both the CAF and PAF groups, BNP levels were increased, and the medications, including diuretics and anticoagulants, were administered more frequently than that of sinus rhythm (SR). Only patients with CAF had older age, lower female proportion, lower eGFR, frequent NYHA class ≥ II, and frequent medications, including β-blockers and calcium channel blockers, compared with those with SR. Increased resting HR, increased LA diameter, and frequent moderate or greater MR were also observed only in the patients. The following characteristics were different between the CAF and PAF groups: proportion of women; eGFR; NYHA class ≥ II; medications, including diuretics, anticoagulants, and amiodarone; resting HR; LA diameter; and frequent moderate or greater MR. Regarding the etiological diagnosis of NICM, DCM was most frequently diagnosed in any group, followed by HCM. Patients with DCM had a higher frequency of CAF. Left ventricular ejection fraction was decreased only in the CAF group, and no significant differences were found in other LV parameters among the three groups. Significant differences in LA parameters were found in the three groups. The CAF group showed the largest LA volumes and the lowest LA empty fractions; in contrast, the SR group showed the smallest LA volumes and the highest LA empty fractions.

We followed up 492 patients with baseline SR (cohort 2), and 29 (5.9%) patients developed NOAF (NOAF group) over a median follow-up period of 609 days. **Table 2** presents

TABLE 1 | Clinical characteristics and CMR findings according to baseline rhythm in cohort 1.

	Total patients ($n = 625$)	Sinus rhythm ($n = 492$)	CAF ($n = 73$)	PAF ($n = 60$)	*P*-value
Age, years	64.4 ± 14.2	63.1 ± 14.6	70.0 ± 10.0[#]	67.3 ± 12.6	<0.001
Female	248 (39.7%)	204 (41.5%)	19 (25.7%)[#]	25 (41.7%)[†]	0.040
Body mass index, kg/m^2	23.0 ± 4.3	23.1 ± 4.4	22.8 ± 4.0	22.9 ± 4.1	0.851
eGFR, mL/min/1.73 m²	77.5 ± 25.7	79.4 ± 26.0	65.6 ± 18.5[#]	76.7 ± 26.5[†]	<0.001
log BNP	4.7 ± 1.3	4.5 ± 1.4	5.4 ± 0.9[#]	5.3 ± 1.1[#]	0.001
NYHA classification ≥II	246 (39.4%)	170 (34.6%)	48 (65.8%)[#]	28 (46.7%)[†]	<0.001
Etiological diagnosis					0.036
LVNC	51 (8.1%)	46 (9.4%)	1 (1.4%)	4 (6.7%)	
Dilated cardiomyopathy	234 (37.4%)	174 (35.4%)	41 (56.2%)	19 (31.7%)	
Hypertrophic cardiomyopathy	198 (31.7%)	159 (32.3%)	19 (26.0%)	20 (33.3%)	
Cardiac sarcoidosis	124 (19.8%)	100 (20.3%)	12 (16.4%)	12 (20.0%)	
Cardiac amyloidosis	18 (2.9%)	13 (2.6%)	0 (0.0%)	5 (8.3%)	
Medication					
ACE-I/ARB	399 (63.8%)	302 (61.4%)	53 (72.6%)	44 (73.3%)	0.044
β-Blocker	384 (61.4%)	288 (58.5%)	57 (78.1%)[#]	39 (65.0%)	0.004
Calcium channel blocker	176 (28.2%)	127 (25.8%)	28 (38.4%)[#]	21 (35.0%)	0.045
Diuretics	250 (40.0%)	159 (32.3%)	58 (79.5%)[#]	33 (55.0%)[#†]	<0.001
MRA	129 (20.6%)	91 (18.5%)	23 (31.5%)[#]	15 (25.0%)	0.033
Anticoagulant	148 (23.7%)	27 (5.5%)	73 (100%)[#]	48 (80.0%)[#†]	<0.001
Amiodarone	22 (3.5%)	13 (2.6%)	1 (1.4%)	8 (13.3%)[†]	<0.001
Echo parameters					
Hear rate, beats/min	69.8 ± 15.6	68.3 ± 14.0	79.1 ± 18.9[#]	70.2 ± 18.9[†]	<0.001
Left atrial diameter, mm	41.7 ± 7.4	40.4 ± 6.6	49.6 ± 8.0[#]	42.2 ± 6.5[†]	<0.001
Moderate or greater MR	49 (8.1%)	33 (6.9%)	11 (15.5%)[#]	5 (8.6%)[†]	0.048
CMR parameters					
Left ventricle					
End-diastolic volume, mL	176.0 ± 72.3	175.3 ± 71.7	178.6 ± 69.7	178.2 ± 80.7	0.908
End-systolic volume, mL	115.6 ± 72.9	113.2 ± 72.3	130.2 ± 69.1	117.3 ± 80.8	0.174
Ejection fraction, %	38.7 ± 15.9	40.0 ± 15.7	30.3 ± 15.2[#]	38.8 ± 15.1	<0.001
Mass, g	115.0 ± 44.3	116.3 ± 45.5	108.4 ± 38.4	112.8 ± 40.8	0.335
Left atrium					
Vmax, mL	93.2 ± 44.6	83.5 ± 33.6	143.7 ± 68.0[#]	110.7 ± 41.5[#†]	<0.001
Vmax index, mL/m^2	57.6 ± 27.7	51.5 ± 20.7	88.3 ± 42.6[#]	69.6 ± 26.4[#†]	<0.001
Vmin, mL	63.1 ± 41.5	52.3 ± 29.1	121.1 ± 58.3[#]	80.8 ± 39.0[#†]	<0.001
Vmin index, mL/m^2	39.0 ± 25.8	32.3 ± 18.0	74.6 ± 36.7[#]	50.9 ± 24.6[#†]	<0.001
Emptying fraction, %	35.9 ± 13.9	39.7 ± 11.9	15.9 ± 5.8[#]	29.1 ± 13.0[#†]	<0.001
Passive emptying fraction, %	16.6 ± 7.8	17.5 ± 8.1	12.3 ± 5.2[#]	14.2 ± 6.2[#]	<0.001
Active emptying fraction, %	23.4 ± 13.7	27.0 ± 12.0	4.0 ± 4.1[#]	17.7 ± 12.7[#†]	<0.001

Values are the mean ± SD or n (%). [#]P < 0.05 vs. sinus rhythm; [†]P < 0.05 vs. CAF.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CAF, chronic atrial fibrillation; CMR, cardiac magnetic resonance; eGFR, estimated glomerular filtration rate; LVNC, left ventricle non-compaction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; Vmax, volume at maximum; Vmin, volume at minimum.

the baseline clinical characteristics of the patients in Cohort 2. Significant differences were observed only in BNP levels and LA diameter. Although no significant difference was observed in LV parameters, the NOAF group showed higher LA volumes and lower LA emptying fractions than the SR group. The LA Vmax of the NOAF group was similar to that of the baseline CAF group or PAF group. The LA emptying fraction of the NOAF group was similar to that of the baseline PAF group and higher than that of the baseline CAF group.

Among the cohorts categorized according to the etiological diagnosis of NICM, there was no difference in LA Vmax, but

TABLE 2 | Clinical characteristics and CMR findings according to follow-up rhythm in cohort 2.

	Sinus rhythm ($n = 463$)	NOAF ($n = 29$)	*P*-value
Age, years	62.89 ± 14.8	67.4 ± 11.5	0.108
Female	194 (41.9%)	19 (65.6%)	0.432
Body mass index, kg/m^2	23.0 ± 4.3	23.9 ± 5.3	0.270
eGFR, mL/min/1.73 m²	79.5 ± 26.1	77.6 ± 24.8	0.701
log BNP	4.5 ± 1.4	5.4 ± 1.0	0.001
NYHA classification ≥II	155 (33.5%)	15 (51.7%)	0.051
Etiological diagnosis			0.789
LVNC	44 (9.5%)	2 (6.9%)	
Dilated cardiomyopathy	164 (35.4%)	10 (34.5%)	
Hypertrophic cardiomyopathy	147 (31.78%)	12 (41.4%)	
Cardiac sarcoidosis	96 (20.7%)	4 (13.8%)	
Cardiac amyloidosis	12 (2.6%)	1 (3.4%)	
Medication			
ACE-I/ARB	284 (61.3%)	18 (62.1%)	0.938
β-Blocker	272 (58.8%)	16 (55.2%)	0.706
Calcium channel blocker	116 (25.1%)	11 (37.9%)	0.139
Diuretics	147 (31.8%)	12 (41.4%)	0.291
MRA	82 (17.7%)	9 (31.0%)	0.093
Anticoagulant	26 (5.6%)	1 (3.5%)	0.596
Amiodarone	13 (2.8%)	0 (0%)	0.360
Echo parameters			
Heart rate, beats/min	68.56 ± 14.1	64.3 ± 13.1	0.116
Left atrial diameter, mm	40.1 ± 6.5	45.7 ± 7.2	<0.001
Moderate or greater MR	30 (6.7%)	3 (11.1%)	0.381
CMR parameters			
Left ventricle			
End-diastolic volume, mL	173.8 ± 70.3	200.3 ± 88.8	0.053
End-systolic volume, mL	112.1 ± 70.7	130.4 ± 94.5	0.186
Ejection fraction, %	40.0 ± 15.7	39.6 ± 16.8	0.889
Mass, g	115.8 ± 45.4	124.7 ± 48.4	0.305
Left atrium			
Vmax, mL	80.4 ± 29.7	131.9 ± 52.1	<0.001
Vmax index, mL/m^2	49.7 ± 18.2	80.6 ± 32.9	<0.001
Vmin, mL	49.6 ± 25.2	94.2 ± 49.0	<0.001
Vmin index, mL/m^2	30.7 ± 15.5	57.8 ± 31.5	<0.001
Emptying fraction, %	40.2 ± 11.7	32.2 ± 12.7	<0.001
Passive emptying fraction, %	17.8 ± 8.9	12.9 ± 5.9	0.001
Active emptying fraction, %	27.3 ± 11.9	22.3 ± 13.1	0.032

Values are the mean ± SD or n (%).

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CAF, chronic atrial fibrillation; CMR, cardiac magnetic resonance; eGFR, estimated glomerular filtration rate; LVNC, left ventricle non-compaction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; Vmax, volume at maximum; Vmin, volume at minimum.

there was a significant difference in the LA emptying fraction (**Supplementary Table 1**). CA was significantly decreased compared with other diagnoses ($p < 0.001$ for all), and CS was significantly increased compared with DCM ($p = 0.001$). Nevertheless, the prevalence of baseline CAF/PAF and NOAF events did not differ among the etiologies ($p = 0.081$ and 0.805, respectively).

Clinical Determinants of NOAF

Univariate analysis in Cohort 2 showed that age, log BNP levels, LA volumes, LA emptying fraction, and LA passive emptying fraction were associated with the development of NOAF (**Supplementary Table 2**). In contrast, LV EF and etiological diagnosis did not show an association. The ROC curve analysis showed that LA Vmax showed the best predictive performance

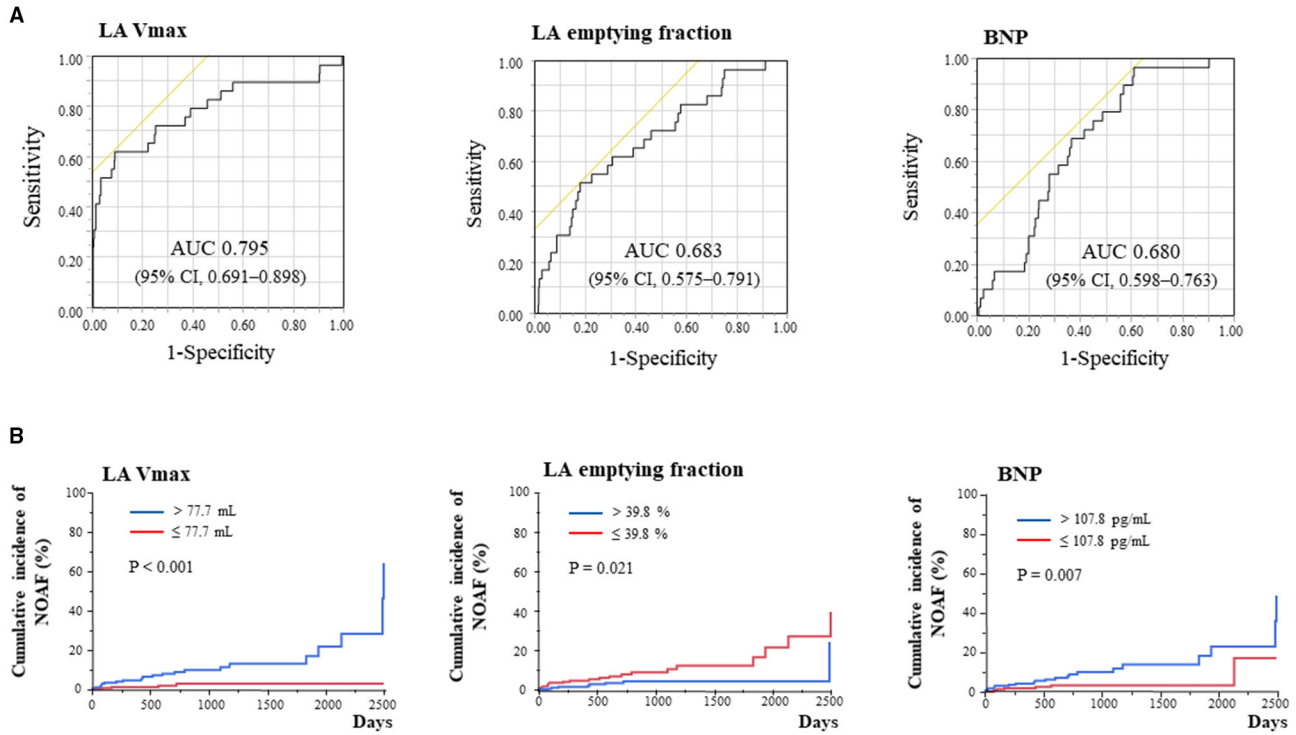

FIGURE 1 | Determinants of new-onset atrial fibrillation (AF) by receiver operating characteristic curve analysis **(A)** and Kaplan–Meier analysis for new-onset AF stratified according to LA Vmax, LA emptying fraction, and BNP **(B)**. AUC, area under the curve; BNP, B-type natriuretic peptide; CI, confidence interval; LA, left atrium; MACE, major adverse cardiac event; NOAF, new-onset atrial fibrillation; Vmax, maximum volume.

of NOAF, with an area under the ROC curve (AUC) of 0.795 (95% CI, 0.691–0.898) (**Figure 1A**). The optimal cutoff value of LA Vmax was 121.6 ml (sensitivity of 62.1% and specificity of 90.7%). When baseline LA Vmax, LA emptying fraction, or BNP levels were divided by the median value, patients with larger LA Vmax, lower LA emptying fraction, or higher BNP level developed NOAF more in cohort 2 (**Figure 1B**). Multivariate Cox proportional risk analysis showed that age and β-blocker use in addition to LA Vmax were independent predictors of NOAF (**Table 3A**). Older patients with higher LA Vmax had a higher risk of developing NOAF than younger patients with lower LA Vmax (odds ratio, 15.64; 95% CI, 2.03–120.30) (**Supplementary Figure 3**). β-Blocker use was associated with a low incidence of NOAF in the groups with higher LA Vmax (**Supplementary Figure 4**).

Clinical Outcomes and the Relationship With LA Geometry/Function

Kaplan–Meier analysis in cohort 1 revealed no significant differences in both MACE and all-cause death among baseline rhythms (**Figure 2A**). Each type of AF at baseline was associated with LA volume and function but not with MACE and all-cause death. Patients with baseline CAF and PAF showed more frequent hospitalization for HF ($p = 0.005$; **Supplementary Table 3**; **Supplementary Figure 5A**). Conversely, Kaplan–Meier analysis in cohort 2 revealed that NOAF and lower LA emptying fraction (≤39.8%) led to a poor prognosis of both MACE and all-cause death (**Figure 2B**). Moreover, patients with NOAF had MACE, all-cause death, and hospitalization for HF more frequently than those with any type of baseline AF.

Univariate analysis of MACE revealed significant associations of MACE with variables such as age; body mass index; diagnosis; NOAF; NYHA ≥2; log BNP level; and β-blocker, mineralocorticoid receptor antagonist and diuretic use, in clinical characteristics, and LV EF, LA Vmin, and LA emptying fraction in CMR findings (**Supplementary Table 2**). In the Kaplan–Meier analysis stratified according to diagnosis, only CA showed poor prognosis with a shorter follow-up period (**Supplementary Table 1**; **Supplementary Figure 5B**). Multivariate Cox proportional risk analysis revealed that NOAF and LA emptying fraction were independent predictors of MACE (HR, 2.28; 95% CI, 1.20–3.97 and HR, 0.98; 95% CI, 0.96–0.99; respectively) after adjusting for age, sex, body mass index, and the diagnosis (**Table 3B**). NOAF was also an independent predictor of all-cause death after adjusting for age, sex, body mass index, and diagnosis (HR, 2.68; 95% CI, 1.08–5.70); however, LA emptying fraction was not associated with an all-cause death (**Table 3C**). LV EF was not associated with both MACE and all-cause death (Model 2), and log BNP was independently associated with both MACE and all-cause death (Model 3).

TABLE 3 | Multivariate cox proportional hazards analysis.

	Model 1		Model 2		Model 3	
Variable	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
(A)						
For the incidence of NOAF						
LA Vmax (mL)	1.03 (1.02–1.03)	<0.001				
LA emptying fraction (%)			0.94 (0.91–0.97)	<0.001		
log BNP					1.71 (1.25–2.38)	<0.001
Age (years)	1.03 (1.01–1.09)	0.006	1.03 (1.00–1.06)	0.041	1.03 (1.00–1.06)	0.054
β-Blocker use	0.37 (0.16–0.84)	0.018	0.44 (0.20–0.99)	0.047	0.46 (0.21–1.01)	0.054
(B)						
For MACE						
NOAF	2.28 (1.20–3.97)	0.014	2.26 (1.19–3.95)	0.015	2.05 (1.08–3.56)	0.029
LA emptying fraction (%)	0.98 (0.96–0.99)	0.002	0.98 (0.96–0.99)	0.005	0.99 (0.87–1.00)	0.139
Age (years)	1.02 (1.00–1.04)	0.027	1.02 (1.01–1.04)	0.007	1.02 (1.00–1.04)	0.014
Sex (male/female)	1.32 (0.88–2.00)	0.183	1.25 (0.84–1.88)	0.279	1.36 (0.91–2.06)	0.129
Body mass index	0.90 (0.85–0.95)	<0.001	0.90 (0.85–0.95)	<0.001	0.92 (0.87–0.97)	<0.001
Diagnosis	—	<0.001				
LV ejection fraction (%)			0.99 (0.98–1.00)	0.163		
log BNP					1.39 (1.15–1.67)	<0.001
(C)						
For all-cause death						
NOAF	2.68 (1.08–5.70)	0.034	2.71 (1.09–5.85)	0.034	2.59 (1.08–3.73)	0.022
LA emptying fraction (%)	0.99 (0.97–1.02)	0.557	0.99 (0.97–1.01)	0.281	1.00 (0.98–1.03)	0.671
Age (years)	1.04 (1.01–1.08)	0.001	1.05 (1.03–1.09)	<0.001	1.05 (1.02–1.08)	<0.001
Sex (male/female)	1.65 (0.89–3.18)	0.114	1.80 (0.99–3.43)	0.055	1.97 (1.08–3.73)	0.031
Body mass index	0.89 (0.82–0.97)	0.006	0.89 (0.82–0.96)	0.002	0.92 (0.85–1.00)	0.037
Diagnosis	–	<0.001				
LV ejection fraction (%)			1.00 (0.97–1.01)	0.657		
log BNP					1.71 (1.31–2.24)	<0.001

BNP, B-type natriuretic peptide; CI, confidence interval; HR, hazard ratio, LA, left atrium; LV, left ventricle; MACE, major adverse cardiac events; NOAF, new-onset atrial fibrillation.

DISCUSSION

Atrial fibrillation and HF frequently coexist, and they are closely interrelated, with each disease predisposing to the other (3). In this study, the relationship of AF type with a wide spectrum of NICM, including LVNC, HCM, DCM, CS, and CA, was explored. Patients with prevalent AF had higher age and increased BNP levels and were more symptomatic. Moreover, they took medications such as diuretics and anticoagulants more frequently. Although whether AF is truly independently associated with poor outcomes in HF remains controversial, and this study showed that baseline CAF and PAF were not associated with an increased incidence of MACE and mortality. Similarly, in HCM or CA, AF prevalence has been reported not to be a major contributor to HF morbidity or mortality (19, 20).

In contrast, NOAF (incident AF) was associated with a higher risk of adverse outcomes, which are consistent with findings in other patient groups, including those with acute HF, chronic HF, acute coronary syndrome, and hemodialysis (21–23). In this study, we explored the clinical significance of NOAF in patients across a broad spectrum of NICM, which included a broad spectrum of LV functions. The incidence and prognostic impact of NOAF did not change across LV EF or the diseases groups (systolic or diastolic dysfunction dominant), suggesting that NOAF may be equally crucial in HF with both reduced and preserved EF. Additionally, patients with younger and lower NYHA were included, and they showed a better prognosis than those in previous studies of HF (24, 25). However, the incidence of NOAF was higher than that reported in previous studies. Factors other than HF severity may be associated with the incidence of NOAF. As shown in **Tables 2**, **3**, increased LA volume or decreased LA function may be one of the most important factors. In particular, several events of HF hospitalization soon after the onset of new AF have been reported (24). Furthermore, in this study, MACE after NOAF occurred at a median of 38 days, calculated from the onset of NOAF, and HF hospitalization was the most frequent event among MACE, as shown in **Supplementary Table 3**. Although its reasons are unknown, NOAF may reflect the instability of HF more generally or it may

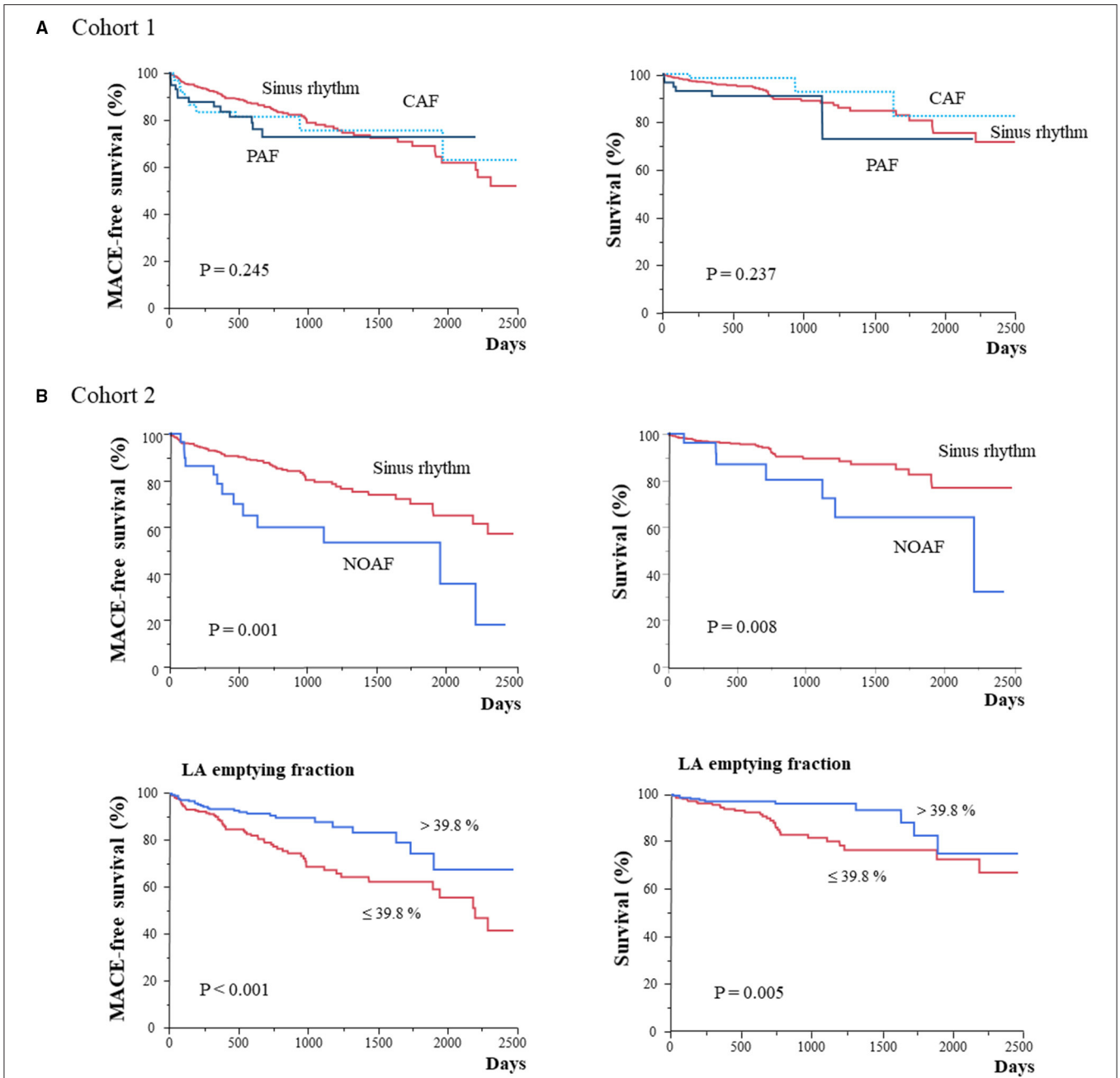

FIGURE 2 | Kaplan–Meier analysis for MACE and all-cause mortality in patients stratified according to AF types or LA function in cohort 1 **(A)** and cohort 2 **(B).** CAF, chronic atrial fibrillation; LA, left atrium; MACE, major adverse cardiac event; NOAF, new-onset atrial fibrillation; PAF, paroxysmal atrial fibrillation; SR, sinus rhythm.

cause HF admission because of less treatment than other AF types (25).

A unique aspect of this study was the measurement of both BNP levels and LA function/geometry at baseline. This is essential because they are both valuable prognostic markers in HF (10, 25). Several studies demonstrated the association between BNP levels and NOAF in various conditions, including in the general population, in those with acute coronary syndrome, and the postoperative state (26, 27). Although baseline BNP level was a significant predictor of NOAF in this study, the association between them was not strong (AUC: 0.680). LA volume was a better predictor (AUC: 0.795) and was superior to BNP level in patients with NICM ($p = 0.016$). Structural and functional changes in LA have been reported to occur before AF development (9, 28), which this study also suggested in NICM. Recently, besides volumetric analysis, deformational (strain and strain rate) imaging with echocardiography has been used to evaluate LA function. Debonnaire et al. reported that both LA

volume and LA strain improved the prediction of NOAF in 242 patients with HCM (29). In addition, the use of β-blocker was negatively associated with the incidence of NOAF in this study. It may decrease the incidence of NOAF through the suppression of the activated sympathetic nervous system (30). It may be useful for further risk stratification to assess novel LA functional imaging, such as deformational (strain and strain rate) imaging or to explore the effect of medications in a cohort of NICM.

Atrial fibrillation progression is often characterized by progression from PAF to CAF. In this study, the deterioration of LA volume and function mirrored this progression; further deterioration of LA volume and function was observed from PAF to CAF. Because PAF or CAF was not associated with MACE or all-cause mortality in this cohort, the deterioration of LA volume and function observed in PAF and CAF did not suggest their direct relationship with the prognosis. However, the LA emptying fraction was associated with a poor prognosis independently of NOAF. A study of HF reported LA dysfunction as a major driver or mediator of clinical decompensation in HF (31). NOAF may be associated with HF decompensation, at least in part, through LA dysfunction; however, how LA dysfunction affects poor prognosis, including HF deterioration, remains unclear. Further studies are necessary to elucidate this for the improvement of clinical management.

This study had several limitations. First, patients across a broad spectrum of NICM at a single center were enrolled; the population may not be completely representative of the entire NICM population. The study population of each diagnosis and the number of patients with NOAF were relatively small, and the total number of events of these patients were also relatively few during follow-up. Any negative findings might be caused by low statistical power. Second, ambulatory serial ECG monitoring might have identified more incident AF than was reported. However, the incidence of NOAF was less or similar to those previously reported (24, 25). While echocardiographic assessment of LA morphology and function is challenging because of the posterior location and thin wall of the LA, CMR has been proposed as the reference method to measure atrial volumes. However, motion artifacts may occur in patients with arrhythmia, such as AF, and data acquisition can be challenging (32). Finally, the study cohort comprised patients who were referred for CMR examination. Thus, the generalizability of our findings might be limited, for example, to patients with severe renal impairment, severe HF, or previously implanted cardiac devices.

CONCLUSIONS

We analyzed 625 consecutive patients across a broad spectrum of NICM who underwent CMR examination, especially in terms of LA geometry and function. Baseline CAF and PAF were well-correlated with the deterioration of LA geometry and function, although they were not associated with an increased incidence of MACE and mortality. Additionally, 5.9% of the patients with baseline SR developed NOAF over a median follow-up of 609 days and were associated with poor prognosis independent of age, sex, body mass index, and diagnosis. LA Vmax showed better predictive performance than LA emptying fraction and BNP. In addition, older age and no β-blocker use were risk factors of NOAF. LA Vmax was not associated with prognosis; rather, the LA emptying fraction was associated with prognosis.

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 Kindai University, Faculty of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MO, MY, and YI: study concept, design, analysis, and interpretation of data. NS, TKa, MO, KK, and MY: data curation. TKu and GN: supervision. MO and MY: writing—original draft. YI: writing—review and editing. 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.2021.781125/full#supplementary-material

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CaMKII-δ9 Induces Cardiomyocyte Death to Promote Cardiomyopathy and Heart Failure

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Heart failure is a syndrome in which the heart cannot pump enough blood to meet the body's needs, resulting from impaired ventricular filling or ejection of blood. Heart failure is still a global public health problem and remains a substantial unmet medical need. Therefore, it is crucial to identify new therapeutic targets for heart failure. Ca^{2+}/calmodulin-dependent kinase II (CaMKII) is a serine/threonine protein kinase that modulates various cardiac diseases. CaMKII-δ9 is the most abundant CaMKII-δ splice variant in the human heart and acts as a central mediator of DNA damage and cell death in cardiomyocytes. Here, we proved that CaMKII-δ9 mediated cardiomyocyte death promotes cardiomyopathy and heart failure. However, CaMKII-δ9 did not directly regulate cardiac hypertrophy. Furthermore, we also showed that CaMKII-δ9 induced cell death in adult cardiomyocytes through impairing the UBE2T/DNA repair signaling. Finally, we demonstrated no gender difference in the expression of CaMKII-δ9 in the hearts, together with its related cardiac pathology. These findings deepen our understanding of the role of CaMKII-δ9 in cardiac pathology and provide new insights into the mechanisms and therapy of heart failure.

Keywords: CaMKII, CaMKII-δ9, cardiomyocyte death, cardiomyopathy, heart failure, hypertrophy

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INTRODUCTION

Heart failure is a complex and heterogeneous syndrome resulting from impairment of ventricular filling or ejection of blood associated with symptoms of dyspnea, fatigue, as well as peripheral and/or pulmonary edema. Heart failure is one of the most prominent causes of hospitalization globally, with 3.6 million newly diagnosed patients annually imposing an unprecedented cost burden on the health care system (1, 2). The pathophysiological mechanisms of heart failure consist of cardiac injuries at multiple levels, including the myocardium, vasculature, pericardium, heart valves, electrical system, or a combination of cardiac abnormalities, among which cardiomyocyte death and hypertrophy are two critical factors.

Cardiomyocyte death significantly contributes to the progression of heart failure (3, 4). Multiple myocardial injury insults lead to cardiomyocyte death. Adult mammalian cardiomyocytes are terminally differentiated cells and have a minimal capacity for self-replacement. The loss of

mammalian cardiomyocytes cannot be replenished from living cells, resulting in compromised cardiac function and heart failure. On the other hand, in response to myocardial injury or chronically increased hemodynamic load, cardiac mass increases due to cardiomyocyte hypertrophy to help maintain ejection performance. However, continued hemodynamic overload leads to the dilation of the heart and the thinning of the cavity walls, resulting in the change of myocardial geometry, an increase of wall stress, and cardiac dysfunction (5, 6).

Cardiomyocyte death and hypertrophy interact with each other and synergistically promote the progression of heart failure. Sustained cardiac pathological stresses result in progressive myocardial hypertrophy that eventually exceeds the capacity of the coronary vasculature to adequately perfuse the myocardial mass, leading to multiple foci of myocardial ischemia, cardiomyocyte death, myocardial fibrosis, and the deterioration of cardiac dysfunction. On the other hand, multiple myocardial injury insults cause cardiomyocyte death, and the surviving myocytes compensate by becoming hypertrophic to maintain normal cardiac function. Despite extensive efforts of evidence-based pharmacologic and device therapies, an unacceptable number of patients suffer impaired functional capacity, poor quality of life, and early death due to heart failure. Furthermore, hospitalized heart failure patients continue to experience unacceptably high post-discharge mortality and readmission rates, which have not been improved in the last two decades (7, 8). Therefore, it is of great importance to identify new therapeutic targets of heart failure.

Ca^{2+}/calmodulin-dependent kinase II (CaMKII) is a serine/threonine protein kinase that modulates various biological functions and pathological processes in the heart (9–11). Excessive CaMKII activation is critically involved in multiple cardiac pathological conditions, such as myocardial ischemic injury (12–15), arrhythmia (16, 17), cardiac hypertrophy and remodeling (18, 19), and cardiomyopathy and heart failure (15, 19), and inhibition of CaMKII over-activation profoundly alleviates these cardiac diseases in animal models (13–15, 19–23). In cardiomyocytes, CaMKII plays a central role in regulating cell survival (12, 24, 25) and hypertrophy (18, 26, 27). CaMKII is encoded by four genes, CaMKII-α, β, γ, and δ, and CaMKII-δ is predominantly expressed in the heart. CaMKII-δ is alternatively spliced to generate 11 different variants (28–30). Different isoforms and splice variants possess distinct or even opposite biological and pathological functions (25, 31–35). Our recent study shows that CaMKII-δ9 is the most abundant CaMKII-δ splice variant in the human heart and acts as a central mediator of DNA damage and cell death in cardiomyocytes (35). The cardiac-specific CaMKII-δ9 transgenic mice develop extensive cardiomyopathy and heart failure. But the role of CaMKII-δ9 in cardiac physiology and pathology, especially its function in myocardial hypertrophy and heart failure, remains far from clear.

Here, we proved that CaMKII-δ9 mediates cardiomyocyte death instead of hypertrophy to elicit cardiomyopathy and heart failure. Thus, this study not only deepens our understanding of the role of CaMKII-δ9 in cardiac pathology, but also provides new insights of the mechanisms of heart failure.

MATERIALS AND METHODS

Animals

Animals were maintained in the Center for Experimental Animals (an Association for Assessment and Accreditation of Laboratory Animal Care-accredited experimental animal facility) at Peking University, Beijing, China. The animals were randomly allocated to experimental groups. Both males and females were used. No non-inclusion or exclusion parameters were used in our studies. Investigators were not blinded to treatments, but no subjective assessments were made. All procedures involving experimental animals (mice, rats, and rhesus monkeys) followed protocols approved by the Committee for Animal Research of Peking University and conformed to the Guide for the Care and Use of Laboratory Animals.

Adult C57BL/6 mice and Sprague-Dawley rats were from Vital River Laboratories, Beijing, China. Rhesus monkeys were from our in-house cohort as previously reported (36). The animals were euthanized by intravenous injection of an overdose of sodium pentobarbital, and the tissues were quickly frozen in liquid nitrogen for protein and total RNA extraction.

The cardiac-specific CaMKII-δ9 transgenic mice was generated as previously described (35).

In vivo KN-93 Treatment

Five-week-old wild-type and CaMKII-δ9 mice received *ip.* injection of either KN-93 (10 μmol/kg; Millipore, 422711) or a comparable volume of saline every other day. The survival rates were recorded for seven weeks, and cardiac function was then assessed by echocardiography.

In vivo z-VAD Treatment

Five-week-old wild-type and CaMKII-δ9 mice received *ip.* injection of either z-VAD (0.5 mg/kg; Sigma, V116) or a comparable volume of saline twice a week. The survival rates were recorded for seven weeks, and cardiac function was then assessed by echocardiography.

Human Heart Samples

Normal human ventricular tissues were from the NIH NeuroBioBank at the University of Maryland, Baltimore, MD as previously described (35).

Animal Surgery and Treatment

Transverse aortic constriction (TAC) was performed in 6-week-old male mice as described before (35). Mice were anesthetized under 3% isoflurane *via* intubation, the chest was opened, the aortic arch was visualized, and a 7-0 silk suture was passed under the arch between the innominate and left common carotid arteries. The suture was secured around both the aorta and a 28-gauge needle, the needle was removed, the chest was closed, and the mouse was extubated. Sham-surgery mice underwent an identical procedure except for the aortic ligation. Mice were provided buprenorphine *via ip.* injection during recovery.

Caspase 3/7 Activity Analysis

According to the manufacturer's instructions, caspase 3/7 activity was measured with a kit from Promega (Cat#: G8091).

Echocardiography

Echocardiographic analysis using a Vevo2100 digital imaging system (Visual Sonics, Toronto, ON, Canada) was performed under 1% isoflurane at 6 and 10 weeks of age, with mid-ventricular M and B mode measurements acquired in the parasternal short-axis view at the level of the papillary muscles. Once the mice were acclimated to the procedures, images were stored digitally on a magnetic, optical disk for review and analysis. Measurements of the LV internal end-diastolic diameter (LVIDd) were taken at the apparent maximal LV diastolic dimension. In contrast, the LV internal end-systolic diameter (LVIDs) measurements were taken at the time of the most anterior systolic excursion of the posterior wall. LV ejection fraction (EF) was calculated by the cubic method: LVEF (%) = $\{(\text{LVIDd})^3 - (\text{LVIDs})^3\}/(\text{LVIDd})^3 \times 100$, and LV fractional shortening (FS) was calculated by FS (%) = (LVIDd - LVIDs)/LVIDd × 100. The data were averaged from five cardiac cycles.

Histological Analysis

Histological analysis of heart tissues was as previously described (12). The CardioTACSTM *in situ* apoptosis detection kit (Roche Applied Science, Cat#: 11684795910) was used for TUNEL staining as previously described (35). Immunohistochemistry was performed on heart tissues with anti-γH2AX antibody and the DNA damage levels were determined by the percentage of γH2AX positive cells.

Gene Expression Analysis and Primers

The following primer pairs were used for quantitative real-time PCR:

Gene	Direction	Sequence 5'-3'
18S	Forward	GGAAGGGCACCACCAGGAGT
18S	Reverse	TGCAGCCCCGGACATCTAAG
ANP	Forward	TTCTTCCTCGTCTTGGCCTTT
ANP	Reverse	GACCTCATCTTCTACCGGCATCT
BNP	Forward	AAGTCCTAGCCAGTCTCCAGA
BNP	Reverse	GAGCTGTCTCTGGGCCATTTC

Amplification was performed as follows: 95°C for 3 s and 40 cycles at 95°C for 15 s and 60°C for 30 s. Data are the average of at least three independent experiments.

Isolation, Culture, and Adenoviral Infection of Ventricular Myocytes

Neonatal rat ventricle myocytes (NRVMs) were isolated from 1-day-old Sprague-Dawley rats, and adenovirus-mediated gene transfer was implemented using methods described previously (35). NRVMs were exposed to KN-93 (5 μM) or isopropanol (ISO,10 μM) treatment.

Adult rat ventricle myocytes (ARVMs) were isolated from the hearts of 2–3-month-old Sprague-Dawley rats using a standard enzymatic technique, then cultured and infected with adenoviral vectors at a multiplicity of infection (MOI) indicated as described previously (35). Briefly, myocytes were plated at a density of 0.5 to $1 \times 10^4/\text{cm}^2$ on coverslips or in dishes precoated with 10 μg/ml laminin. The culture medium was M199 (Sigma) plus 5 mmol/L creatine, 2 mmol/L l-carnitine, 5 mmol/L taurine, 0.1% insulin-transferrin-selenium-X, 1% penicillin and streptomycin, and 25 mmol/L HEPES, pH 7.4, at 37°C. Adenovirus-mediated gene transfer was implemented by adding adenoviral vectors (35) into the culture dish. The experiments were done with cells cultured 24 h after infection unless specified otherwise.

Western Blot

Western blot was performed as previously described (12).

RNA Interference-Mediated Gene Silencing

For gene-silencing assays, siRNAs with 19 nucleotides in length, carrying a dTdT overhang at the 3' terminus, were designed using the Invitrogen website. Cardiomyocytes were transfected with siRNA using Lipofectamine RNAiMAX (Invitrogen) following the manufacturer's instructions (25).

Gene	Sequence 5'-3'
Scrambled	UUCUCCGAACGUGUCACGU
CaMKII-δ9	GCUACUGGGCAUCAUCAUA

Materials

Antibodies against the following proteins were used: UBE2T for mouse [Aviva Systems Biology, ARP-43145 (Lot#: QC13585-40506; 1:1000)], t-CaMKII-δ [GeneTex, GTX111401 (Lot#: 40058; 1:1000)], γH2AX (Millipore, 05-636, clone JBW301 (Lot#: 2884537; 1:1000 for western blots, 1:200 for immunohistochemistry), Cleaved Caspase-3 [Cell Signaling Technology, 9661 (1:1000)] and GAPDH [EASYBIO, BE0023, clone 2B8 (1:10000)]. Antibody against Exon 16 of CaMKII-δ9 was generated as described (35). ISO, z-VAD, and Doxorubicin were from Sigma-Aldrich. KN-93 was from Millipore (Cat# 422711).

Statistical Analysis

Data are expressed as mean ± S.E.M. Statistical analysis was performed with GraphPad Prism version 8.4 (GraphPad Software, Inc.). Data sets were tested for normality of distribution with the Kolmogorov-Smirnov test. Data groups (two groups) with normal distributions were compared using the two-sided unpaired Student's *t*-test. The Mann-Whitney *U*-test was used for nonparametric data. One-way or two-way ANOVA assessed comparisons between multiple groups with Bonferroni *post hoc* analysis. $^*P < 0.05$; $^{**}P < 0.01$; NS, not significant. No statistical method was used to predetermine sample size.

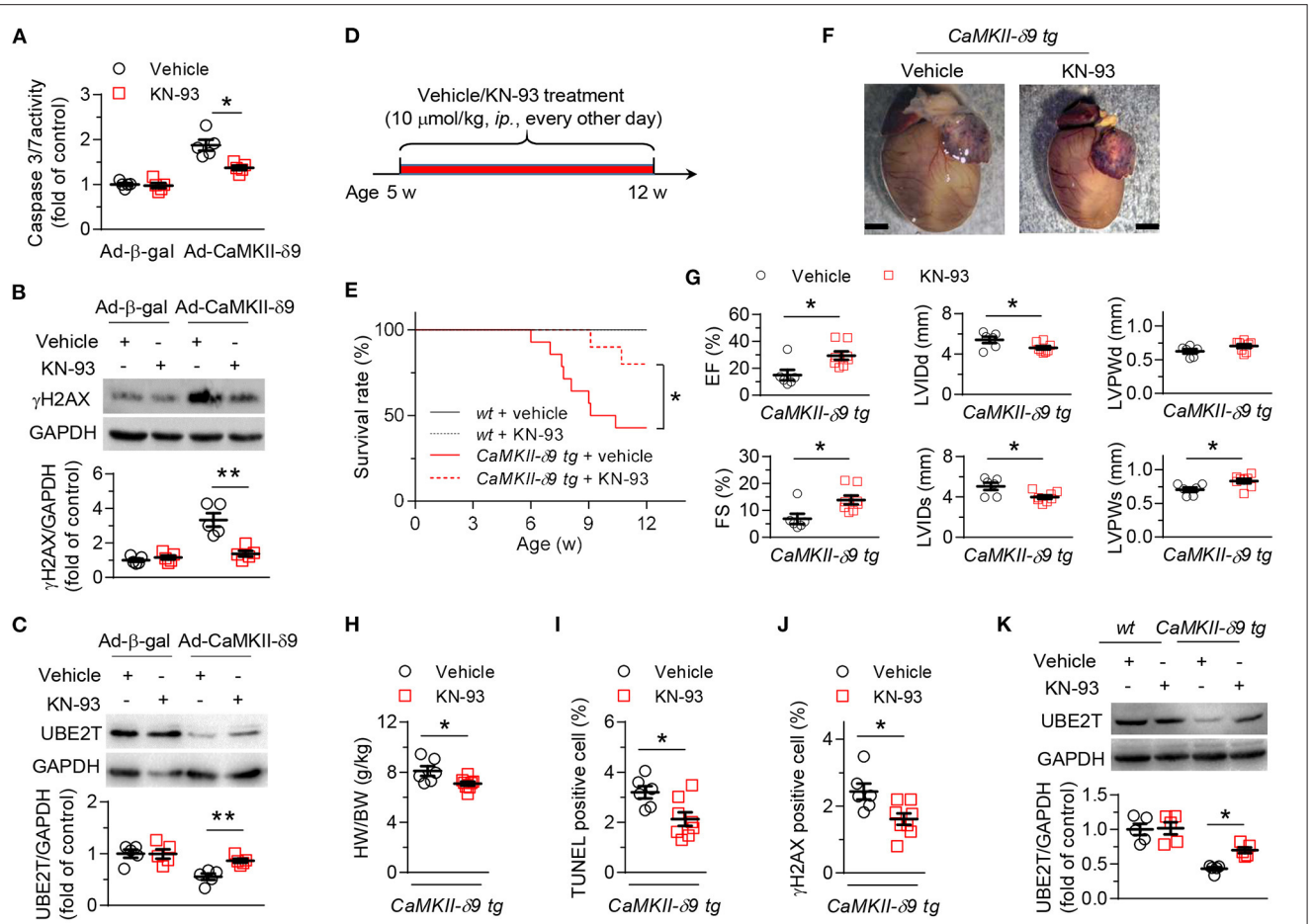

FIGURE 1 | KN-93 treatment prevents CaMKII-δ9-induced cardiomyopathy and heart failure. **(A–C)**, Cell viability assayed by caspase 3/7 activity **(A)** and representative western blots and statistical data showing the levels of γH2AX **(B)** and UBE2T **(C)** in NRVMs infected with Ad-β-gal or Ad-CaMKII-δ9 with or without KN-93 treatment (5 μM) ($n = 5$). **(D)** Experimental protocol for *in vivo* KN-93 treatment in *CaMKII-δ9 tg* mice. The mice were treated with KN-93 (10 μmol/kg, *i.p.*) every other day from 5 to 12 weeks of age. **(E)** Kaplan-Meier survival curves of *wt* and *CaMKII-δ9 tg* mice with or without KN-93 treatment ($n = 8$ for *wt* vehicle, $n = 7$ for *wt* KN-93, $n = 14$ for *CaMKII-δ9 tg* vehicle, $n = 10$ for *CaMKII-δ9 tg* KN-93). **(F–J)** Gross morphology of the hearts **(F)**, statistical data of the left ventricle echocardiography **(G)**, ratio of heart weight to body weight **(H)**, and statistical data of TUNEL **(I)** and γH2AX **(J)** staining of the hearts from *CaMKII-δ9 tg* mice with or without KN-93 treatment. EF, ejection fraction; FS, fractional shortening; LVIDd and LVIDs, diastolic and systolic left ventricular internal diameter; LVPWd and LVPWs, diastolic and systolic left ventricular posterior wall thickness. Scale bar, 2 mm ($n = 6$ for vehicle, $n = 8$ for KN-93). **(K)** Representative western blots and statistical data showing the levels of UBE2T from the hearts of *wt* and *CaMKII-δ9 tg* mice with or without KN-93 treatment ($n = 5$). Data are mean ± S.E.M. $^*P < 0.05$, $^{**}P < 0.01$; two-way ANOVA **(A–C,K)**, log-rank (Mantel-Cox) test, or Student's *t*-test **(E,G–J)**.

RESULTS

CaMKII Inhibition Prevents CaMKII-δ9-Induced Cardiomyopathy and Heart Failure

First, we investigated whether CaMKII kinase activity was required for CaMKII-δ9-induced cardiomyocyte death, cardiomyopathy, and heart failure. KN-93 is the classic CaMKII inhibitor, inhibiting CaMKII kinase activity (37) and ameliorating multiple cardiac diseases in experimental models (38). We first set up cardiomyocyte injury models with cultured NRVMs with CaMKII-δ9 overexpression and found that pretreatment of KN-93 (5 μM) alleviates the CaMKII-δ9-induced cardiomyocyte death as indexed by caspase 3/7 activity (**Figure 1A**). We have previously shown that CaMKII-δ9 induced DNA damage in cardiomyocytes through the degradation of UBE2T (35). Here, we proved that in NRVMs, KN-93 suppressed CaMKII-δ9-mediated UBE2T degradation and subsequent DNA damage (**Figures 1B,C**).

We have constructed the mice with cardiac-specific overexpression of CaMKII-δ9 (*CaMKII-δ9 tg* mice) (35). In *CaMKII-δ9 tg* mice, treatment with KN-93 (10 μmol/kg, *ip.*, every other day) from the age of 5 weeks attenuates premature animal death, cardiac hypertrophy, myocardial dysfunction, and cardiomyocyte DNA damage and cell death (**Figures 1D–K**). Therefore, CaMKII kinase activity is required for CaMKII-δ9-induced cardiomyocyte death, cardiomyopathy, and heart failure.

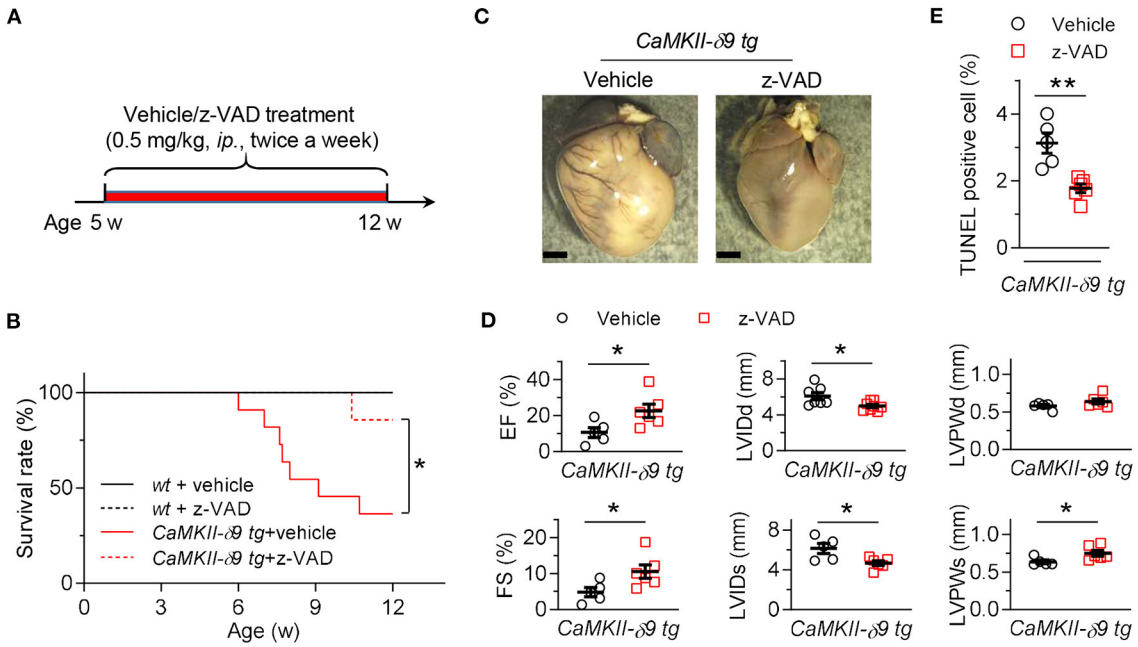

FIGURE 2 | Inhibition of cardiomyocyte death alleviates CaMKII-δ9-induced cardiomyopathy and heart failure. **(A)** Experimental protocol for *in vivo* z-VAD treatment in *CaMKII-δ9 tg* mice. The mice were treated with z-VAD (0.5 mg/kg, *i.p.*) twice a week from 5 to 12 weeks of age. **(B)** Kaplan-Meier survival curves of *wt* and *CaMKII-δ9 tg* mice with or without z-VAD treatment ($n = 6$ for *wt* vehicle, $n = 5$ for *wt* z-VAD, $n = 11$ for *CaMKII-δ9 tg* vehicle, $n = 7$ for *CaMKII-δ9 tg* z-VAD). **(C–E)** Gross morphology of the hearts **(C)**, statistical data of the left ventricle echocardiography **(D)**, and statistical data of TUNEL staining of the hearts **(E)** from *CaMKII-δ9 tg* mice with or without z-VAD treatment. Scale bar, 2 mm ($n = 5$ for vehicle, $n = 6$ for z-VAD). Data are mean ± S.E.M. NS, not significant; $^*P < 0.05$, $^{**}P < 0.01$; log-rank (Mantel-Cox) test **(B)**, or Student's *t*-test **(D,E)**.

Inhibition of Cardiomyocyte Death Alleviates CaMKII-δ9-Induced Cardiomyopathy and Heart Failure

Based on the phenotypes of the *CaMKII-δ9 tg* mice, there are three possible functions of CaMKII-δ9 in the heart: First, it directly induces cardiomyocyte hypertrophy, which indirectly causes myocyte death when hypertrophy progresses to decompensation, or it directly induces cardiomyocyte death, and the surviving myocytes compensate by becoming hypertrophic, or both.

To distinguish these possibilities, we first treated the *CaMKII-δ9 tg* mice with z-VAD (5 mg/kg, *ip.*, twice a week), a caspase inhibitor, from the age of 5 weeks to inhibit cardiomyocyte death (**Figure 2A**). Our data showed that the premature animal death in *CaMKII-δ9 tg* mice was markedly attenuated by z-VAD treatment (**Figure 2B**). Furthermore, cardiomyocyte death, cardiac hypertrophy, and heart dysfunction in *CaMKII-δ9 tg* mice were also ameliorated by z-VAD (**Figures 2C–E**), indicating that the cytosolic execution of apoptosis contributes to CaMKII-δ9-induced cardiomyocyte death, and cardiomyocyte death is essential for CaMKII-δ9-induced cardiomyocyte death, cardiomyopathy, and heart failure.

CaMKII-δ9 Does Not Directly Regulate Cardiac Hypertrophy

We next investigated the role of CaMKII-δ9 in cardiomyocyte hypertrophy. In the mouse hearts two weeks after sham or TAC surgery, CaMKII-δ protein abundance was markedly increased (**Figure 3A**). To avoid complex *in vivo* compensations, we used cultured NRVMs in conjunction with adenoviral gene transfer. We found that although total CaMKII-δ protein was upregulated in hypertrophic hearts, overexpression of CaMKII-δ9 did not alter the expression of cardiac hypertrophic genes, including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). In contrast, as a positive control, isoproterenol treatment profoundly increased their expression (**Figure 3B**). Moreover, the knockdown of CaMKII-δ9 did not alter the hypertrophy phenotype in NRVM treated with isopropanol (**Figures 3C,D**). These data indicate that cardiac CaMKII-δ9 is not directly involved in cardiomyocyte hypertrophy. The myocardial hypertrophy in *CaMKII-δ9 tg* mice is the compensatory response of the surviving cardiomyocyte to maintain cardiac function.

CaMKII-δ9 Downregulates UBE2T/DNA Repair Signaling to Induce Adult Cardiomyocyte Death

Our previous study has shown that CaMKII-δ9 binds to ubiquitin-conjugating enzyme E2T (UBE2T) to promote its phosphorylation and degradation, disrupting UBE2T-dependent DNA repair and leading to the accumulation of DNA damage and genome instability, which results in cardiomyocyte death (35). However, the study was performed in the context of immature cardiomyocytes, including NRVMs and embryonic

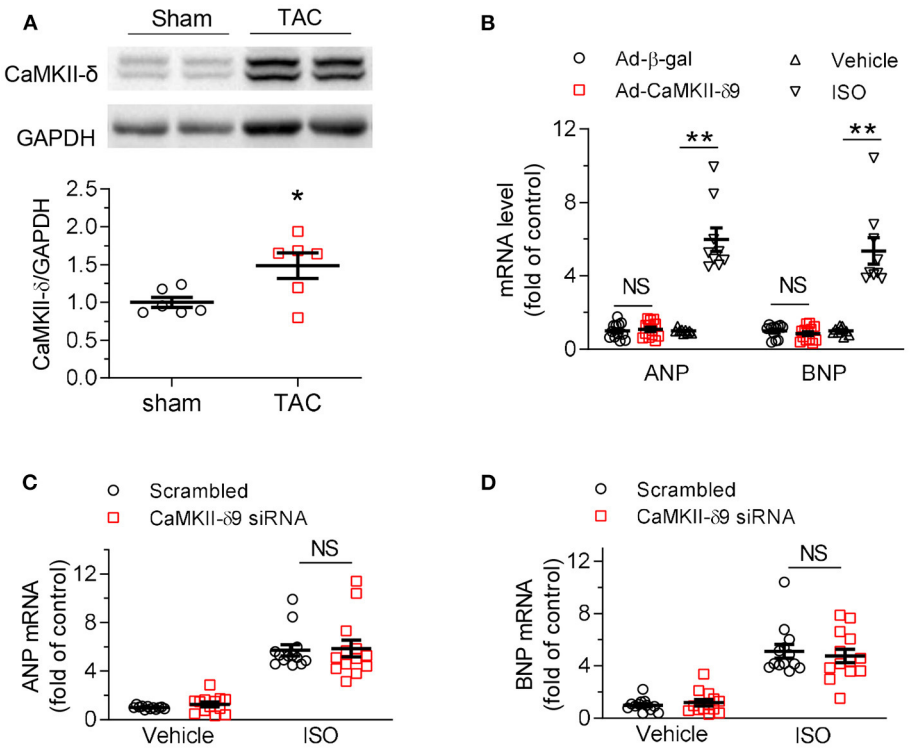

FIGURE 3 | CaMKII-δ9 does not directly regulate cardiac hypertrophy. **(A)** Representative western blots and statistical data showing the levels of CaMKII-δ in the hearts of the mice 2 weeks after sham or transverse aortic constriction (TAC) surgery. $n = 6$. **(B)** Averaged data of mRNA levels of ANP and BNP assayed by real-time PCR in NRVMs infected with Ad-β-gal or Ad-CaMKII-δ9 (50 MOI, 48 h; Ad-β-gal, $n = 12$; Ad-CaMKII-δ9, $n = 13$). The NRVMs treated with isoproterenol (ISO, 10 mM, 24 h) were used as positive control ($n = 9$). **(C,D)** Averaged data of mRNA levels of ANP **(C)** and BNP **(D)** assayed by real-time PCR in NRVMs transfected with scrambled or CaMKII-δ9 siRNA with or without ISO treatment (10 μM, 24 h; Vehicle scrambled, $n = 12$; other groups, $n = 13$). Data are mean ± S.E.M. $^*P < 0.05$, $^{**}P < 0.01$; NS, not significant; Student's *t*-test **(A,B)**, or two-way ANOVA **(C,D)**.

stem cell-derived cardiomyocytes. Given the differences between immature and mature cardiomyocytes in terms of morphology, gene expression, and proliferation capacity, here, we investigated the role of CaMKII-δ9 in adult cardiomyocytes, together with the underlying mechanisms.

First, we compared the protein abundance of CaMKII-δ9 in NRVMs with the adult hearts of multiple species, including human, monkey, rat, and mice (**Figure 4A**). Since these four species share the same amino-acid sequence encoded by exon 16 of CaMKII-δ (**Figure 4B**), the anti-exon 16 antibodies would be expected to work equally in these species. The protein abundance of CaMKII-δ9 in the heart of human, monkey, mice, and rat (adult) was 3.54 ± 0.19, 3.25 ± 0.44, 2.00 ± 0.20 and 1.53 ± 0.31-fold of that in NRVMs, respectively (**Figure 4A**), suggesting that the levels of CaMKII-δ9 are higher in adult hearts.

Functionally, our data indicated that similar to the findings in NRVMs, at a comparable expression level, CaMKII-δ9 elicited much more severe cell death, DNA damage, and UBE2T degradation than CaMKII-δ2 in ARVMs (**Figures 5A–C**). Consistently, knockdown of CaMKII-δ9 with its specific siRNA prevented doxorubicin-induced cell death, DNA damage, and UBE2T degradation in ARVMs (**Figures 5D–F**). These data indicate that enhanced CaMKII-δ9 activation triggers the death of both adult and neonatal cardiomyocytes by suppressing UBE2T-dependent DNA repair signaling. Therefore, although CaMKII-δ9 differs in protein abundance between neonatal and adult cardiomyocytes, its function and downstream signaling are the same.

There Is No Gender Difference in CaMKII-δ9-Induced Cardiac Pathology

Previous studies have shown significant differences in the role of CaMKII-δ2 and -δ3 in males and females, and CaMKII activation is not necessarily deleterious in female cardiopathology (39). Thus, in order to fully understand the clinical significance of CaMKII-δ9 in the prevention and therapy of heart failure, we compared the possible gender differences of CaMKII-δ9 in terms of its expression and function in animals.

We found that there was no gender difference of myocardial CaMKII-δ9 abundance in *wt* and *CaMKII-δ9 tg* mice (**Figures 6A,B**). In addition, animal viability, cardiac morphology and function, as well as cardiomyocyte apoptosis and DNA damage did not differ, either (**Figures 6C–F**). In this way, there is no gender difference in terms of the expression and function of CaMKII-δ9 in the mice hearts.

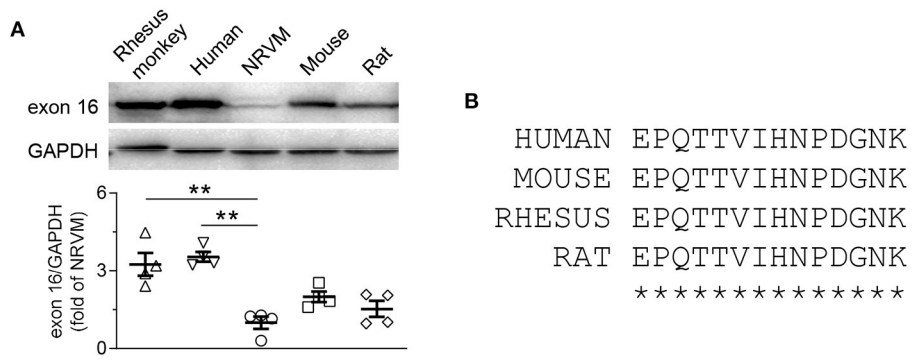

FIGURE 4 | CaMKII-δ9 is abundant in the adult hearts of different species. **(A)** Representative western blots and statistical data showing the levels of CaMKII-δ9 in the hearts of rhesus monkey and human, neonatal rat ventricular myocytes (NRVMs), adult mouse together with rat ($n = 4$). Data are mean ± S.E.M. $^{**}P < 0.01$; one-way ANOVA. **(B)** Amino acid sequences of the peptides encoded by the exon 16 of CaMKII-δ of human, mouse, rhesus monkey and rat.

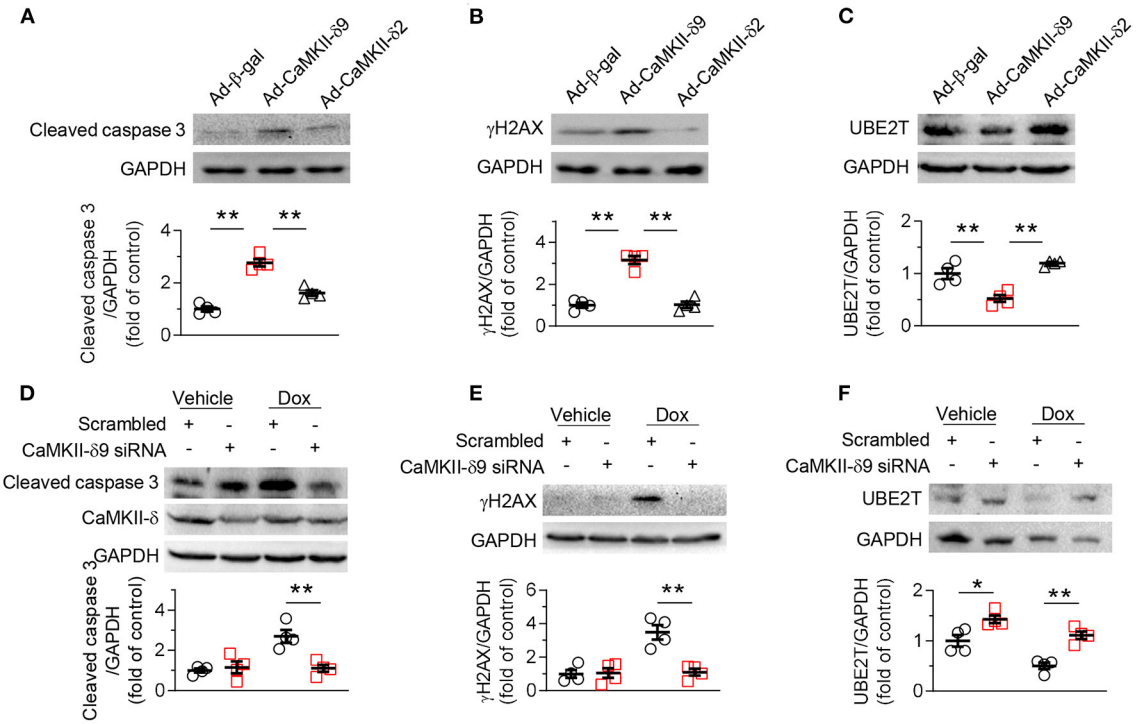

FIGURE 5 | CaMKII-δ9 mediates DNA damage and cell death in adult cardiomyocytes. **(A–C)** Representative western blots and statistical data showing the levels of cleaved caspase 3 **(A)** γH2AX **(B)** and UBE2T **(C)** in adult rat ventricular myocytes (ARVMs) infected with Ad-β-gal, Ad-CaMKII-δ9, or Ad-CaMKII-δ2 (100 MOI, 24 h) ($n = 4$). **(D–F)** Representative western blots and statistical data showing the levels of cleaved caspase 3 **(D)**, γH2AX **(E)** and UBE2T **(F)** in ARVMs infected with scrambled or CaMKII-δ9 siRNA with or without Dox treatment (1 mM, 16 h) ($n = 4$). Data are mean ± S.E.M. $^{*}P < 0.05$, $^{**}P < 0.01$; one-way ANOVA **(A–C)** or two-way ANOVA **(D–F)**.

DISCUSSION

In the current study, we demonstrate the pathophysiological function of CaMKII-δ9 in the development of cardiomyopathy and heart failure, especially distinguished its role in hypertrophy and cardiomyocyte death. Specifically, CaMKII-δ9 mediates cardiomyocyte death, instead of hypertrophy, to promote the progression of cardiomyopathy and heart failure. In addition, we show that the function and the corresponding signaling pathway of CaMKII-δ9 are similar in immature and mature cardiomyocytes without gender difference.

Heart failure is a global public health problem and heavy finical burden to the patients. Despite significant efforts in the basic and clinical research to pursue the strategy of its prevention and therapy, it remains a huge unmet medical need. Cardiomyocyte death plays an essential role in the progression

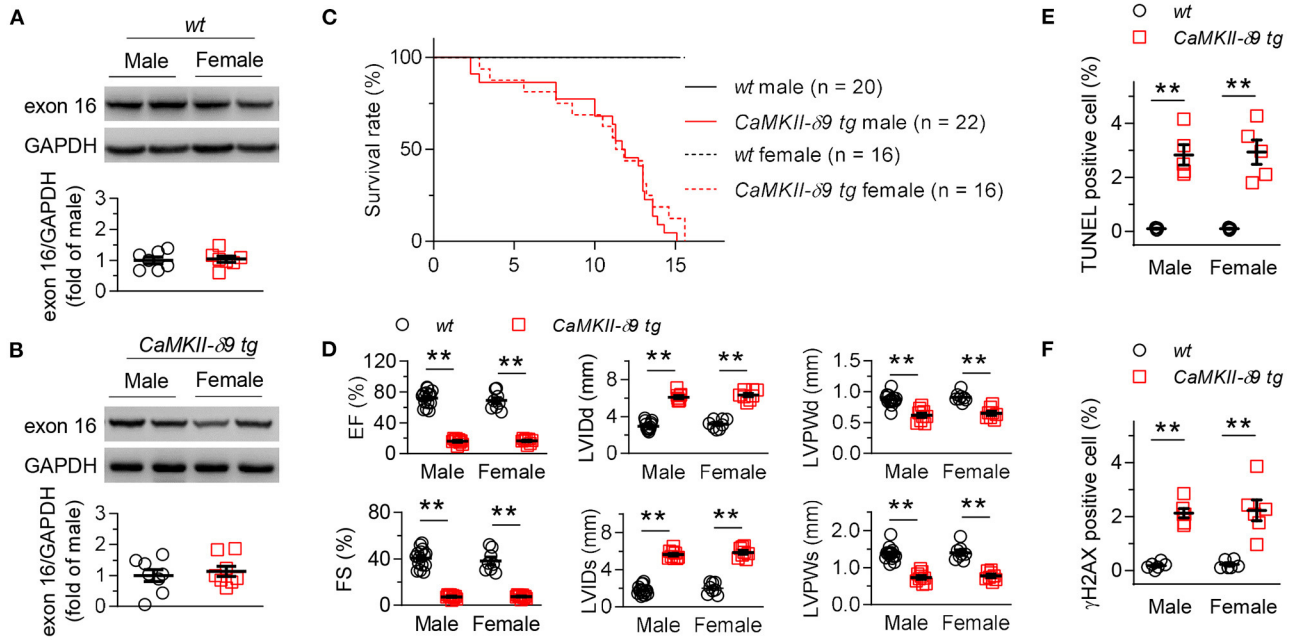

FIGURE 6 | No gender difference in the CaMKII-δ9-induced cardiac pathology. **(A,B)** Representative western blots and statistical data showing the levels of CaMKII-δ9 from the hearts of *wt* (**A**, $n = 7$) and *CaMKII-δ9 tg* mice (**B**, $n = 8$). **(C)** Kaplan-Meier survival curves of male and female *wt* and *CaMKII-δ9 tg* mice ($n = 20$ for *wt* male, $n = 22$ for *CaMKII-δ9 tg* male, $n = 16$ for *wt* female and *CaMKII-δ9 tg* female). **(D)** Statistical data of the left ventricle echocardiography of male and female *wt* and *CaMKII-δ9 tg* mice at 10 weeks of age ($n = 15$ for *wt* male, $n = 9$ for *CaMKII-δ9 tg* male, $n = 8$ for *wt* female and *CaMKII-δ9 tg* female). EF, ejection fraction; FS, fractional shortening; LVIDd and LVIDs, diastolic and systolic left entricular internal diameter; LVPWd and LVPWs, diastolic and systolic left ventricular posterior wall thickness. **(E,F)** Statistical data of TUNEL (**E**, $n = 5$) and γH2AX (**F**, $n = 6$) staining of the hearts of male and female *wt* and *CaMKII-δ9 tg* mice at the age of 10 weeks ($n = 5$). Data are mean ± S.E.M. $^{**}P < 0.01$; Student's *t*-test **(A,B)**, log-rank (Mantel-Cox) test **(C)**, or two-way ANOVA **(D–F)**.

of cardiomyopathy and heart failure, and the inhibition of cardiomyocyte death alleviated heart failure (40–42). CaMKII is a key player in mediating cardiomyocyte death, and inhibition of CaMKII profoundly protects the cardiomyocyte against cell death induced by multiple pathological insults.

Further studies showed that different CaMKII-δ splice variants exert opposite functions in regulating cardiac cell viability. The cytosolic variant, CaMKII-δ2 (also named CaMKII-δC) facilities cardiomyocyte death, whereas the nuclear variant, CaMKII-δ3 (also named CaMKII-δB), is protective (25, 31–33). We recently provided evidence that CaMKII-δ9, instead of CaMKII-δ2, is the most critical cytosolic CaMKII variant in the human heart (35). Functionally, CaMKII-δ9 is more potent in inducing cardiomyocyte death than CaMKII-δ2 and plays an essential role in developing cardiomyopathy and heart failure (35). Here, we further demonstrate that CaMKII-δ9 directly elicits cardiomyocyte death, but not cardiac hypertrophy, to mediate the progression of heart failure. Thus, we showed a clear picture of the pathophysiological action of CaMKII-δ9, the major variant in human hearts, in the mediation of cardiomyopathy and heart failure, suggesting a new therapeutic strategy to target CaMKII-δ9 against human heart failure. Importantly, our data proved that CaMKII-δ9 downregulated UBE2T, impaired DNA repair machinery, and consequently elicited cardiomyocyte death and heart failure in the adult hearts of both male and female animals, which further enhances the clinical perspective of CaMKII-δ9 in the therapy of cardiac diseases.

During heart failure, CaMKII (in the human heart, mainly CaMKII-δ9) was activated by multiple cardiac pathological insults, including neurohumoral agonist signaling (43), oxidant stress (44–47), hyperglycemia (48, 49), ischemic injury (12, 13, 50–52), cardiac toxic drugs (12, 53), and other adverse stimuli associated with increased intracellular calcium levels (54, 55). The activated CaMKII mediates the phosphorylation of Ca^{2+} homeostatic proteins to enhance their activity and improve the performance of physiological events such as excitation-contraction coupling and fight/flight mechanical responses, which helps maintain normal cardiac function. However, excessive CaMKII activation caused by continuous myocardial stress promotes cardiac myocyte death and the deterioration of cardiomyopathy. We recently identified DNA damage as the specific downstream effector of CaMKII-δ9 in the induction of cardiac injury, and CaMKII-δ9 is much more potent in the induction of cardiomyocyte death than CaMKII-δ2 (35). In addition, some other mechanisms including inflammation (46, 50, 52, 56), mitochondrial stress (57), endoplasmic reticulum stress (47, 58–60), and p53 activation (61) have been shown to act as the downstream signaling of CaMKII-induced cardiomyocyte death. But compared with other splice variants, especially CaMKII-δ2, whether CaMKII-δ9 exerts similar functions in regulating these mechanisms still merits further investigation.

CaMKII has also been established to be a central mediator of cardiomyocyte hypertrophy. CaMKII is activated during cardiac hypertrophy, and inhibition of CaMKII profoundly alleviates myocardial hypertrophy, cardiomyopathy, and heart failure (22, 62, 63). Mechanically, CaMKII phosphorylates multiple substrates, including myocyte enhancer factor 2 (MEF2), histone deacetylases (HDACs), and histone H3, to induce a hypertrophic transcriptional response in cardiomyocytes (64–66). But all the previous studies are based on CaMKII-δ2 and CaMKII-δ3. Here in our study, we showed that different from the other variants, CaMKII-δ9 did not directly increase the expression levels of the hypertrophic genes in cardiomyocytes, and inhibition of CaMKII-δ9 failed to block isoproterenol-induced cardiomyocyte hypertrophy, implicating that CaMKII-δ9 is not involved in the regulation of cardiac hypertrophic response. In human cardiomyocytes, CaMKII-δ3 and CaMKII-δ9 are the major CaMKII splice variants, localized in the nuclei and cytosol, respectively. Our current data combined with the previous studies suggest that there is functional specialization of these variants in addition to the distinct subcellular localization. CaMKII-δ9 is responsible for regulating calcium handling and contraction and induces cardiomyocyte death; on the other hand, CaMKII-δ3 mediates the hypertrophic gene expression and protects against cardiac cell death. Therefore, the specific intervention of CaMKII-δ splice variant to target specific cardiac physiological and pathological functions is a promising strategy to improve the therapy of heart failure and other cardiac diseases.

In addition to ischemic heart diseases, heart failure can be caused by many other diseases and pathological conditions, including hypertension, diabetes, and anti-cancer drugs. Since CaMKII has been shown to play a central role in cardiomyocyte death induced by multiple insults (12, 13, 24, 25), we postulate that CaMKII-δ9-mediated cardiomyocyte death may be involved in heart failure elicited by various pathological insults.

CONCLUSION

In conclusion, we provided the evidence that CaMKII-δ9 mediates cardiomyocyte death, but not cardiac hypertrophy, to elicit cardiomyopathy and heart failure. Furthermore, CaMKII-δ9 promotes cardiomyocyte death and heart failure in both male and female animals. Our findings not only deepen our understanding of the role of CaMKII-δ9 in cardiac pathology but also provide new insights into the mechanisms and therapy of heart failure.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The animal study was reviewed and approved by the Institutional Animal Care and Use Committee of Peking University.

AUTHOR CONTRIBUTIONS

MZ, JZ, and YZ proposed the hypothesis, generated the initial idea, conducted key experiments and data analysis, and wrote the manuscript. WZha, QH, LJ, PX, WZhe, and HS researched data and contributed to discussion. All authors contributed to the article and approved the submitted version.

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Prognostic Value of Serum Galectin-3 in Chronic Heart Failure: A Meta-Analysis

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Objective: To evaluate the association between serum galectin-3 and all-cause death (ACD) and cardiovascular death (CVD) in patients with chronic heart failure (CHF).

Methods: The PubMed and Embase databases and Clinical Trials Registry (www.clinicaltrials.gov) were searched for studies with data on serum galectin-3 and ACD and CVD in CHF patients. The hazard ratios (HRs) of ACD and CVD were calculated and presented with 95% CIs. HRs were pooled using fixed effects or random effects models when appropriate. Sensitivity analysis, meta-regression and subgroup analysis were applied to find the origin of heterogeneity. Visual inspection of Begg's funnel plot and Egger's test were performed to assess the possibility publication bias.

Results: Pooled data included the results from 6,440 patients from 12 studies in the meta-analysis. Higher serum galectin-3 was associated with a higher risk of ACD (HR, 1.38; 95% CI, 1.14–1.67) and CVD (HR, 1.13; 95% CI, 1.02–1.25) in CHF patients. In the subgroup analyses, higher serum galectin-3 was associated with an increased risk of ACD in all subgroups. The pooled HR of the shorter follow-up group (1.78; 95% CI, 1.50–2.11) was significantly higher than the pooled HR of the longer follow-up group (1.15; 95% CI, 1.05–1.25). Sensitivity analysis of eliminating one study in each turn indicated that Koukoui et al.'s study had the largest influence on the risk of all-cause death. All-cause death publication bias was not detected (Pr>|z| = 0.35 for Begg's test and P>|t| = 0.15 for Egger's test).

Conclusions: Serum galectin-3 has prognostic value of both all-cause death and cardiovascular death in CHF. Serum galectin-3 could be useful for risk classification in patients with CHF.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=193399.

Keywords: galectin-3, chronic heart failure, all cause death, cardiovascular death, meta-analysis

INTRODUCTION

Chronic heart failure (CHF) is a common clinical syndrome in cardiology with high morbidity and mortality worldwide (1). Despite significant advances in the diagnosis and treatment, the prognosis for patients with CHF remains poor. About 17.9 million people die from cardiovascular disease each year, of which 9.6 percent are due to heart failure (2). Lack of precise, repeatable and effective prognostic biomarkers may be one of the reasons for poor prognosis in patients with heart failure. Thus, we urgently need to find novel different prognostic biomarkers, which may be able to increase new pathophysiological insight and to guide the precise preventive and therapeutic strategies in CHF patients.

Myocardial fibrosis is a major determinant of clinical outcomes in patients with CHF. Fibrosis markers, such as galectin-3, soluble suppression of tumorigenicity 2 (sST2), human epididymis protein 4 (HE4), metalloproteinases (TIMP)-1, and matrix metallopeptidase (MMP)-9 have been evaluated in HF (3–13). Galectin-3, a β-galactoside–binding lectin mainly secreted by activated macrophages, is associated with myocardial fibrosis and the progression of HF (5, 14, 15). Galectin-3, as a marker of myocardial fibrosis, has been included in the European and American HF guidelines, with a class IIb recommendation (16, 17). However, galectin-3 is not widely used in clinical practice. In an earlier meta-analysis, elevated levels of galectin-3 were found to be associated with mortality in CHF patients (18). However, some recently published studies that were not included in that meta-analysis have reported that the association of galectin-3 with all-cause death (ACD) and cardiovascular death (CVD) are inconsistent (19–21). Therefore, in this study, a meta-analysis was performed to systematically evaluate the prognostic role of serum galectin-3 in patients with CHF.

MATERIALS AND METHODS

Our meta-analysis was performed followed the Preferred Reporting Items of PRISMA statement. We registered this meta-analysis in the PROSPERO database (CRD42020193399).

Search Strategy

We conducted the meta-analysis according to the Meta-analysis of Observational Studies in Epidemiology Group (22). We performed a comprehensive literature search of studies in the PubMed and Embase databases Clinical Trials Registry (www.Clinicaltrials.gov) up to April 10, 2020. Two search themes were combined using the Boolean operator "and." The first theme was heart failure, combined exploded versions of medical subject headings (MeSH) *heart failure*, *cardiac failure*, *heart decompensation*, *myocardial failure*, *congestive heart failure*. The second theme, *galectin 3*, combined exploded versions of MeSH terms *galectin 3*, *galectin-3*, or *Gal-3*. The exact search string was used for pubmed and modified to suit Embase database: ((("Heart Failure"[Mesh]) OR ((((Cardiac Failure) OR Heart Decompensation) OR Myocardial Failure) OR Congestive Heart Failure))) AND (("Galectin 3"[Mesh]) OR ((galectin-3) OR Gal-3)).

Literature Inclusion and Exclusion Criteria

Studies that met the following criteria were included in the analysis: (1) enrollment of outpatients with CHF (either HFrEF or HFpEF); (2) follow-up studies with adult participants (aged ≥ 18 years); (3) serum galectin-3 was measured; (4) the relationship between galectin-3 and all-cause death (ACD) was reported, possibly, also for cardiovascular death (CVD); (5) multivariable adjusted hazard ratio (HR) and the corresponding 95% confidence interval (CI) were available; (6) English language. Exclusion criteria: (1) studies on patients with end-stage HF; (2) studies that cannot provide valid data for estimating HR and 95% CI; (3) only unadjusted risks were provided for associated outcomes; (4) duplicate data or analyses.

Data Extraction and Quality Assessment

On the basis of the predefined criteria, two independent authors (Zhendong Cheng and Kefeng Cai) evaluated and screened the candidate studies. When a disagreement arised, two authors reached a consensus by discussing it with the third author (Chaoxiang Xu). The following basic information were recorded each study: first author, country, year of publication, sample size, percentage of males, mean age, follow-up time, LVEF of the participants, and plasma galectin-3 levels. The quality of each included study was assessed using the Newcastle-Ottawa Scale (NOS) by two independent authors (Zhendong Cheng and Kefeng Cai) (23). The NOS assesses studies according to 9 issues. The 9 iconic questions were assessed as "Yes" (clear fit), "Unclear," and "No" (not meeting the requests). According to the evalution issues, biases were classified as high risk, unclear, and low risk.

Statistical Analysis

The primary end point measure was the risk of all-cause death (ACD) associated with serum galectin-3. The secondary end point measure was the risk of cardiovascular death (CVD) associated with serum galectin-3. From each study, multivariate adjusted outcome data (hazard ratios (HRs) and 95%CIs) for all-cause death (ACD) and cardiovascular death (CVD) were recorded for analysis (24). The heterogeneity of the included studies was estimated by Cochran's Q test and Higgins I-squared statistics. A $P < 0.10$ or $I^2 > 50\%$ indicated existence of significant heterogeneity.

The pooled HRs and 95% CIs were calculated by using both the random-effects and fixed-effects model. If there was no or low heterogeneity, the fixed effects model was used, Otherwise a random effects model was adopted. To explore the origin of heterogeneity, we conducted subgroup analysis of the primary end point according to mean age (<65 vs. ≥65 years); sample size (<300 vs. ≥300); follow-up period (<40 vs. ≥40 months); publication year (<2015 vs. ≥2015). Meta-regression analysis was applied to explore the potential impact of population characteristics on primary outcome. In addition, a sensitivity analysis was conducted to explore the heterogeneity of different studies. The pooled HR was recalculated by omitting 1 study at a time. We evaluated publication bias for all cause death (ACD) by using Begg's funnel plot and Egger's test (25).

All the statistical analyses were conducted using STATA version 12.0 (StataCorp LP, College Station, TX, USA). The

graphic displays of Newcastle-Ottawa Scale (NOS) assessment were performed by RevMan 5.2 (The Cochrane Collaboration, Copenhagen, Denmark). All p values were two tailed with a statistical significance level of 0.05.

RESULTS

Literature Search Results and Characteristics

The search process is summarized in **Figure 1**. Initially, in the primary search from the PubMed and Embase databases, we retrieved a total of 1,546 articles. After meticulous inspection of the articles. Twelve studies involving 6,440 participants were selected for our meta-analysis (10, 19–21, 26–33). There were no disagreements on the inclusion of studies among reviewers. The basic patient characteristics of the included studies are shown in **Table 1**. Of the 12 studies, 10 studies enrolled only patients with reduced LVEF (19–21, 26–28, 30–33), whereas 2 studies also considered patients with preserved LVEF (10, 29). HRs and 95% CIs were provided directly in all studies, and HRs were calculated via multivariate analysis (10, 19–21, 26–33). Five of these studies enrolled >300 patients (21, 28, 30, 31, 33) and 7 studies had <300 patients (10, 19, 20, 26, 27, 29, 32). All studies were from Western countries, 10 were from Europe (10, 19–21, 27–32), one was from the United States (26), and one was from Europe, the United States and Canada (33). The mean age of the patients varied from 50 to 76 years, and the duration of follow up varied from 8 to 116 months. All studies included both sexes, with the proportion of men amounting to 76.9%. Four reported all-cause and cardiovascular death (19, 21, 28, 30), 1 reported only cardiovascular death (33), and 7 reported only all-cause death (10, 20, 26, 27, 29, 31, 32). Therefore, there were 11 and 5 studies for analyses of all-cause and cardiovascular death, respectively. **Figure 2** summarizes the Newcastle-Ottawa Scale (NOS) assessments of the eligible studies.

Galectin-3 and ACD

Eleven studies (10, 19–21, 26–32) evaluated the association between serum galectin-3 and the risk of ACD in CHF patients. Because there was significant heterogeneity ($I^2 = 77.9\%$, $P < 0.1$), a random effects model was adopted. Our results showed that elevated serum galectin-3 was associated with a higher risk of ACD in CHF (HR, 1.38; 95% CI, 1.14–1.67; **Figure 3**).

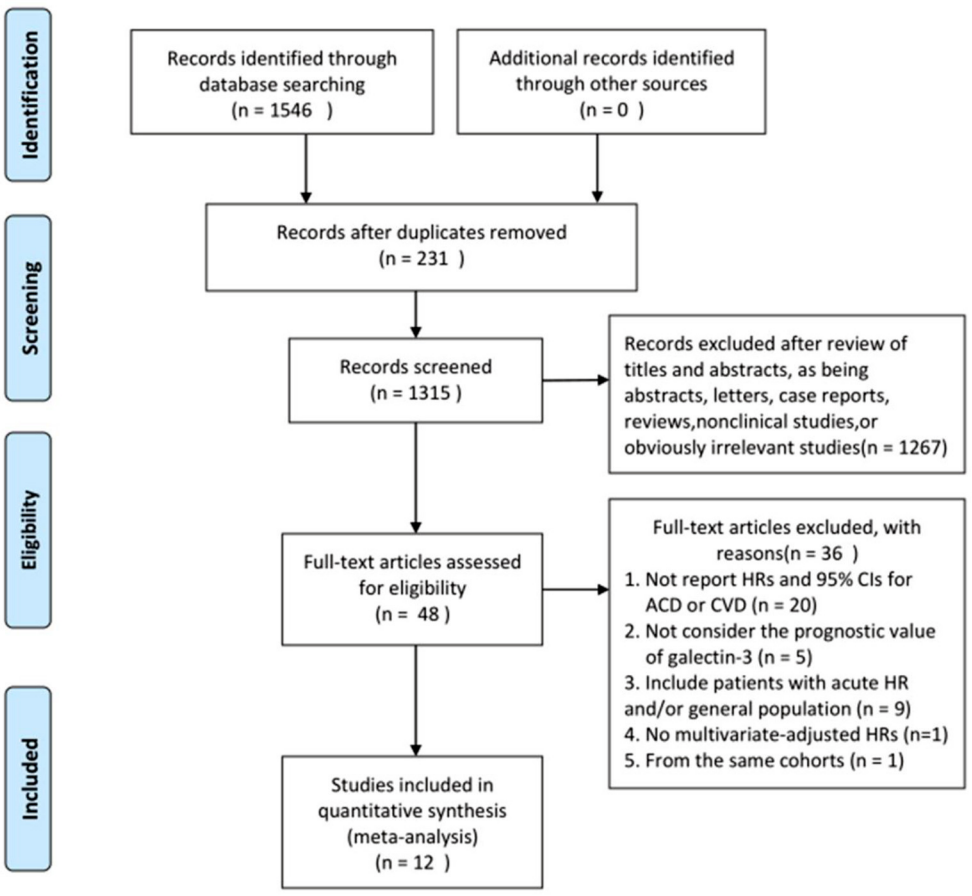

FIGURE 1 | Flowchart of study selection. HRs, hazard ratios; CIs, confidence intervals; ACD, all cause death; CVD, cardiovascular death.

TABLE 1 | Characteristics of the studies included in meta-analysis.

References	Country	Sample size (*n*)	Age (years)	Male (%)	HFrEF (%)	LVEF (%)	Follow-up time (month)	Galectin-3 assay	Galectin-3 levels (ng/ml)	Outcomes reported
Tang et al. (26)	United States	133	57 ± 13	74	100	26 ± 6	60	ELISA Bender MedSystems	13.9 (12.1–16.9)	ACD
Ueland et al. (27)	Norway	168	56 ± 12	78	100	31 ± 14	35 ± 16	ELISA BG Medicine	15.3 (median)	ACD
Gullestad et al. (28)	Norway; Sweden; United Kingdom	1,462	72 ± 7	76	100	32 ± 7	32	ELISA BG Medicine	T1:<16.7; T2:16.7–21.6; T3:<21.6	ACD; CVD
Lok et al. (10)	Netherlands	232	71 ± 0.6	73	97	NA	104 ± 12	ELISA BG Medicine	17.6 (13.3–21.4)	ACD
Jungbauer et al. (29)	Germany	149	62 ± 11	81	97	NA	23 (17–30)	ELISA BG Medicine	35.1 (33.1–37.6)	ACD
Bayes-Genis et al. (30)	Spain	876	70 (61–77)	72	100	34 (26–43)	60	ELFA BioMerieux	16.5 (12.6–22.7)	ACD; CVD
Koukoui et al. (20)	Netherlands	202	58 ± 13	77	100	30 (26–34)	14 (6–20)	bioMérieux, Marcy l'Etoile, France	14 (9.9–19.8)	ACD
Sanders-van Wijk et al. (31)	Italy	631	66 ± 11	82	100	31 ± 7	18	ELISA BG Medicine	18.8 (15.5–24.1)	ACD
Alonso et al. (21)	Netherlands	385	68 ± 10	69	100	33 ± 13	59 ± 34	ELFA BioMerieux	17.4 (14–23.4)	ACD; CVD
Binas et al. (32)	Germany	262	50 ± 13	75	100	30 ± 8	47 (12–91)	ELISA kit (R&D Systems)	4.8 ± 2.3	ACD
Dupuy et al. (19)	France	164	76 (66–82)	69	100	35 (25–45)	42 (12–47)	ELFA BioMerieux	19.8 (14.23–29.73)	ACD; CVD
Zile et al. (33)	United States; Canada; Sweden; United Kingdom	1,776	67 ± 10	81	100	NA	8	ELISA BG Medicine	17.1 (13.9–21.2)	CVD

HFrEF, Heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NA, not available; NOS score, the Newcastle-Ottawa Scale score; ACD, all cause death; CVD, cardiovascular death.

FIGURE 2 | Quality evaluation of the eligible studies. **(A)** Review authors' judgments presented as percentages across included studies; **(B)** Review authors' judgements about each domain for each included study.

Galectin-3 and CVD

Five studies (19, 21, 28, 30, 33) reported the association between serum galectin-3 and the risk of CVD in CHF. There was no substantial heterogeneity (I^2 = 0.0%, P = 0.478); therefore, a fixed effects model was adopted. Our results showed that elevated serum galectin-3 was associated with a

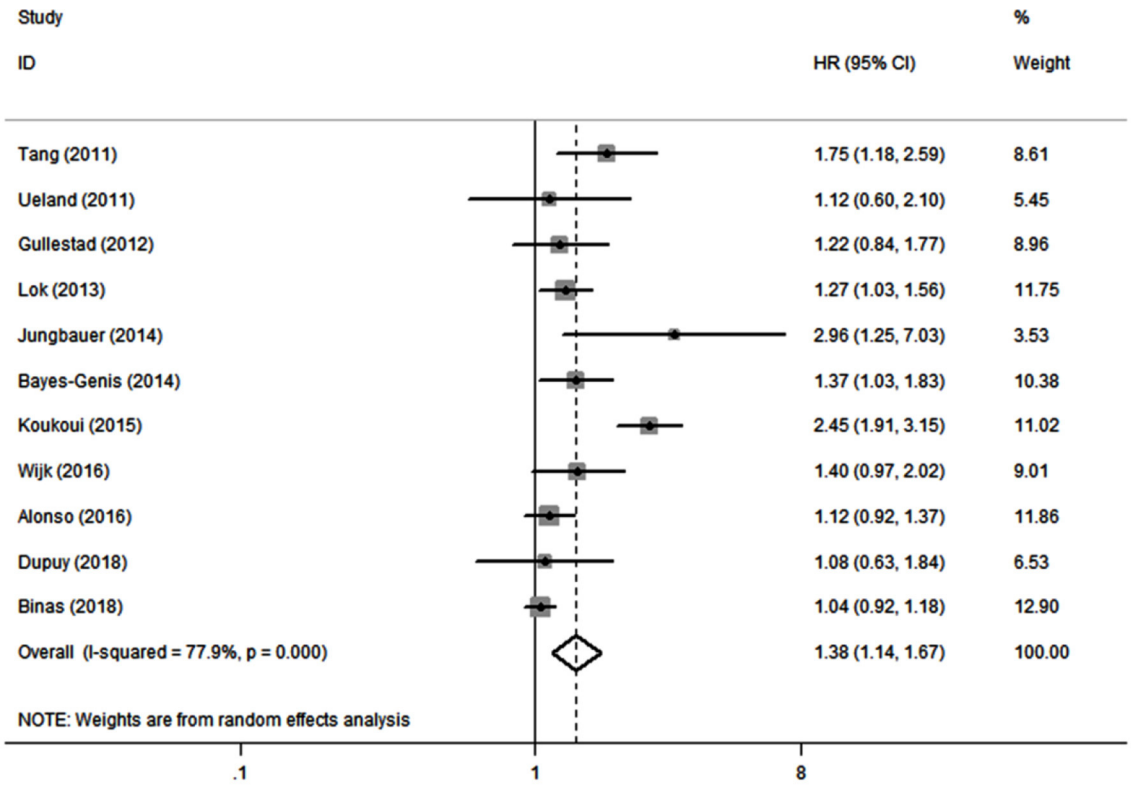

FIGURE 3 | Meta-analysis of the association between galectin-3 and risk of ACD in CHF patients. Results are presented as individual and pooled HR, and 95% CI.

higher risk of CVD in CHF (HR, 1.13; 95% CI, 1.02–1.25; **Figure 4**).

Subgroup Analyses, Meta-Regression Analyses, and Sensitivity Analyses

In the subgroup analyses, elevated serum galectin-3 was associated with an increased risk of ACD in all subgroups, with analyses conducted according to participant age, follow-up duration, participant number, and publication year of the original study (**Table 2**). The increased risk was more evident in the shorter follow-up (≤40 months) subgroup. The pooled HR of shorter follow-up (1.78; 95% CI, 1.50–2.11) was higher than the pooled HR of longer follow-up (1.15; 95% CI, 1.05–1.25). Due to the limited available studies, we did not perform a subgroup analysis of CVD.

In 11 studies that reported the risk of ACD, meta-regression analysis showed no significant associations among study characteristics (participant age, follow-up duration, participant number, and publication year of the original study) and risk of ACD (all $P > 0.05$).

The sensitivity analyses confirmed that the association between ACD and galectin-3 did not change with the use of random effects models or fixed effects models for the meta-analysis. A sensitivity analysis of omitting one study at a time revealed that Koukoui et al. study (20) had the largest impact on the overall results: the pooled HR omitting this study was 1.24 (95% CI, 1.09–1.40) (**Figure 5**).

Analysis of Publication Bias

Begg's tests and Egger's tests (**Figure 6**) were conducted to assess publication bias. ACD publication bias was not detected ($P>|t| = 0.15$ for Egger's test and $Pr>|z| = 0.35$ for Begg's test).

DISCUSSION

In this meta-analysis, we combined the outcomes of 6,440 CHF patients from 12 individual studies. The aggregated results indicated that serum galectin-3 is an independent predictor of ACD and CVD in CHF patients. Eleven studies reported an association between serum galectin-3 and the risk of ACD in CHF patients, with a pooled HR of 1.38 (95% CI: 1.14–1.67, **Figure 3**). Five studies presented data on the association between serum galectin-3 and the risk of CVD, with a pooled HR of 1.13 (95% CI, 1.02–1.25; **Figure 4**). Taking our aggregate results into consideration, serum galectin-3 may be a strong and independent biomarker in the prognosis of CHF.

The result of ACD is consistent with a previous meta-analysis published in 2015 (34), which is the current analysis concerning the prognostic value of serum galectin-3 in patients with CHF. However, only articles published before 2014 were enrolled, and this results necessary to be updated and validated.

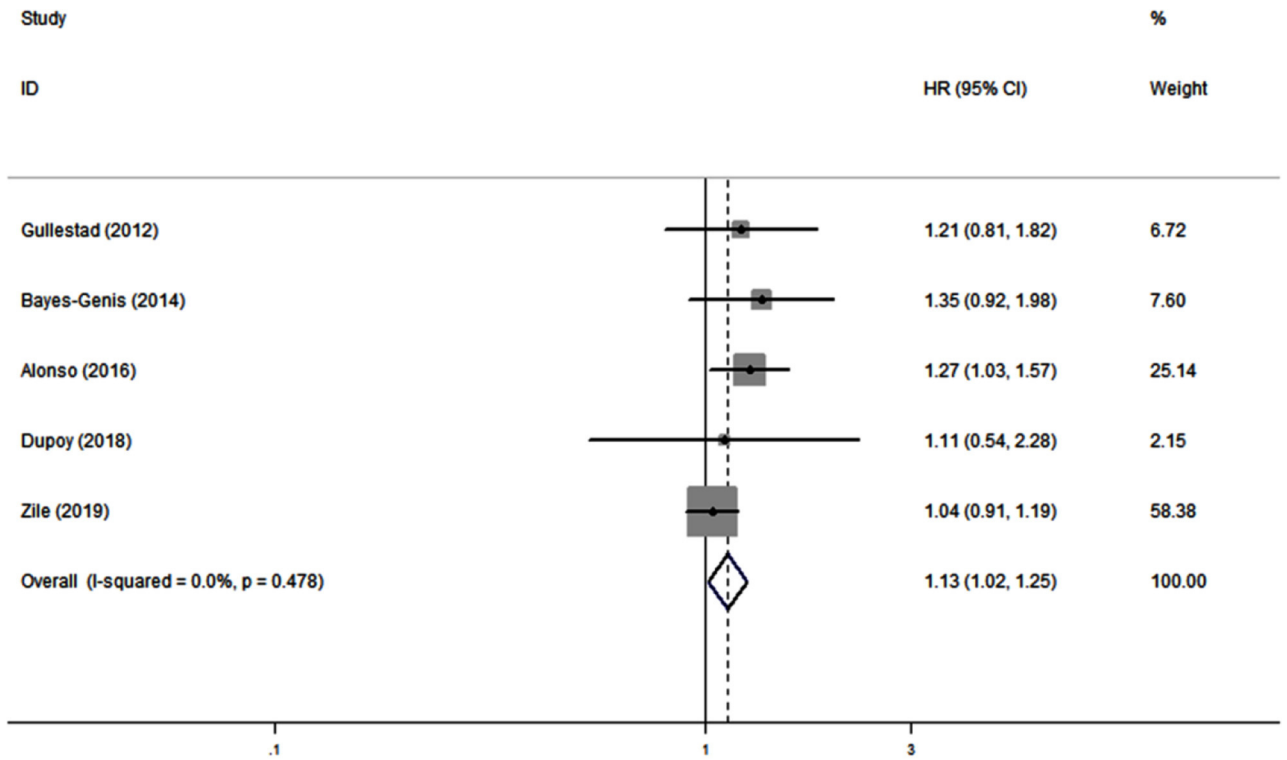

FIGURE 4 | Meta-analysis of the association between galectin-3 and risk of CVD in CHF patients. Results are presented as individual and pooled HR, and 95% CI.

TABLE 2 | Subgroup analyses of the association between galectin-3 and risk of ACD in CHF patients.

Subgroup	Number of studies	HRs (95% CIs)	*P* value for heterogeneity	I^2 value	*P* value between groups
Mean age					
<65	5	1.28 (1.15,1.42)	0.00	90.7	0.648
≥65	6	1.23 (1.10,1.38)	0.822	0.0	
Sample size					
<300	7	1.27 (1.16,1.39)	0.000	86.1	0.685
≥300	4	1.23 (1.07,1.41)	0.6	0.0	
Follow-up duration					
<40	5	1.78 (1.50,2.11)	0.004	73.9	0.00
≥40	6	1.15 (1.05,1.25)	0.095	46.6	
Publication year of the original study					
<2015	6	1.36 (1.18,1.56)	0.323	14.2	0.182
≥2015	5	1.21 (1.11,1.33)	0.00	89.4	

Moreover, although there was significant heterogeneity ($I^2 = 80$), no further analyses were performed. Compared with this meta-analyses, our study provides significant strengths. We evaluated the predictive role of serum galectin-3 for ACD and CVD in CHF patients. Moreover, sensitivity analyses, meta-regression analyses and subgroup analyses were applied to search for the origin of heterogeneity.

BNP and NT-proBNP are the most well-established biomarkers used in evaluating prognosis of patients with heart failure, which are included in the current guideline and widely used in clinical practice (16, 17). Novel biomarkers in HF may supplement the traditional ones (BNP and NT-proBNP) routinely used by providing additional prognostic, or stratification utility, and so optimizing the treatment of patients. Galectin-3 and sST2 are the only novel HF biomarkers that have been included in the European and American HF guidelines, with a class II b recommendation (16, 17). However, their clinical value is still uncertain.

Galectin-3, a chimeara-type β-galactoside binding lectin, is a crucial molecule in cardiac fibrosis (5, 35). Galectin-3 not only activates multiple profibrotic factors, facilitates proliferation and transformation of fibroblasts, and mediates the production of collagen (36–39). It can also stimulates macrophages to engulf apoptotic cells and cellular debris (40, 41). Animal studies have shown that galectin-3 is involved in cardiac re-modeling, and inhibition of the synthesis of galectin-3 by genetic technology or drugs can reduce cardiac remodeling and alleviate myocardial fibrosis (12, 13, 15, 42–44). In human studies, several studies demonstrated a significant prognostic value of galectin-3, independently from BNP/NT-proBNP and other prognostic variables in patients with HF, as well as in the general population (18, 45–47). However, the relationship between galectin-3 levels and HF in previous studies remains under debate. Some recently published studies have found that

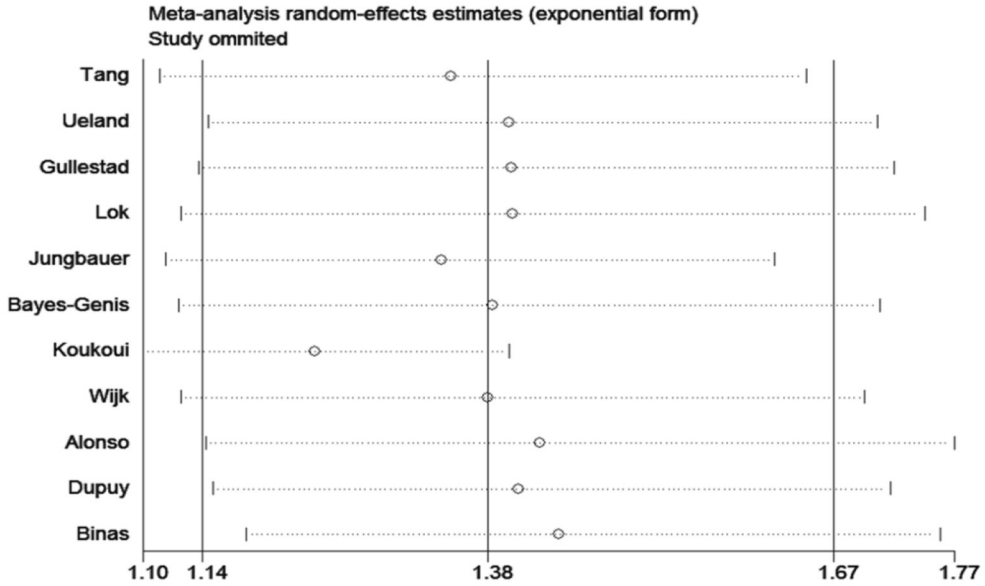

FIGURE 5 | Sensitivity analysis [Removing each study (author's name) one at a time].

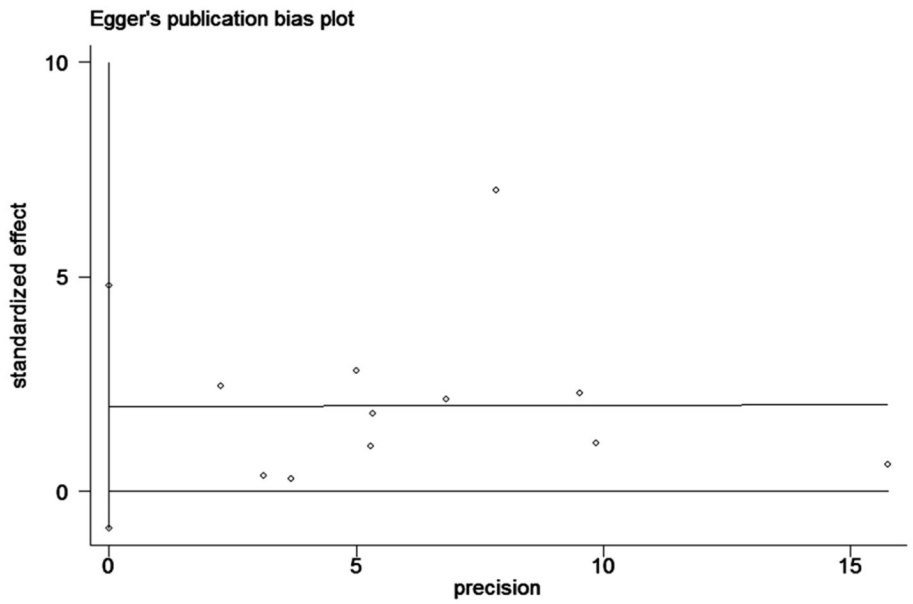

FIGURE 6 | The funnel plot of publication bias.

serum galectin-3 levels were not directly associated with specific cardiac parameters or major adverse cardiac events of CHF (19, 21, 32, 33, 48). A recent study in which endomyocardial biopsies were obtained from HF patients found that myocardial galectin-3 levels were not correlated with plasma galectin-3 levels, and plasma galectin-3 were not associated with cardiac fibrosis (49). The underlying mechanism may be that, except for cardiac strain and cardiomyocyte-specific cell death, galectin-3 is expressed in multiple organs and/or tissues, such as the kidney, gastric cancer, breast cancer, and lung (12, 50–52). From the results of our meta-analysis, higher serum galectin-3 levels were associated with a higher risk of mortality in chronic HF patients. Because HF is a multi-system syndrome affecting many tissues and organs, and galectin-3 is a biomarker not organ-specific but specific for individual pathogenesis, in particular inflammation or fibrosis, it is likely that other organs

or tissues could also contribute to increased serum galectin-3 levels. Thus, it is not surprising that they have a strong prognostic value. In the subgroup analyses, elevated serum galectin-3 was associated with an increased risk of ACD in all subgroups. Interestingly the pooled hazard ratio (HR) of the shorter follow-up group (<40 months) was significantly higher than the pooled HR of the longer follow-up group. We think it is associated with higher long-term mortality in patients with heart failure. The 5-year survival rate for heart failure patients is even lower than for some patients with cancer. Therefore, galectin-3 may be more suitable for evaluating the short-term prognosis of patients with chronic heart failure. Our study further confirms that galectin-3 is a significant predictor of ACD and CVD in CHF patients. It would help clinicians to adopt timely prevention and effective therapeutic strategies for CHF patients. Our study provides additional evidence for the development of clinical guidelines.

Some limitations of our meta-analysis should be mentioned. First, there was a high heterogeneity across the included studies in HR for ACD ($I^2 = 77.9\%$, $P < 0.1$), which may result from differences in follow-up time and participant characteristics. While there was moderate to high heterogeneity in many subgroups, the pooled HRs revealed consistent positive correlations in different subgroups. A sensitivity analysis of eliminating one study at a time revealed that Koukoui et al.'s study may be the origin of heterogeneity. Second, most of the included studies in the meta-analysis were of high quality. However, some of the involved studies were *post hoc* analyses in designing, which might affect the quality of the meta-analysis. Third, the involved studies in this meta-analysis were all from Western countries, and most of the participants had HF with reduced left ventricular ejection fraction. Thus, further well-designed studies in a wide range of regions and populations are needed to confirm our conclusions. Finally, this study was limited to English publications only, so publication bias may exist.

In conclusion, this meta-analysis provides evidence that higher serum galectin-3 was independently associated with poor prognosis in CHF patients. Given the high morbidity and mortality rates of CHF, our study has significant clinical and public health importance.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

ZC, KC, CX, QZ, XX, DX, and QZ was involved in conceiving the design of the meta-analysis, analyzing and interpreting data, or drafting/revising 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.2022.783707/full#supplementary-material

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Social Inequalities in Non-ischemic Cardiomyopathies

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Heart failure (HF) has various characteristics, such as etiology, clinical course, and clinical characteristics. Several studies reported the clinical findings of the characteristics of non-ischemic cardiomyopathy. There have been issues with genetic, biochemical, or pathophysiological problems. Some studies have been conducted on non-ischemic cardiomyopathy and social factors, for instance, racial disparities in peripartum cardiomyopathy (PPCM) or the social setting of hypertrophic cardiomyopathy. However, there have been insufficient materials to consider the relationship between social factors and clinical course in non-ischemic cardiomyopathies. There were various methodologies in therapeutic interventions, such as pharmacological, surgical, or rehabilitational, and educational issues. However, interventions that could be closely associated with social inequality have not been sufficiently elucidated. We will summarize the effects of social equality, which could have a large impact on the development and progression of HF in non-ischemic cardiomyopathies.

Keywords: cardiomyopathy, inequality, race, sex, hypertrophic cardiomyopathy, dilated cardiomyopathy

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INTRODUCTION

The disparity is a topic that has recently attracted attention again in the health service. There have been increasing numbers of reports on the disparities in clinical interventions in the field of heart failure (HF) (1–3). In particular, women and racial minorities are likely to be subjected to inequities in medical therapy (4, 5). In fact, the clinical course of HF is significantly affected by social and environmental factors (2). In non-ischemic cardiomyopathy, there are some studies on the association between social parameters and clinical course. However, the relationship between the social environment and the clinical course of the disease varies from place to place, and it is difficult to create a universal review. In particular, the analysis of regional disparities across nations is extremely complicated. Due to differences in economic conditions, medical system, and culture, it is difficult to analyze the disparity between nations (6). To make the issue more solvable, one valid method is to analyze the effect of social factors in the same background of culture and medical system. As mentioned above, efforts to make it universal are necessary. Furthermore, it should not be overlooked that individual clinical studies may also have implications for social disparities (**Figure 1**).

Heart failure itself is a group of diseases closely related to the social environment, but cardiomyopathy, which often has a genetic background, may have a different relationship with the social environment. In this review, we focus on the different aspects of this relationship.

A recent publication analyzed the association between economic factors and the clinical course of HF for each Gini tertile, a summary measure of income or wealth inequality, in different parts of the world over different countries (7). It demonstrated that patients from

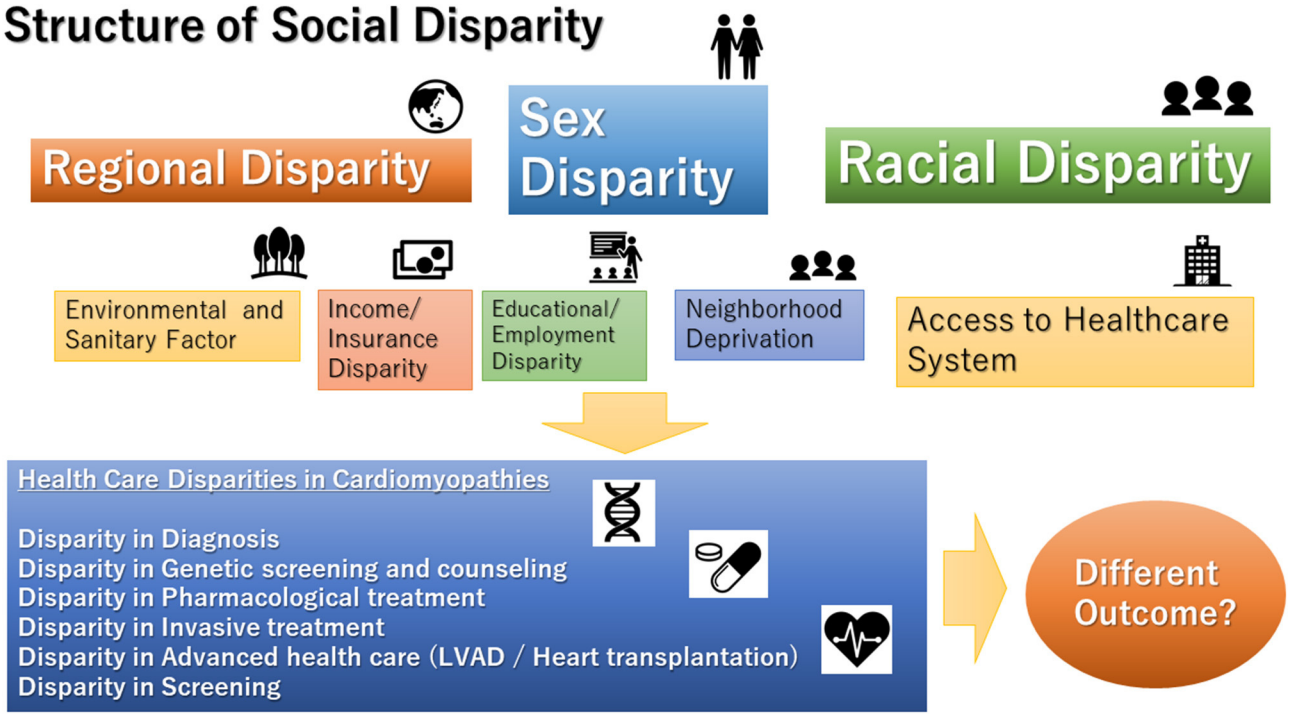

FIGURE 1 | Structure of social disparities in cardiomyopathies. LVAD, left ventricular assist device.

lower-income countries [hazard ratio (*HR*) 1·58, (95% *CI* 1·41–1·77)], or with greater income inequality [from the highest Gini tertile; 1·25, (1·13–1·38)] had a higher 1-year mortality compared with patients from regions with higher income or lower income inequality. The relationship with the socioeconomic factor differs depending on the cause of HF. Acute HF is associated with high postdischarge mortality, particularly in patients with HF with reduced ejection fraction from low-income regions with high-income inequality, while patients with HF with preserved ejection had lower 1-year mortality with little variation by income level. From the report of Asia, there was significant heterogeneity among Asian patients with stable HF and the important influence of ethnicity and the level of regional income on the characteristics of the patients (8).

In particular, non-ischemic cardiomyopathy has the following special aspects. Many have a family history, often having a genetic abnormality as a factor; many cases have a long-term disease, such as juvenile-onset; and there is a certain frequency of high-severity cases due to the long-term disease. It can have a strong influence on life courses, such as pregnancy and employment (9). Furthermore, because the frequency of the disease is comparatively low, medical care from a professional point of view may be superior.

In fact, the rate of premature morbidity and mortality remains unacceptably high in cardiomyopathy (10); therefore, there may be an element in which the disparity is likely to become apparent (11). Furthermore, socioeconomic status (SES) might affect the adherence of the patient to medical advice and therapies (12). In addition, low income was associated with a higher mortality rate with lower ambulatory-based healthcare resources (13).

Generally, there were common pathways of disparities, such as hospital bed density, health worker density, education index, and race. Regarding the difference in a clinical course due to the difference in race, there may be a genetic factor, but there is a possibility that it is a result that reflects the difference in the social environment depending on the race. Differences in the region of residence might also affect disparities in clinical management. Pierce et al. (14) reported different trends in HF-related mortality between rural and urban regions in the United States. Age-adjusted mortality rates were consistently higher for residents in rural compared with urban counties [73.2 (95% *CI*: 72.2–74.2) vs. 57.2 (56.8–57.6), respectively]. Residence in socioeconomically disadvantaged communities also affected clinical courses (15). In addition, the disparity derived from a medical professional is possible, such as the shortage of cardiac professionals. In fact, the echocardiographic assessment is critically required to diagnose non-ischemic cardiomyopathy (16). A study in Denmark demonstrated that the diagnosis of cardiac dysfunction in the early stage assessed by echocardiography was associated with the educational level (17).

There were several disparities according to the treatment of HF. A previous study in Sweden reported reduced access to angiotensin-converting-enzyme inhibitor (ACEI) treatment in unemployed patients, which demonstrated the adjusted odds ratio (*OR*) for no ACEI dispensation for unemployed patients of 1.59 [95% *CI* 1.46–1.73] (18). It showed that low employment status, low-income level, low educational level, or birth in a foreign country affected the continuation of ACEI. Meanwhile, the study in the United States did not demonstrate racial differences in the survival benefit derived from the use of

beta-blockers (19). According to the up-titration of beta blocker to the optimal dose, some disparities might be developed by the availabilities of the support for good adherence (20, 21). In recent trials that evaluated the effects of sacubitril/valsartan in the United States, no particular differences in effects were observed depending on race (22). In contrast, a study published in Denmark showed that attendance in cardiac rehabilitation is affected by social factors, such as educational attainment (23). The study in Denmark demonstrated inequalities in the care of HF by educational or income level (24). For instance, an income in the lowest tertile was associated with lower odds of prescription of ACEI/ARB [adjusted *OR* 0.80, (95% *CI*: 0.67–0.95)] and beta-blockers [adjusted *OR* 0.88, (95% *CI*: 0.86–1.01)], referral to exercise training [adjusted *OR* 0.59, (95% *CI*: 0.53–0.64)], and patient education [adjusted *OR* 0.66; (95% *CI*: 0.59–0.74)] compared with an income in the highest tertile. Regarding device treatment, the rate of implantable cardioverter-defibrillator implantation is low in females (25). In terms of sudden death, low educational level and low neighborhood SES were independently associated with an increased incidence of sudden cardiac death (26). The reasons included different levels of psychological stress and access to primary care and emergency medical services. According to the cardiac resynchronization therapy (CRT), the U.S. registry showed that it suffered from utilization disparities: male patients received more CRT devices compared with female patients; and whites received more CRT devices compared with Blacks (27). In addition, a recently published report from the U.S. database demonstrated sex disparities in choice of CRT device, with women less likely to receive a CRT-defibrillator (D) device compared with CRT-(pacing) P. They also showed that the patients in urban hospitals or higher bed capacity were more likely to receive CRT-D (28). Moreover, insurance status affects the decision of implantation of CRT (29). As described above, the disparity may occur in various clinical aspects in HF.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is a common genetic heart condition affecting the myocardium. There is a wide range of variability in the clinical course of HCM; however, the most important clinical events are the development of HF, atrial fibrillation, and sudden death (30).

The clinical course of HCM is determined by several factors, such as genetic status, echocardiographic findings, and pathological features. Patients with HCM are recommended to obtain shared decision medical care (31). Team-based specialized care is optimal for the improvement of patients with HCM.

According to the impact of socioeconomic factors, there was a fine review about racial disparity in HCM (32). In addition, Thomas et al. performed a retrospective cohort study of HCM that investigated the clinical course and SES and specialty care in the Yale inherited cardiomyopathy program. They showed that socioeconomically vulnerable patients with HCM had a higher mortality rate when they were not referred to specialty care (33). Low SES patients without the specialty care cohort had significantly higher all-cause mortality compared with high SES patients [adjusted *HR* 10.06 (95% *CI* 4.38–23.09; $p < 0.001$)]. On the contrary, no significant differences were observed in the clinical course between different SES if patients were referred to a specialized HCM care team. Ingles et al. (34) demonstrated that SES determined health service use or clinical outcomes in the HCM setting. There was an overrepresentation of patients from very advantaged and major metropolitan areas, suggesting that the inaccessibility of a specialty clinic was of great importance for the clinical course. In fact, team-based care was provided by cardiologists, electrophysiologists, surgeons, genetic counselors, medical engineers, transplant coordinators, and social workers. Patients with HCM should be regularly evaluated with multifaceted modalities, such as electrocardiographic monitoring, echocardiography, MRI, and cardiopulmonary exercise tests. This point also suggests the superiority of team-based management.

Recently, there was a large-scale study on the relationship between race and clinical outcome of HCM, including genetic abnormalities using a U.S.-based cohort. The study demonstrated that Black patients were less likely to be referred for subspecialty HCM care, less likely to undergo invasive septal reduction (14.6 vs. 23.0%; $p = 0.007$), and less frequently underwent genetic tests (26.1 vs. 40.5%; $p = 0.006$) (35). Furthermore, Black patients had a higher percentage of advanced HF with NYHA III and IV. Race-derived disparities consist of inequalities in care provision, decreased recognition of the disease, delays in timely management, barriers to accessing care, and environmental factors, such as lower SES. This factor seems to apply to other cardiomyopathies.

Additionally, there are disparities in the detection of genetic abnormalities. Interestingly, there may not be sufficient variant classification algorithms for patients in minority group populations because robust genomic investigations are not performed using reference cohorts in the genotyping of minority patients (36).

In terms of treatment, implantable cardioverter-defibrillator devices (ICD) are underused in women and racial minorities regardless of demographics, hospital characteristics, and comorbidities (37).

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy (DCM) is a common cause of HF among various cardiomyopathies (38). DCM is familial in 20–50% of cases, and various exposures to an additional insult, such as chemotherapy, might determine the development of HF. On the contrary, the sanitary environment might affect the development of DCM because there were several findings on the association between viral infection and DCM. Miura et al. demonstrated that the lower education levels and cold or hot workplaces exhibited a significant association with the development of DCM (39). Some heavy metals were associated with DCM probability (40). Although there are still few reports on the relationship between environmental factors and DCM, it is one of the routes of disease disparity, such as the sanitary environment, and further

research is required in the future. However, there may be some unknown interaction between the genome and environmental circumstances (41).

The difference by race was also demonstrated in DCM (42). Coughlin et al. (43) demonstrated that Blacks had an increased risk of developing idiopathic DCM with relative odds of 2.6 in the United States. They explained that the increased risk for Blacks was not due to income, educational attainment, alcohol consumption, cigarette smoking, or a history of hypertension, obesity, diabetes, or asthma. In contrast, Khan et al. demonstrated a higher all-cause mortality in Black patients with cardiomyopathy [*HR*: 1.15, (95% *CI* 1.07–1.25; $p < 0.001$)] (44) and demonstrated that it was possibly due to the inadequate delivery of treatment and access to care.

The diagnosis of DCM can be triggered by HF, but there are also some cases in which cardiac dysfunction is diagnosed by regular examination and cases in which cardiac dysfunction is confirmed by the diagnosis of related family members. Indeed, the addition of genetic tests in asymptomatic relatives of patients with DCM to guide periodic clinical surveillance is cost-effective (45, 46). However, the situation where such a system, e.g., genetic counseling, is actually possible has not been generally achieved, and in that sense, there is a disparity due to regional and socio-economical differences.

Based on the treatment, the current management for DCM does not vary from that of HF. However, as the cause of DCM is investigated in the future, more upstream treatment will be performed (47). Specifically, the ultimate therapy to address genetic abnormalities might improve the clinical course in patients with DCM with a genetic abnormality background. It is almost but not yet realized, but when it is realized, the aspect of professional treatment will become stronger and a disparity may occur.

More specialized medical care is required for secondary cardiomyopathy, and there will be a significant risk of diversity. However, it seems to be beyond the scope of this study.

In a U.S. cohort of pediatric cardiomyopathy, African-American and Hispanic children hospitalized with myocardial disease, such as myocarditis, exhibited approximately 30% higher odds for mortality than their Caucasian counterparts (48). The authors considered that barriers to care before hospitalization could contribute to disparate disease severity, leading to a different outcome.

PERIPARTUM CARDIOMYOPATHY

Peripartum cardiomyopathy (PPCM) is a disease of systolic HF that occurs toward the end of pregnancy and months after delivery in the absence of preexisting heart disease. Recently, genetic predisposition in PPCM was reported to be shared with those in DCM (49). Therefore, the problem in PPCM has some similarities with that in DCM. However, there were some specific reports on PPCM. In a large cohort of women with PPCM in the University of Pennsylvania Health System, there were different clinical courses between various racial backgrounds (50). African-American women were diagnosed later in the postpartum period and were more likely to have a significantly reduced ejection fraction (<30%) (56.5 vs. 39.5%, $p = 0.03$), leading to higher recovery failure. When examining its mechanism, the same group demonstrated a neighborhood concentrated disadvantage index independently associated with adverse outcomes in women with PPCM (51). It is demonstrated that low area-based education persisted as significantly correlating with sustained cardiac dysfunction [relative risk (*RR*) 1.49; (95% *CI* 1.02–2.17)]. The report from Europe showed that the mode of presentation was largely similar, while there were marked differences in sociodemographic parameters, such as the Human Development Index and Gini index of inequality in patients with PPCM from different regions (52). Many reports revealed that SES has a strong influence on outcomes in relation to pregnancy (53–55), and it is considered that there is an element that causes the impact of SES on PPCM as a result of the affinity between pregnancy and SES.

On the contrary, there were some studies on the environmental factors in the development of PPCM. There were non-racial regional disparities in the clinical characteristics and outcomes of patients with PPCM in Nigeria, which might partly be explained by selenium supplementation (56).

LEFT VENTRICULAR ASSIST DEVICE

Advanced cases of HF in cardiomyopathy are managed using LVAD or heart transplantation. Significant differences in left ventricular assist device (LVAD) implantation were based on sociodemographic risk factors. However, it should be fully considered that this issue is highly dependent on the medical system.

Using the United Network for Organ Sharing (UNOS) database, Okoh et al. performed a retrospective cohort analysis of patients who were implanted with a continuous flow LVAD between 2008 and 2018. There was no difference in survival between the respective races (57). Conversely, Breathet et al. (58) suggested that the LVAD implantation rates for Blacks did not increase proportionally, suggesting continued racial disparities, possibly due to the underinsurance or lack of social support.

In contrast, the area deprivation index had little impact on survival after LVAD implantation (59). Another study showed that low SES might not affect the clinical course after LVAD implantation (60). The readmission ratio was also not changed by the low SES (61). SES does not independently impact the survival and readmission after HeartWare HVAD and Heartmate III LVAD implantation. These findings suggested that the clinical course after LVAD implantation is not significantly affected by social background.

HEART TRANSPLANTATION

Based on heart transplantation, there are wide-range differences in the efficacy and situation of organ donation between different places (62, 63). Therefore, in addition to the disparity due to the local and social environment, some factors depend on each socioeconomic state in each place, although it is

greatly influenced by the situation of transplantation in each place. Based on this, socioeconomic disparities were reported in the UNOS registry. Low SES and low educational levels were associated with poorer outcomes after a heart transplant, resulting in approximately 20–30% increased risk (64). There were similar reports on heart transplantation in a wide range of populations (65, 66); one mechanism that explains its adherence to the treatment after heart transplantation, such as appropriate immunosuppressive medications. Furthermore, race is considered a critical factor that determines the clinical course after heart transplantation. According to the UNOS registry, after adjusting for recipient, transplant, and socioeconomic factors, Black recipients had a significantly higher risk of posttransplant mortality (67). Financial limitations might influence the adherence to follow-up visits in the posttransplant period. In patients who were successfully bridged with an LVAD to heart transplantation, similar reports demonstrated that the African-American race is associated with the increased rates of graft failure after transplantation and decreased in 5-year survival compared with the Caucasian race (68).

Recently, the SES disparities decreased over time (67). The gap between the middle and highest classes decreased; however, the lowest SES still exhibited a significant risk over time. Sex disparities also existed in pediatric heart transplantation (69). There were also clinical disparities in the decision-making process of clinicians to allocate advanced heart therapies, such as LVAD and heart transplantation, due to biased patient state recognition (70, 71).

LIMITATION

There are several limitations to this study. First, the sex disparity could not be adequately considered in this study. Unlike race disparity, sex disparity may be more closely related to differences in biological background and social involvement, requiring a more careful delineation. However, the complicated issue should be analyzed in a more concise way in the future. Second, in this study, the social disparity in non-ischemic cardiomyopathy was often examined, inferred from the racial disparity, which was often derived from the U.S.-based research. Indeed, few reports of the disparity are due to regional differences, economic conditions, or social conditions. However, it is necessary to study the impact of actual social disparity in non-ischemic cardiomyopathies.

CONCLUSION

There may be publication bias for the disparity. Many studies in this time of disparity reported racial differences, but this difference depends on the region. Although sufficient scores for factors, such as accessibility to specialized facilities, caregiver support, and community awareness, have not been evaluated adequately, the analysis on social disparity remains inadequate. As described above, various levels of disparity occur due to various factors in society, affecting the clinical course of the disease. Efforts to reduce disparities require not only summarization through manuscript publication, but also accurate information on understanding, administrative considerations, and countermeasures at each site. Although some factors are difficult to obtain for universal findings, this study actually leads to clinical results and should not be overlooked or considered a necessary study issue.

AUTHOR CONTRIBUTIONS

EA performed conceptualization, methodology, data curation, validation, original draft preparation, writing, reviewing, and editing.

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frontiers in Cardiovascular Medicine

CASE REPORT
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Case Report: Early Identification of Subclinical Cardiac Tamponade in a Patient With a Left Ventricular Assist Device by the Use of Sublingual Microcirculatory Imaging: A New Diagnostic Imaging Tool?

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Clinical diagnosis of cardiac tamponade can be difficult in patients with continuous flow left ventricle assist devices (cf-LVADs). This is even more so because of the lack of adequate bedside echocardiographic windows. Previous studies on monitoring sublingual microcirculation showed deterioration of end-organ perfusion in patient with cardiogenic shock. In this paper we report alterations in the sublingual microcirculation in a cf-LVAD patient prior to clinical manifestation of tamponade. Our case report suggests that such real-time monitoring of the microcirculation may provide a new diagnostic modality for early recognition of cardiac tamponade.

Keywords: left ventricular assist device, microcirculation, cardiac tamponade, heart failure, diagnosis

INTRODUCTION

The identification of (sub)acute cardiac tamponade following cardiac surgery is difficult to assess at the bedside. Patients may be (relatively) asymptomatic early in the course, but once intrapericardial pressure reaches a critical value limiting the cardiac output, the clinical course can be dramatic. In continuous flow left ventricle assist device (cf-LVAD) patients this is especially the case, due to the lack of pulsatility as a diagnostic indication. Recent studies observing sublingual microcirculatory alterations using incident dark-field (IDF) imaging may potentially provide a new bedside imaging modality for clinical assessment of shock (1, 2). IDF imaging consists of a hand-held device with a pen-like image guide probe (Braedius Medical, Huizen, the Netherlands) incorporating concentrically placed light emitting diodes incorporating IDF illumination with a set of high-resolution lenses projecting images on to a computer-controlled high-density image sensor synchronized to an illumination unit (3).

In this paper we report the presence of microcirculatory alterations in a cf-LVAD patient with cardiac tamponade before its clinical presentation.

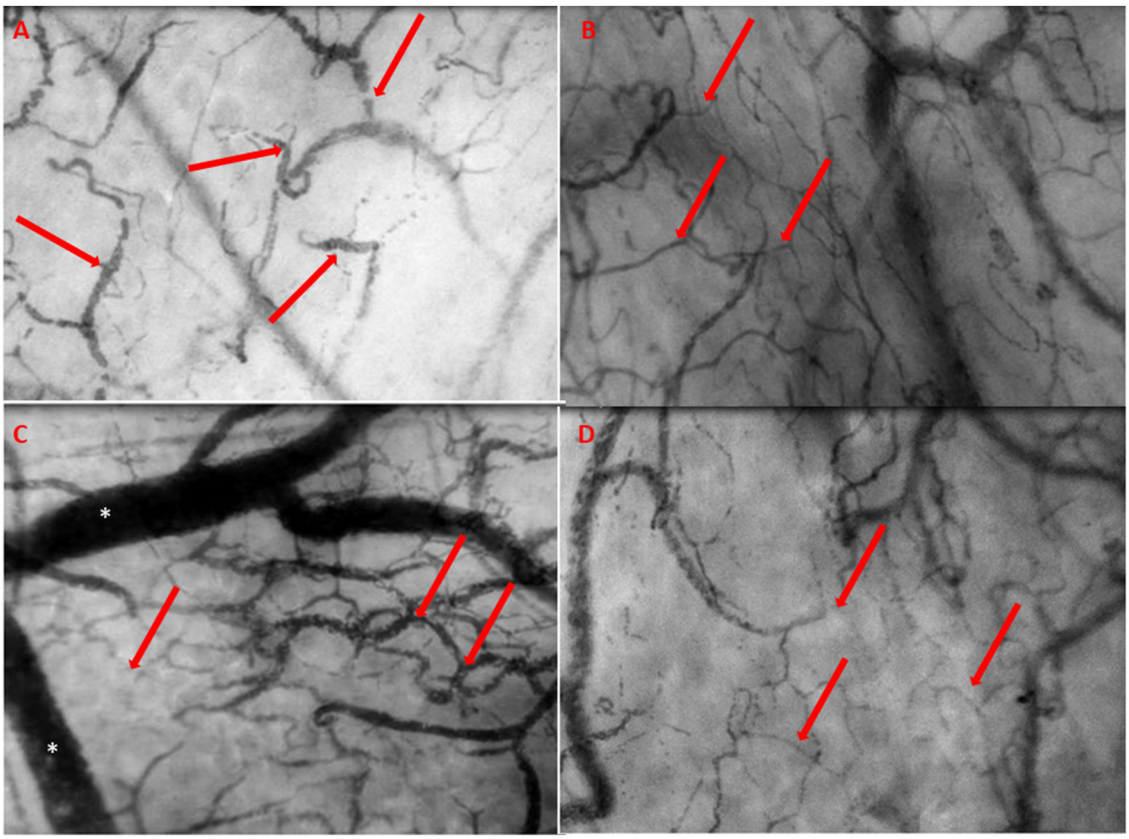

FIGURE 1 | (A) The day prior to LVAD implantation. The microcirculation is typical as seen in heart failure characterized by slow, sludging flow (red arrows), stasis of red blood cells, and low capillary density. **(B)** The day after LVAD implantation with improved microcirculatory flow with a high red blood cell (RBC) velocity, concordant blood flow in all quadrants, and increased capillary density (red arrows). **(C)** The day of event, 10 days post-surgery, showing severe deterioration of microcirculation with severe stasis of red blood cells (red arrows) and severe congestion and distention of the venules (*). **(D)** Prior to discharge**,** quietly normalized microcirculatory flow (red arrows) after revealing cardiac tamponade.

CASE DESCRIPTION

A 39-year-old man, with a history of resection of the subvalvular aortic membrane and myectomy (30 years ago), was referred to our hospital because of progressive heart failure as a result of severe left ventricular (LV) systolic dysfunction with concomitant severe aortic regurgitation (AR). Conservative surgery with correction of AR was considered inappropriate due the severity of LV dysfunction. His exercise capacity appeared to be severely limited with a VO2 max of 13 kg/min (38% of predicted value). Due to further deterioration, a HeartMate II (Abbott, Chicago, USA) LVAD was implanted as a bridge-to-transplantation (BTT). His recovery was complicated by postoperative bleeding on day 5 requiring rethoracotomy. As part of a clinical research project, intermittent sublingually microcirculation measured using Cytocam-IDF imaging was initiated (4). The day before LVAD implantation, the sublingual microcirculation was typical as seen in the state of severe heart failure, characterized by slow, sludging movement of the red blood cells (**Figure 1A** and **Supplementary Video 1**). The day after LVAD implantation, the microcirculation improved significantly, with high red blood cell (RBC) velocity (**Figure 1B** and **Supplementary Video 2**). On day 10 after the LVAD implantation, the patient was apparently clinical stable with a heart rate of 90 beats/min, blood pressure of 99/73 mmHg, and normal diuresis. Also, his LVAD parameters were within the normal range: 8,600 rpm, flow 4.8 L/min (N = 3–10 L/min), pulsability index (PI) 7.0 ([(power max − power min)/power average] × 10), and power 4.7 Watt (N < 8 Watt). However, during this phase, microcirculatory imaging revealed a severe failure of microcirculatory function, reflected by a clear stasis of blood cells (**Figure 1C** and **Supplementary Video 3**). Later that evening the clinical condition of the patient deteriorated and clinical investigations were initiated. There was a situation with near collapse, followed by low flow alarms of the LVAD. The patient complained of dizziness and decreased PI of the HeartMate II. His blood pressure was 84/70 mmHg and his heart rate 90 beats/min. The transthoracic echocardiography showed pericardial thrombus formation at the posterior site without evident signs of tamponade. Given the unclear clinical status, an additional CT scan was performed showing evident signs of cardiac tamponade with thrombus formation around the right ventricle and posterior to LV.

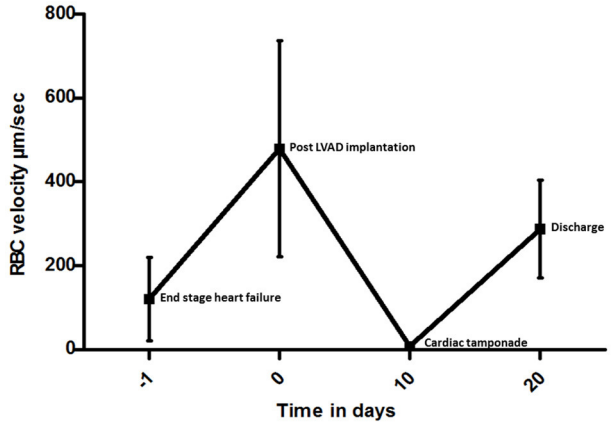

FIGURE 2 | Space-time diagram analysis of red blood cell (RBC) velocity measured in five representative capillary video sequences at each time point in individual vessels from the day before LVAD to discharge. The RBC values are shown with bars giving the standard deviation.

Subsequently a resternotomy was performed to relieve the cardiac tamponade. This surgical intervention resulted in a quick clinical recovery with restoration of microcirculatory blood flow as shown by sublingual measurements (**Figure 1D** and **Supplementary Video 4**). Additionally, off-line analysis of the microcirculatory movies using Automated Vascular Analyses software (AVA; MicroVision Medical©) allowed a quantitative analysis of the sublingual microcirculation and the velocity distributions to be made (5). Space-time diagram analysis showed that the velocity of red blood cell flow was significantly reduced during the event, and slowly recovered in the following days following treatment of cardiac tamponade until discharge (**Figure 2**). Further clinical recovery was uneventful.

DISCUSSION

(Sub)acute cardiac tamponade is a cardiac complication after open heart surgery, potentially lethal if diagnosed late (6). It usually results from accumulation of pericardial fluid, blood, and thrombus formation, leading to impaired cardiac filling and hemodynamic compromise. In this report, we present unique images of microcirculatory alterations in a cf-LVAD patient before the clinical manifestation of cardiac tamponade.

Postoperative bleeding and tamponade are considered major complications after implantation of cf-LVADs. Common hemodynamic characteristics of cardiac tamponade, including tachycardia, shock, or pulsus paradoxus, may be masked by the set values of the cf-LVAD (7). Transthoracic echocardiography is the first-line bedside cardiac imaging modality. However, due to blurred echo windows in LVAD patients, the diagnosis of pericardial effusion and resulting cardiac tamponade can be very challenging. However, echocardiography is readily available and portable, lacks ionizing radiation, and is highly sensitive for pericardial effusion. It is also very specific for diagnosis of pericardial tamponade in acute settings. If it does not result in feasible windows, computed tomography with additional information with assessment of the entire chest including associated abnormalities in the mediastinum, lungs, and adjacent structures is possible due to the larger field of view compared with that of echocardiography. IDF imaging is implemented in a hand-held device with a pen-like image guide (Braedius Medical, Huizen, the Netherlands) incorporating concentrically placed light emitting diode illumination when a set of high-resolution lenses projects images on to a computer-controlled high-density image sensor synchronized to an illumination unit (3). The patient-friendly and portable characteristics are comparable with that of echocardiography. Recently, IDF imaging has been validated for clinical assessment of microcirculatory alterations in critically ill patients (4). Further use of microcirculatory off-line analysis using Semi-Automated Vascular Analyses software (5) allows for quantitative analysis of sublingual microcirculation and the velocity distributions to be made (5). Using the method for space-time diagram analysis, significant alterations in the velocity of red blood cell flow were found. The images captured by echocardiography and a CT scan (8 h after sublingual microcirculatory alterations were present) after clinical deterioration during this cardiac tamponade are shown in **Figure 3**.

The study identified significant evidence for loss of hemodynamic coherence between the macrocirculation and microcirculation (8). Microcirculatory shock is the failure of microcirculation to support tissue perfusion and oxygenation, despite a normal restoration of systemic hemodynamics. A severely disrupted microcirculation might coexist with a restored systemic hemodynamic. Variables may not necessarily result in a correction of tissue and microcirculatory perfusion (9). Although this is to our knowledge the first description of microcirculatory IDF analysis in a patient with a continuous flow left ventricular assist device, there are limitations. This technique is not new and has to be implemented on larger populations with cf-LVADs. There are studies in the past that have described continuous flow circulatory support devices for temporary use (10–15). Furthermore, a limitation of our study is that we did not prove a direct causal effect between microcirculatory alterations and tamponade. Such alterations could also have been caused by acute right-sided heart failure, a pulmonary embolism causing severe obstructive shock, or in some cases, the condition of the pump itself, like pump thrombosis. Further technical limitations have to be taken into consideration as recently described (16). The assessment of red blood cell displacement as a measure of the microcirculatory convection capacity using current tools represents an even bigger challenge. Although measurement of the absolute red blood cell velocity of selected capillaries has been realized using manual space–time diagram analysis, applying this manual method to all capillaries rendered in an IDF image sequence for accurate and unbiased representation of red blood cell velocity within the field of view is not feasible (17).

In conclusion, in this case report we described the presence of microcirculatory alterations in a cf-LVAD patient in advance of the clinical manifestation of pericardial tamponade. Our study suggests that microcirculatory imaging may add a new modality in the arsenal of hemodynamic monitoring devices

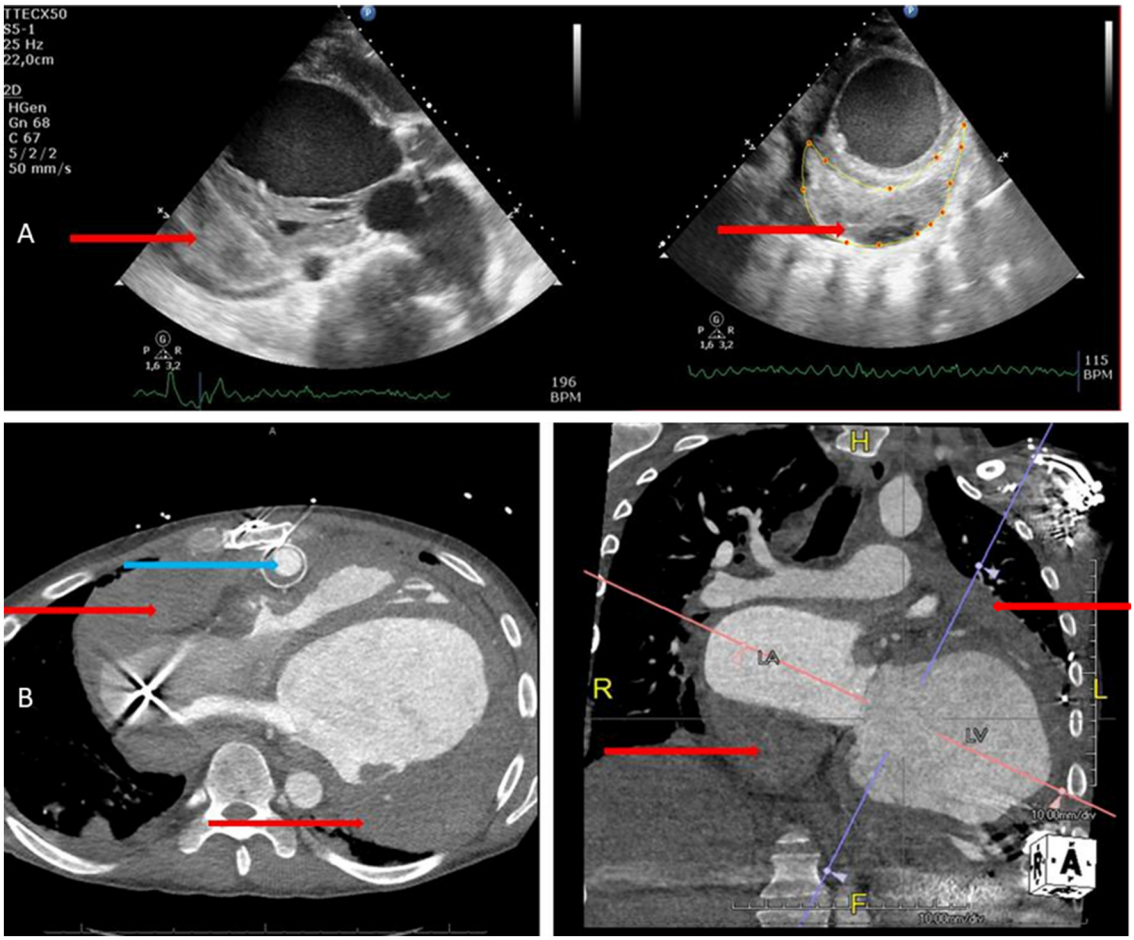

FIGURE 3 | (A) Echocardiography images in parasternal long and short axis views showing thrombus formation (red arrows) in the pericardial space at the posterior area. **(B)** CT images of the whole thorax from transversal and anterior views showing thrombus formation (red arrows) around the left ventricle, and the atria images collected with echocardiography which are voluminous and more detailed and also show the HeartMate II outflow graft very clearly (blue arrow).

for identification of the early presence of tamponade in LVAD patients. This could probably add a new dimension in the early diagnosis and bedside monitoring of post-cardiac surgery patients, especially in patients with cf-LVADs.

PATIENT PERSPECTIVE

I am happy that doctors all over the world are learning from my case and I do not mind my condition being discussed. I do not want anyone to go through what I had to after an LVAD implantation.

As a young man with end-stage heart failure I have been given an LVAD implantation as a bridge to heart transplant. There were bleeding problems a couple of days after the operation in the ICU. There was a need for re-operation during my stay in the normal ward as well. Due to the LVAD in my thorax, echocardiography views were difficult to assess leading to CT scans. Dr. Akin asked me, as part of a clinical research project, to look under my tongue before the operation for intermittent microcirculation measurement using a camera. There were alterations seen in the microcirculation during my stay in the hospital before and after the LVAD implantation. For further optimizing the circulation after a LVAD implantation, such a technique could be useful in the future. Therefore, I give my consent for follow-up, during my out-patient clinical visits as well. It was very easy to measure this sublingually microcirculation by holding the camera with my hand and helping with the acquisition of the videos. I am very pleased with all the attention and care I received in the hospital. The doctors and nurses were nice to me. In the end, I hope that doctors all over the world have learnt something from reading my case.

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SA, CI, and KC performed the IDF imaging, contributed to the manuscript revision, participated in the design of the study, and contributed to the manuscript revision. AS participated in the interpretation of the data and drafted and revised the manuscript. CI was involved in the image analysis and the manuscript revision. All authors read and approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.818063/full#supplementary-material

Supplementary Video 1 | The day prior to LVAD implantation. The microcirculation is typical as seen in heart failure characterized by slow, sludging flow (red arrows), stasis of red blood cells, and low capillary density.

Supplementary Video 2 | The day after LVAD implantation with improved microcirculatory flow with a high red blood cell (RBC) velocity, concordant blood flow in all quadrants, and increased capillary density (red arrows).

Supplementary Video 3 | The day of event, 10 days post-surgery, showing severe deterioration of microcirculation with severe stasis of red blood cells (red arrows) and severe congestion and distention of the venules (*).

Supplementary Video 4 | Prior to discharge, quietly normalized microcirculatory flow (red arrows) after revealing cardiac tamponade.

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Conflict of Interest: CI has developed SDF imaging and is listed as an inventor on related patents that were commercialized by Micro Vision Medical (MVM) under a license from the Academic Medical Center (AMC). He receives no royalties or benefits from this license. He has been a consultant for MVM in the past but has not been involved with this company for more than 5 years and holds no shares or stock. Braedius Medical, which is a company that is owned by a relative of CI, has developed and designed a handheld microscope, namely, the CytoCam-IDF imaging microscope. The images used in the present study were obtained using this technology. CI has no financial relationship with Braedius Medical of any sort. Currently he is C.S.O. and holds shares in a company called Active Medical BV whose business is providing services and products related to clinical microcirculation.

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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Increased Rapid Eye Movement Sleep Is Associated With a Reduced Risk of Heart Failure in Middle-Aged and Older Adults

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Objectives: Rapid eye movement (REM) sleep is closely related to all-cause mortality. The aim of this study is to explore the role of REM sleep on the incident heart failure (HF).

Methods: We selected 4490 participants (2480 women and 2010 men; mean age, 63.2 ± 11.0 years) from the Sleep Heart Health Study. HF was identified as the first occurrence during a mean follow-up period of 10.9 years. REM sleep including percentage of REM sleep and total REM sleep time were monitored using in-home polysomnography at baseline. Multivariable Cox regression analysis was utilized to explore the relationship between REM sleep and HF.

Results: In total, 436 (9.7%) cases of HF were observed during the entire follow-up period. After adjusting for potential covariates, an increased percentage of REM sleep (per 5%) was independently associated with a reduced incidence of HF [hazard ratio (HR) 0.88, 95% confidence interval (CI) 0.82–0.94, $P < 0.001$]. A similar result was also found between total REM sleep time (increased per 5 min) and incident HF (HR 0.97, 95% CI 0.95–0.99, $P < 0.001$). Moreover, the fourth quartile of both percentage of REM sleep (HR 0.65, 95% CI 0.48–0.88, $P = 0.005$) and total REM sleep time (HR 0.64, 95% CI 0.45–0.90, $P = 0.010$) had lower risk of incident HF when compared with the first quartile.

Conclusion: An increased percentage of REM sleep and total REM sleep time were associated with a reduced risk of HF. REM sleep may be a predictor of the incident HF.

Clinical Trial Registration: [ClinicalTrials.gov], identifier [NCT00005275].

Keywords: percentage of REM sleep, total REM sleep time, sleep heart health study, polysomnography, heart failue

Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; HF, heart failure; CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; HR, hazard ratio; MI, myocardial infarction; MrOS, Outcomes of Sleep Disorders in Older Men; PSG, polysomnography; REM, rapid eye movement; SHHS, Sleep Heart Health Study; T90, percent time below oxygen desaturation 90%.

INTRODUCTION

Sleep is an essential physiological phenomenon occurring in alternation with wakefulness, and good quality sleep is vital for maintaining health and homeostasis (1, 2). According to the World Health Organization, 27% of individuals worldwide suffer from sleep disorders. With the increasing pressure of work, study, and life, sleep issues have severely affected nearly 50–70 million people's physical and mental health in the United States (3). There is growing evidence that poor sleep contributes to cardiovascular disease (CVD) and its risk factors, such as coronary artery disease, stroke, diabetes mellitus, hypertension, and obesity (4–8). However, the relationship between sleep and CVD deserves further investigation.

Rapid eye movement (REM) sleep and non-REM sleep are two critical stages of sleep. REM sleep, about 20–25% of total sleep time, is usually characterized by eye movement, increased heart rate and blood pressure, muscle relaxation, and low voltage and fast frequency in the electroencephalogram (9, 10). Recently, several studies have shown that individuals with a decreased percentage of REM sleep have high all-cause mortality (11, 12). Matthews et al. demonstrated that there was a close correlation between the percentage of REM sleep and sleep/wake ratios of blood pressure (13).

Despite the certainty of knowledge on the effects of REM sleep, the relationship between REM sleep and heart failure (HF) remains unclear. The purpose of this study was to explore whether there is an association between REM sleep (including percentage REM sleep and total REM sleep time) and incident HF based on the Sleep Heart Health Study (SHHS) datasets.

MATERIALS AND METHODS

Study Population

Data were derived based on an existing dataset from the SHHS (ClinicalTrials.gov, identifier NCT00005275), which was a community-based multicenter prospective cohort study performed by the National Heart, Lung, and Blood Institute to investigate the cardiovascular and other consequences of sleep-disordered breathing between baseline (November 1, 1995 and January 31, 1998) and 2011. The detailed method and design of this study have been reported previously (14, 15). Briefly, a total of 6441 participants aged 40 years and older were recruited from several "parent" cohorts including the Atherosclerosis Risk in Communities study, the Cardiovascular Health Study, the Framingham Offspring and Omni study, the Strong Heart Study, the Health and Environment and Tucson Epidemiologic Study, and studies of hypertension in New York. All participants in the SHHS signed written consent, and the study protocol was approved by the institutional review board of each participating institution to collect sleep and questionnaire data. The data underlying this article are available in National Sleep Research Resource, at https://doi.org/10.25822/ghy8-ks59. The datasets were derived from sources in the public domain. Our access to the SHHS database was provided after acquiring a signed agreement with the Brigham and Women's Hospital. The SHHS shared dataset from the National Sleep Research Resource does not include 637 individuals from the Strong Heart Study due to sovereignty issues. Exclusion criteria for our study were (1) previous CVD outcomes (n = 535); (2) participants who use CPAP or a mouthpiece (n = 7); and (3) no follow-up data (n = 772). Finally, 4490 participants were included in the present study (**Supplementary Figure 1**).

Sleep Parameters

Polysomnography (PSG) is essential for the diagnosis and management of many sleep parameters. All individuals in the current study underwent electroencephalography-based overnight unattended PSG (P-Series, Compumedics, Abbotsville, VIC, Australia) at home (15). Supplementary Material showed the details regarding the specific technical aspects of the PSG measurement. The time and percentage of REM sleep were captured using PSG monitoring. In addition, the percentage of REM sleep was categorized into quartiles: Q1 (<15.8%; n = 1113), Q2 (15.8–20.1%; n = 1134), Q3 (20.2–24.0%; n = 1145), and Q4 (>24.0%; n = 1098). Moreover, total REM sleep time was also divided into quartiles: Q1 (<54.0 min; n = 1113), Q2 (54.0–73.5 min; n = 1162), Q3 (73.6–91.5 min; n = 1110), and Q4 (>91.5 min; n = 1105). Other sleep structure parameters, including time in stage 1 (min), time in stage 2 (min), time in stage 3 (min), percentage stage 1, percentage stage 2, and percentage stage 3, were also included in the current analysis. Sleep duration was defined as the total time in bed (Time from lights off to lights on, rounded to nearest minute) based on the PSG record. The apnea–hypopnea index (AHI) obtained from the PSG was identified as the number of apneas or hypopneas recorded during the study per hour of sleep, accompanied by at least a 4% drop in oxygen saturation (15).

The Identification of Heart Failure

The criteria for HF was based on clinical signs and symptoms (such as rales, edema, dyspnea, and orthopnea), physiologic tests (decreased systolic function), and supportive findings (chest radiography or functional cardiac imaging), as previous study reported (16). HF was defined as the first occurrence during the average 10.9 years' follow-up. The control group for HF patients was defined as participants who had no CVD outcomes at baseline and did not develop HF during the follow-up period when investigated the association between REM sleep and HF. Myocardial infarction (MI), stroke, and CVD death were also identified in the follow-up time. All the CVD events were evaluated in the parent cohorts using explicit protocols and identified for SHHS using follow-up interviews, written annual questionnaires, telephone contacts with study participants or next-of-kin, surveillance of local hospital records and community obituaries, and linkage with the Social Security Administration Death Master File (17).

Covariates

Covariates including age, sex, race, education, marital status, smoking status, body mass index (BMI), alcohol use, caffeine use, benzodiazepine use, hypertension, diabetes mellitus, triglyceride, cholesterol and high-density lipoprotein (HDL) cholesterol,

percent time below oxygen desaturation 90% (T90), and AHI were obtained from the SHHS baseline examination.

Statistical Analyses

Continuous and categorical variables were summarized using Student's *t*-test and Chi-squared tests, respectively. The results are presented as mean (±SD) and number (percentages). Moreover, unadjusted Kaplan–Meier survival curves were drawn to investigate the overall survival of individuals with different REM sleep quartiles. Cox regression analysis was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) in the relationship between REM sleep and HF. Multivariable Cox regression analysis adjusted for age, sex, race, education, marital status, smoking status, BMI, alcohol use, caffeine use, benzodiazepine use, hypertension, diabetes mellitus, triglyceride, cholesterol, HDL, sleep duration, T90, and AHI to examine the associations between REM sleep and HF. Subgroup analysis stratified by sex (men vs. women) and AHI (≥15 vs. <15 events/h) was performed when explore the role of REM sleep on the incidence of HF. All statistical analyses were conducted using SPSS (version 24.0; SPSS Inc.). A two-sided $P < 0.05$ was considered to be statistically significant.

RESULTS

Study Population

Table 1 shows the study characteristics in participants with and without HF. The present study included 4490 individuals [2480 women (55.2%)] with a mean age of 63.8 ± 11.0 years. A total of 436 (9.7%) cases of HF was observed during the follow-up period. Individuals with HF were older and had more smokers, hypertension, diabetes mellitus than controls. In addition, HF patients had low level of percentage of REM sleep, total REM sleep time, T90, and AHI compared with controls.

The Relationship Between Rapid Eye Movement Sleep and Incident Heart Failure

Unadjusted Kaplan–Meier survival curves showed that HF event rates increased with a decrease in REM sleep percentage (**Figure 1A**; Log-rank test: $P < 0.001$). After adjusting for age, sex, race, education, marital status, smoking status, BMI, alcohol use, caffeine use, benzodiazepine use, hypertension, diabetes mellitus, triglyceride, cholesterol, HDL, sleep duration, T90, and AHI (natural log-transformed), multivariable Cox regression analysis showed that an elevated percentage of REM sleep (per 5%) was significantly associated with a reduced risk of HF (HR 0.88, 95% CI 0.82–0.94, $P < 0.001$). Moreover, individuals in the fourth quartile of percentage REM sleep had a significantly lower risk of HF than those in the first quartile (HR 0.65, 95% CI 0.48–0.88, $P = 0.005$) (**Table 2**).

We also explored the association between total REM sleep time and HF. Similar to the results for REM sleep percentage, total REM sleep time (increased per 5 min) was found to be independently associated with HF (HR 0.97, 95% CI 0.95–0.99, $P < 0.001$). In addition, individuals in the fourth quartile of the total REM sleep time had the highest overall survival rate (**Figure 1B**; Log-rank test: $P < 0.001$). Total REM sleep time

TABLE 1 | Study characteristics in participants with and without HF.

Characteristics	Total *n* = 4490	HF *n* = 436	Controls *n* = 4054	*P*-value
Age, years	63.2 ± 11.0	73.6 ± 7.8	62.1 ± 10.7	< 0.001
Sex (%)				0.035
Men	2010 (44.8)	216 (49.5)	1794 (44.3)	
Women	2480 (55.2)	220 (50.5)	2260 (56.7)	
Race (%)				0.751
White	3904 (87.0)	377 (86.5)	3527 (87.0)	
Others	586 (13.0)	59 (13.5)	527 (13.0)	
Education (%)				< 0.001
≤15 years	2564 (62.9)	316 (74.2)	2248 (61.6)	
>15 years	1511 (37.1)	110 (25.8)	1401 (38.4)	
Marry (%)				< 0.001
Married	3548 (80.3)	314 (72.4)	3234 (81.2)	
Others	870 (19.7)	120 (27.6)	750 (18.8)	
Smoking status, *n* (%)				0.023
Current smoker	440 (9.9)	45 (10.4)	395 (9.8)	
Former smoker	1925 (43.0)	211 (48.6)	1714 (42.4)	
Never smoker	2112 (47.1)	178 (41.0)	1934 (47.8)	
BMI, kg/m^2	28.3 ± 5.0	29.0 ± 4.9	28.2 ± 5.0	0.003
Hypertension, *n* (%)	1633 (36.4)	282 (64.7)	1351 (33.3)	< 0.001
Diabetes mellitus, *n* (%)	286 (6.5)	79 (18.4)	207 (5.2)	< 0.001
Alcohol use, *n* (%)				0.001
At least one drink per day	1838 (43.7)	154 (35.8)	1684 (44.6)	
None	2369 (56.3)	276 (64.2)	2093 (55.4)	
Caffeine use, *n* (%)				0.010
At least one intake per day	2749 (61.3)	242 (55.6)	2507 (62.0)	
None	1732 (38.7)	193 (44.4)	1539 (38.0)	
Benzodiazepine use, *n* (%)	241 (5.4)	33 (7.6)	208 (5.1)	0.030
Triglyceride, mL/dL	150.2 ± 99.4	155.7 ± 93.0	149.6 ± 100.1	0.231
Cholesterol, mL/dL	206.9 ± 38.1	204.6 ± 38.5	207.1 ± 38.0	0.194
HDL, mL/dL	51.1 ± 15.8	49.4 ± 13.8	51.3 ± 16.0	0.007
Sleep duration, h	7.3 ± 0.9	7.3 ± 1.0	7.3 ± 0.9	0.849
AHI, events/h	9.7 ± 13.0	12.1 ± 13.1	9.5 ± 13.0	< 0.001
T90, %	3.3 ± 9.9	5.5 ± 13.5	3.0 ± 9.4	< 0.001
Sleep structure				
REM sleep time (min)	72.4 ± 29.0	62.7 ± 28.3	73.4 ± 28.9	< 0.001
Time in stage 1 (min)	18.7 ± 13.1	20.0 ± 15.0	18.6 ± 12.9	0.061
Time in stage 2 (min)	208.6 ± 56.8	205.3 ± 60.5	208.9 ± 56.4	0.204
Time in stage 3 (min)	65.2 ± 44.4	60.7 ± 47.4	65.7 ± 44.0	0.027
REM sleep time (%)	19.6 ± 6.7	17.7 ± 7.2	19.8 ± 6.7	< 0.001
Time in stage 1 (%)	5.2 ± 3.8	5.8 ± 4.5	5.2 ± 3.8	0.004
Time in stage 2 (%)	57.3 ± 13.1	59.1 ± 14.1	57.1 ± 12.9	0.005
Time in stage 3 (%)	17.9 ± 11.9	17.3 ± 12.7	17.9 ± 11.8	0.348
Follow-up time, years	10.9 ± 2.8	9.4 ± 3.0	11.1 ± 2.7	< 0.001

AHI, apnea–hypopnea index; BMI, body mass index; HDL, high-density lipoprotein; HF, heart failure; REM, rapid eye movement; T90, percent time below oxygen desaturation 90%. Results are presented as mean ± SD or number (percentage). The P-values represent the difference between two groups.

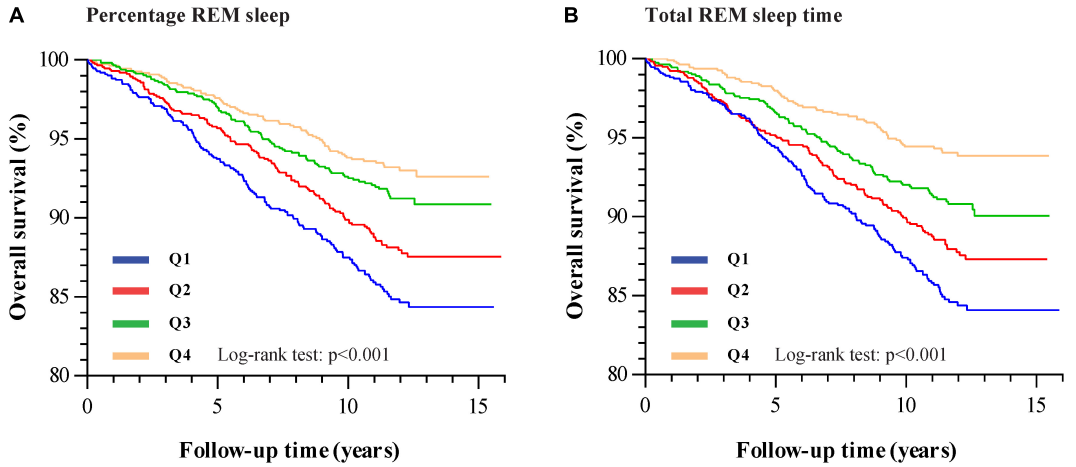

FIGURE 1 | Kaplan–Meier plots of overall survival for HF stratified by percentage REM sleep quartiles [**(A)** Q1: <15.8%; Q2: 15.8–20.1%; Q3: 20.2–24.0%; Q4: >24.0%] and total REM sleep time quartiles [**(B)** Q1: <54.0 min; Q2: 54.0–73.5 min; Q3: 73.6–91.5 min; Q4: >91.5 min].

TABLE 2 | Hazard ratios and 95% CIs for REM sleep associated with incident HF.

REM sleep traits	Persons (*n*)	Event, *n* (%)	Univariable model		Age and gender adjusted		Multivariable adjusted	
Percentage REM sleep	**4490**	**436 (9.7)**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Q4 (>24.0%)	1098	148 (13.5)	0.44 (0.33–0.58)	< 0.001	0.57 (0.43–0.76)	< 0.001	0.65 (0.48–0.88)	0.005
Q3 (20.2–24.0%)	1145	126 (11.0)	0.55 (0.43–0.72)	< 0.001	0.67 (0.51–0.86)	0.002	0.78 (0.59–1.04)	0.087
Q2 (15.8–20.1%)	1134	91 (8.0)	0.78 (0.61–0.98)	0.036	0.87 (0.69–1.10)	0.253	1.07 (0.84–1.38)	0.577
Q1 (<15.8%)	1113	71 (6.4)	1 (Ref)		1 (Ref)		1 (Ref)	
Continuous (per 5%)			0.80 (0.75–0.85)	< 0.001	0.85 (0.80–0.91)	< 0.001	0.88 (0.82–0.94)	< 0.001
Total REM sleep time	4490	436 (9.7)	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Q4 (>91.5 min)	1105	149 (13.5)	0.37 (0.28–0.50)	< 0.001	0.56 (0.42–0.76)	< 0.001	0.64 (0.45–0.90)	0.010
Q3 (73.6–91.5 min)	1110	130 (11.7)	0.59 (0.46–0.76)	< 0.001	0.71 (0.54–0.91)	0.008	0.79 (0.59–1.06)	0.107
Q2 (54.0–73.5 min)	1162	95 (8.2)	0.78 (0.62–0.99)	0.041	0.85 (0.67–1.08)	0.179	0.94 (0.73–1.21)	0.611
Q1 (<54.0 min)	1113	62 (5.6)	1 (Ref)		1 (Ref)		1 (Ref)	
Continuous (per 5 min)			0.94 (0.92–0.95)	< 0.001	0.96 (0.94–0.97)	< 0.001	0.97 (0.95–0.99)	< 0.001

95% CI, 95% confidence interval; HF, heart failure; HR, hazard ratio; REM, rapid eye movement sleep. Percentage REM sleep quartiles (Q1: <15.8%; Q2: 15.8–20.1%; Q3: 20.2–24.0%; Q4: >24.0%). Total REM sleep time quartiles (Q1: <54.0 min; Q2: 54.0–73.5 min; Q3: 73.6–91.5 min; Q4: >91.5 min). The comparison was made in the participants with and without HF. Ref is referred to the first quantile of percentage REM sleep or total REM sleep time. Multivariable Cox regression analysis adjusted by age, sex, race, education, marital status, smoking status, BMI, alcohol use, caffeine use, benzodiazepine use, hypertension, diabetes mellitus, triglyceride, cholesterol, HDL, sleep duration, T90, and AHI (natural log-transformed).

within the fourth quartile was associated with a lower risk of HF (HR 0.64, 95% CI 0.45–0.90, $P = 0.010$) than in the first quartile (**Table 2**). We also showed the results of final fully adjusted model in our **Supplementary Tables 1**, **2**.

The Association of Rapid Eye Movement Sleep With Myocardial Infarction, Stroke, and Cardiovascular Disease Death

During the follow-up time, 282 cases of MI, 201 cases of stroke, and 238 cases of CVD death occurred. We also explored role of percentage REM sleep and total REM sleep time on the incidence of MI, stroke, and CVD death. Both percentage REM sleep (HR 0.90, 95% CI 0.81–0.99, $P = 0.032$) and total REM sleep time (HR 0.97, 95% CI 0.94–0.99, $P = 0.010$) were associated with decreased risk of CVD death, but not associated with MI and stroke (**Table 3**).

Other Sleep Structure Parameters and Cardiovascular Disease Events

We also investigated the role of sleep characteristics (including time in stage 1, time in stage 2, time in stage 3, percentage stage 1, percentage stage 2, and percentage stage 1) on the incidence of HF, MI, stroke, and CVD death. No significant association was found after adjusting for potential confounding variables (**Supplementary Table 3**).

Subgroup Analysis

We further conducted subgroup analysis stratified by AHI $\geq$ 15 and AHI < 15 events/h and sex (men vs. women) to further explore the role of REM sleep percentage and total REM sleep time on the incidence of HF. The results showed that both percentage and total time of REM sleep were still associated with incident HF in these subgroup analyses

TABLE 3 | Hazard ratios and 95% CIs for REM sleep associated with MI, stroke, and CVD death.

REM traits	CVD events	Event, *n* (%)	REM sleep quartiles				Overall trend (per 5 unit)
			Q1 (low)	Q2	Q3	Q4 (high)	
Percentage REM sleep (%)	MI	282 (6.3)	1 (Ref)	1.03 (0.72–1.46)	0.98 (0.68–1.41)	0.98 (0.67–1.41)	1.01 (0.92–1.11)
	Stroke	201 (4.5)	1 (Ref)	0.86 (0.58–1.29)	0.72 (0.47–1.11)	0.90 (0.60–1.36)	0.95 (0.85–1.05)
	CVD death	238 (5.3)	1 (Ref)	0.75 (0.52–1.08)	0.72 (0.49–1.07)	0.74 (0.50–1.09)	0.90 (0.81–0.99) *
Total REM sleep time (min)	MI	282 (6.3)	1 (Ref)	0.93 (0.65–1.33)	1.05 (0.72–1.52)	1.09 (0.71–1.65)	1.00 (0.98–1.03)
	Stroke	201 (4.5)	1 (Ref)	0.75 (0.50–1.12)	0.78 (0.51–1.21)	0.75 (0.46–1.22)	0.98 (0.96–1.01)
	CVD death	238 (5.3)	1 (Ref)	0.78 (0.54–1.12)	0.74 (0.50–1.10)	0.71 (0.45–1.11)	0.97 (0.94–0.99)#

*95% CI, 95% confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; REM, rapid eye movement sleep. Percentage REM sleep quartiles (Q1: <15.8%; Q2: 15.8–20.1%; Q3: 20.2–24.0%; Q4: >24.0%). Total REM sleep time quartiles (Q1: <54.0 min; Q2: 54.0–73.5 min; Q3: 73.6–91.5 min; Q4: >91.5 min). The comparison was made in the participants with and without individual CVD events (MI, stroke, and CVD death), respectively. Ref is referred to the first quantile of percentage REM sleep or total REM sleep time. Multivariable Cox regression analysis adjusted by age, sex, race, education, marital status, smoking status, BMI, alcohol use, caffeine use, benzodiazepine use, hypertension, diabetes mellitus, triglyceride, cholesterol, HDL, sleep duration, T90, and AHI (natural log-transformed). *$P < 0.05$; #$P < 0.01$.*

(**Supplementary Tables 4**, **5**). Moreover, no significant interaction was found in these analyses (all the $P_{interaction} > 0.05$).

DISCUSSION

In the present study, we utilized a large-scale community-based population from SHHS to investigate the association between REM sleep and incidence of HF. Our study was a cohort-study design and the comparison of percentage REM sleep and total REM sleep time was made in the individuals with and without HF. REM sleep traits including percentage REM sleep and total REM sleep time were monitored by over-night PSG at home. Our multivariable Cox regression analysis demonstrated that middle-aged and older adults with an elevated percentage of REM sleep and total REM sleep time had a reduced risk of incident HF.

Poor lifestyles and behaviors are considered the main causes of negative cardiovascular outcomes (18). Sleep, a basic human behavior, is believed to be related to the risk of CVD and other health outcomes (19, 20). REM sleep is an important aspect of human sleep and often accompanied with vivid dreaming and high level of brain activity, which also has substantial effects on the physiological functions of the individual (21, 22). Previous studies showed that participants with a depressed mood spent less time in REM sleep (23). Besides, decreased REM sleep time in individuals is found to be closely related to worsening cognitive performance (24, 25). Matthews et al. also demonstrated a significant correlation between a lower proportion of REM sleep and a greater sleep/wake ratio of blood pressure (13). Increasing evidences have shown that REM sleep is vital to human health, but there was no evidence regarding the role of REM sleep on the incident HF. In this study, we provided evidences that both increased percentage REM sleep and total REM sleep time were significantly associated with low risk of incident HF. Sleep disordered breathing (SDB) is characterized by abnormal respiration during sleep and may influence the sleep continuity (26). SDB was also closely related to an increased risk of incident HF (27). Azarbarzin et al. found that sleep apnea-specific hypoxic burden was associated with the HF risk (28). We therefore adjusted AHI and T90 in our multivariable Cox regression analysis. Moreover, we performed subgroup analysis stratified by SDB severity (AHI $\geq$ 15 vs. AHI $<$ 15 events/h) to examine whether SDB was potential confounders in the relationship between REM sleep and HF. The results revealed that percentage REM sleep and total REM sleep time were still associated with incidence of HF in subgroup analysis. Our findings indicated that REM sleep traits including percentage REM sleep and total REM sleep time might be marker to predict incident HF.

Previous studies showed that REM sleep is associated with all-cause mortality (11, 12). A decreased percentage of REM sleep was found to be associated with high CVD mortality in the Outcomes of Sleep Disorders in Older Men (MrOS) Sleep Study Cohort, but this relationship was not found in the Wisconsin Sleep Cohort (12). We also explored the role of REM sleep on the MI, stroke, and CVD death. Our results found a significant association of both percentage of REM sleep and total REM sleep time with CVD death based on SHHS, which could support the results of MrOS. However, no significant association was found between REM sleep and incidence of MI and stroke.

Previous studies revealed that the initiation and maintenance of REM sleep was related to the brainstem, forebrain, and hypothalamus (29). Gonnissen et al. showed that the changes of REM sleep time could be caused by circadian misalignment. Besides, reduced REM sleep may be associated with HPA-axis dysregulation and decreased insulin sensitivity (30). Additionally, decreased REM sleep was also found to have a high cortisol concentration (31). We speculate that the abnormal circadian rhythm and neuroendocrine function may contribute to the increased risk of CHF. The underlying biological mechanisms of REM sleep leading to an increased risk of HF still deserved further investigation.

The current study has some strengths. To our knowledge, it is the first to investigate the effect of REM sleep on the incidence of HF. REM sleep, including percentage and total time, was objectively monitored using PSG records, and our findings were based on a large community-based population. Nevertheless, this study also has several limitations. The objects of our analysis were mostly middle-aged and older Caucasian adults; therefore, the generalization of our conclusions to young people and other races merits careful consideration. Second,

objective REM sleep was evaluated using a single-night PSG and may not fully reflect the significant value of REM sleep. Multiple long-term PSG monitoring may provide more accurate sleep parameters. Third, several parent cohorts oversampled snorers to increase the study-wide prevalence of SDB in SHHS. Therefore, our study population could not represent the general community population. Finally, we lack of data such as B-type natriuretic peptide (BNP), kidney function and left ventricular parameters such as ejection fraction, end-diastolic volume and end-systolic volume in the SHHS database that is closely related to the HF. We will investigate the effect of REM sleep on the changes of BNP, renal function and left ventricular function in our following study.

CONCLUSION

Our study provides evidence that increased percentage and total time of REM sleep were associated with a decreased risk of incident HF in middle-aged and older adults. Percentage REM sleep and total REM sleep time may be predictors for the incidence of HF. Monitoring REM sleep to fully understand the nocturnal autonomic nervous activity of people may contribute to prevent HF in the early stages.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://doi.org/10.25822/ghy8-ks59.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Boston University, Case Western Reserve University, Johns Hopkins University, Missouri Breaks Research, Inc., New York University Medical Center, University of Arizona, University of California at Davis, University of Minnesota – Clinical and Translational Science Institute, and University of Washington. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BY and XM raised the idea for the study and handled the supervision in our study. BZ, XJ, JY, QM, LB, ZY, and WW contributed to the study design, writing, and review of the report. BY acquired the data in SHHS and participated in further data analysis. All authors approved the final version of the report.

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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.2022.771280/full#supplementary-material

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Prognostic Power of Pulmonary Arterial Compliance Is Boosted by a Hemodynamic Unloading Test With Glyceryl Trinitrate in Heart Failure Patients With Post-capillary Pulmonary Hypertension

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Background: Pulmonary hypertension (PH) is an established risk factor in patients with heart failure (HF). However, right heart catheterisation (RHC) and vasoreactivity testing (VRT) are not routinely recommended in these patients.

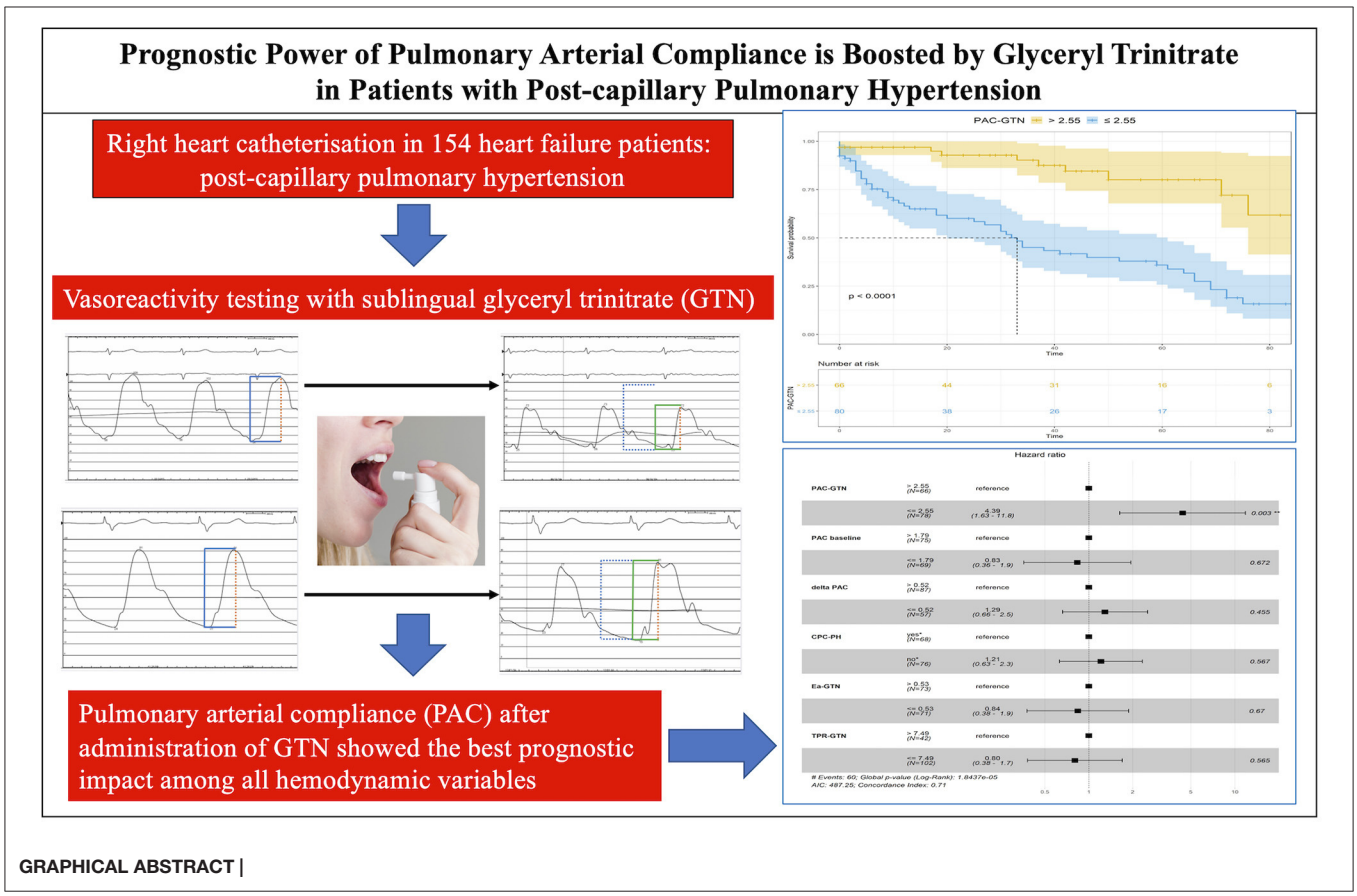
Methods: The primary objective of the present study was to explore the impact of VRT using sublingual glyceryl trinitrate (GTN) on transplant/ventricular assist device-free survival in HF patients with post-capillary PH. RHC parameters were correlated retrospectively with the primary outcome.

Results: The cohort comprised 154 HF patients with post-capillary PH undergoing RHC with GTN-VRT at a tertiary heart failure centre. Multiple parameters were associated with survival. After adjustment for established prognosis-relevant clinical variables from the MAGGIC Score, variables with the most relevant odds ratios (OR) obtained after GTN-VRT were: calculated effective pulmonary arterial (PA) elastance (adjusted OR 2.26, 95%CI 1.30–3.92; $p = 0.004$), PA compliance (PAC-GTN; adjusted OR 0.45, 95%CI 0.25–0.80; $p = 0.006$), and total pulmonary resistance (adjusted OR 2.29, 95%CI 1.34–3.93; $p = 0.003$). Forest plot analysis including these three variables as well as PAC at baseline, delta PAC, and the presence of combined post- and pre-capillary PH revealed prognostic superiority of PAC-GTN, which was confirmed by Kaplan-Meier analysis.

Conclusions: In our cohort of symptomatic HF patients with post-capillary PH, improved PAC after administration of GTN was associated with survival independent

of established hemodynamic and clinical risk factors. VRT using GTN may be better described as unloading test due to GTN's complex effects on the circulation. This could be used for advanced prognostication and should be investigated in further studies.

Keywords: pulmonary arterial compliance, glyceryl trinitrate (GTN), vasoreactivity testing, post-capillary pulmonary hypertension, hemodynamics, prognosis



GRAPHICAL ABSTRACT |

INTRODUCTION

Post-capillary pulmonary hypertension (PH) is an established risk factor in patients with left heart failure (LHF), and those with advanced pulmonary vascular remodeling are known to have worse prognosis than those without. Increased vascular stiffness as a consequence of specific changes in the pulmonary vasculature leads to enhanced right ventricular afterload and right heart failure, which drives mortality in these patients (1). However, there is an ongoing debate concerning which hemodynamic parameters best mirror the extent of fixed pulmonary arterial stiffening and thus best identify patients with poor prognosis. Pulmonary vascular resistance (PVR) and pulmonary arterial compliance (PAC) seem to be the strongest prognostic indices in patients with PH associated with LHF (2–5). However, current guidelines define the subgroup of post-capillary PH with worse prognosis using a combination of PVR >3 wood units (WU) and/or diastolic pressure gradient (DPG) ≥7 mmHg, denoted combined post- and pre-capillary pulmonary hypertension (CpcPH), in contrast to isolated post-capillary pulmonary hypertension (Ipc-PH), which is associated with a slightly better prognosis (6). Recently, a modified classification was proposed, with PVR ≥ 3 WU as a single indicator of CpcPH (7).

Abbreviations: PH, pulmonary hypertension; HF, heart failure; RHC, right heart catheterisation; VRT, vasoreactivity testing; GTN, glyceryl trinitrate; LHF, left heart failure; PVR, pulmonary vascular resistance; PAC, pulmonary arterial compliance; DPG, diastolic pressure gradient; CpcPH, combined post- and pre-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension; TD, thermodilution; SV, stroke volume; TPR, total pulmonary resistance; PA, pulmonary arterial; PP, pulmonary arterial pulse pressure; Ea, effective PA elastance; PAPi, PA pulsatility index; RV, right ventricular; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure.

Isolated hemodynamic measurements are subject to significant spontaneous variations. The use of serial measurements, e.g., after acute vasoreactivity testing (VRT), likely improves hemodynamic prognostication (8, 9). However, in patients with post-capillary PH, VRT is recommended only as a part of the evaluation for heart transplantation, with fixed PH being a potential contraindication because of a particularly high risk for postoperative right heart failure (6, 10). Beyond this scenario, information gained from an acute vasodilator challenge is of uncertain clinical significance, possibly owing to the heterogeneity of vasodilators used for testing in LHF patients, missing standard protocol and the lack of studies on prognostic implications (11). Despite these facts, VRT is part of the standard hemodynamic workup of patients with LHF in several heart failure centres; according to local customs, sublingual glyceryl trinitrate (GTN) may be used as vasodilator (12). GTN as an arterial and venous vasodilator may be advantageous in LHF patients compared with selective pulmonary vasodilators such as inhaled nitric oxide or iloprost, because the latter may lead to an increase of left ventricular filling pressures and pulmonary edema (11).

The purpose of the present study was to explore the association of VRT results using sublingual GTN with outcomes in LHF patients with post-capillary PH. We hypothesized that application of GTN could provide incremental prognostic information by unmasking substantial pulmonary vascular disease.

MATERIALS AND METHODS

Study Population

The study cohort comprised the ongoing, prospectively recruiting Kerckhoff-Klinik HF Registry. The dataset included 154 consecutive patients registered from 10/2009 to 02/2016 who were assessed for heart failure by right heart catheterization (RHC) that included vasoreactivity testing with GTN. Inpatients (n = 85, 55%) were hospitalized because of worsening heart failure (31.8%), acutely decompensated heart failure (28.2%), diagnostic workup for evaluation of dyspnea (23.5%), and suspected pulmonary hypertension (16.5%). Inclusion criteria were a diagnosis of LHF with preserved or reduced left ventricular (LV) function according to current guidelines, availability of sufficient hemodynamic data, mean pulmonary artery pressure (mPAP) >20 mmHg and pulmonary artery wedge pressure (PAWP) >15 mmHg. PAWP between 10 and 15 mmHg at rest was accepted in a few cases (n = 12) if PAWP increased >25 mmHg during exercise or if clear features of left heart disease such as LV hypertrophy, reduced LV function, and/or significant left atrial enlargement were present. All patients included underwent guideline-compliant treatment for HF excluding PH targeted drugs. Exclusion criteria were loss to follow-up (at least one follow-up visit was required apart from the evaluation visit with RHC), severe heart valve stenosis, congenital heart defects, and constrictive pericarditis (**Supplementary Figure 1**).

The investigation conforms with the principles outlined in the Declaration of Helsinki. All patients enrolled in the registry gave written informed consent. Data collection and analyses were approved by the ethics committee of the Faculty of Medicine at the University of Giessen (approval no. 220/15; 26 January, 2016).

Outcomes

The primary outcome measure was defined as survival free from heart transplantation (HTX) and left ventricular assist device (LVAD) implantation. Survival data were obtained through clinically indicated follow-up visits or telephone contact.

Basic Diagnostics

All patients underwent transthoracic echocardiography according to recommendations of the respective guidelines as part of the clinical work-up with determination of left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), estimated systolic pulmonary artery pressure (sPAP), and valve assessment. Baseline laboratory examinations including N-terminal brain natriuretic peptide (NT-proBNP) and estimated glomerular filtration rate (eGFR), based on serum creatinine, were carried out by the respective in-house central laboratory as part of the clinical routine care.

Hemodynamic Assessment and Vasodilator Challenge

RHC was performed in recompensated, stable patients under local anesthesia with insertion of a Swan-Ganz catheter (7F Thermodilution Catheter, Biosensors International, Singapore or Edwards Lifesciences) via the internal jugular vein or a cubital vein as described previously (13). The zero reference level for the pressure transducer was placed at the mid-thoracic level as recommended for the supine position, and all pulmonary pressures were taken at end-expiration and averaged over a minimum of 3 cardiac cycles. Baseline measurements were repeated after 20 min of rest. Those patients able to perform bicycle exercise (n = 90, 58%) were measured again during exercise. Instead of bicycle exercise, volume challenge (passive leg raise) was performed in 17 patients (11%) for additional measurements. After exercise / volume challenge, return to resting values was required for continuation of the examination. If mPAP was >20 mmHg and systolic blood pressure >100 mmHg, GTN was administered sublingually at an initial standard dose of 1.2 mg. GTN administration was repeated according to in-house standard operating procedures. The waiting time for repetition of measurements was a minimum of 5 min. A definition of positive response to GTN challenge was not determined in advance.

Cardiac output (CO) was determined by the thermodilution (TD) technique. The calculated parameters were: stroke volume (SV = CO/heart rate); total pulmonary resistance (TPR = mPAP/CO); pulmonary arterial (PA) pulse pressure (PP = sPAP–dPAP); PA compliance (PAC = SV/PP); effective PA elastance (Ea = (1.65 x mPAP−7.79)/SV) (14); PA pulsatility index (PAPi = PP/RAP); mean right ventricular (RV) power (mPAPxCO); total RV power (1.3 x mean RV power); oscillatory RV power (total–mean RV power) (15). Measurements before GTN administration are referred to as "baseline," after administration as "-GTN," and the difference between the two as "delta."

Statistical Analysis

Data are expressed as mean ± standard deviation or median [interquartile range] for normally or non-normally distributed parameters, respectively. Adherence to a Gaussian distribution was determined using the Shapiro test.

For independent samples, comparison was made with the Independent-Samples Kruskal-Wallis test for non-normally distributed parameters, the Student *t* test for normally distributed parameters, and Fisher's exact test for categorical parameters, as appropriate. For dependent samples, the paired *t* test was used for normally distributed parameters, and otherwise the Wilcoxon signed rank test.

We selected variables with the best predictive value for transplant/LVAD-free survival based on their ability to improve the predictive value of the MAGGIC score variables, an established score for risk prediction in patients with heart failure (16–18). Odds ratios (OR) were calculated based on the z-scores of each variable and are referenced as risk per standard deviation. Receiver operator characteristic (ROC) analysis with the calculated area under the curve (AUC) were used to describe an association of a variable with survival. Based on the results of ROC analysis, optimal cutoff values for prediction of mortality were calculated using the Youden index. Furthermore, based on these cutoff values multivariable Cox proportional hazards models and the Kaplan-Meier method were used for survival analyses. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using either R version 3.6.0 (survival package 3.2-3, survminer package 0.4.8) or GraphPad Prism version 8.4.3 (471).

RESULTS

Baseline Characteristics

This mono-centric analysis included 154 patients (39% female). Median age was 71 (IQR 62–76) years and 75% of the patients presented with symptoms according to NYHA class III. NT-proBNP levels [median 1890 (IQR 973-4182) pg/ml] were markedly elevated. Median LVEF was 45 [25–55]%, and the median TAPSE was 15 mm [12–19]. Classification according to heart failure type was as follows: 74 patients with preserved EF (≥50%), HFpEF; 12 with mid range reduced EF (40–49%), HFmrEF; and 68 with reduced EF (<40%), HFrEF). Duration of heart failure ≥ 18 months was present in 27% of HFpEF, 75% of HFmrEF and 79% of HFrEF patients. In HFpEF patients, 84% had a history of hypertension, 36% had coronary artery disease, 28% suffered from diabetes, 81% had atrial fibrillation, and 2 patients had hypertrophic cardiomyopathy. In HFmrEF patients, the etiology of HF was hypertensive in 33% and ischemic in 25%; 2 patients had dilated and 3 valvular cardiomyopathy. In HFrEF patients, 54% had ischemic etiology, and 34% had dilated cardiomyopathy, 7% valvular cardiomyopathy, 3% hypertensive cardiomyopathy; 1 patient had congenital heart disease.

Nearly all patients (94%) were treated with diuretics; guideline-directed medical therapy was present as indicated. Patients had a high frequency of atrial fibrillation/flutter (73%) and device therapy (51%). Baseline characteristics, also stratified by our PAC-GTN cutoff, are provided in **Table 1**.

Effects of GTN Administration

Median administered GTN dose was 2.4 (IQR 1.6-3.2) mg. GTN vasodilator challenge led to a significant change in most hemodynamic parameters, except heart rate and the PVR/SVR ratio (**Supplementary Table 1***)*. There were no significant side effects of GTN, especially no serious hypotension. Hemodynamics before and after GTN administration, stratified by our PAC-GTN cutoff, are provided in **Table 2**. Comparing survivors with those who died or underwent HTX/LVAD, survivors showed a smaller increase in SV (median +3.11 vs. +6.52 ml) but a markedly larger decrease in PP (−9.0 vs. −3.5 mmHg) and a subsequent larger increase (improvement) in PAC (+0.89 vs. +0.30 ml/mmHg) than those meeting the end point (**Figure 1**). Furthermore, there were numerous differences in response to GTN between these groups.We compared the hemodynamic parameters before and after GTN administration in different types of LHF (HFpEF, HFmrEF and HFrEF). There were no significant differences in baseline PAP. After GTN administration, patients with HFpEF showed the lowest increase in CO and decrease of Ea and systemic vascular resistance, but the largest reduction of PP. Patients with HFrEF had the lowest increase of PAC and decrease of PP, and also lowest fall in systolic blood pressure (**Supplementary Table 2**).

Association of GTN-Dependent Hemodynamics and Outcome

The median follow-up was 30 [8–57] months in our cohort. Within this period 62 (40.3%) patients died, 3 (1.9%) underwent HTX, and 1 (0.6%) underwent LVAD implantation. Overall survival free from HTX and LVAD implantation was 57.2%.

Univariate regression analysis revealed multiple associations between hemodynamic parameters and survival, both at baseline and post-GTN testing. Variables with the best ability to improve the predictive value of the MAGGIC score variables were selected. The components of the MAGGIC-Score are tagged within **Table 1**, and data on the univariate associations and the MAGGIC score are given in **Supplementary Table 3**. The three hemodynamic measures showing the strongest association (lowest adjusted *p*-values in combination with highest AUC) with outcome were Ea-GTN, TPR-GTN, and PAC-GTN, all after GTN challenge.

The areas under the curve (AUC) in the ROC analysis of these parameters (adjusted for the MAGGIC score variables) to discriminate patients with poor outcome were 0.89 (95% CI 0.83-0.95) for Ea-GTN, 0.89 (0.84–0.95) for TPR-GTN, and 0.89 (0.84–0.95) for PAC-GTN. The respective odds ratios (OR) adjusted for the MAGGIC score variables were 2.26 (1.30–3.92) per SD increase ($p = 0.004$) for Ea-GTN, 2.29 (1.34–3.93) per SD increase ($p = 0.003$) for TPR-GTN, and 0.45 (0.25–0.80) per SD increase ($p = 0.006$) for PAC-GTN.

Optimal cut-off values for mortality, calculated using the Youden index, were 0.53 mmHg/ml for Ea-GTN, 7.49 WU for TPR-GTN and 2.55 ml/mmHg for PAC-GTN. The predictive value of these derived cut-off values was compared with the

TABLE 1 | Baseline characteristics.

	Data availability	All $n = 154$	PAC-GTN > 2.55 $n = 66$[§]	PAC-GTN ≤ 2.55 $n = 82$[§]	*p*-Value*
All-cause mortality/HTX/LVAD Median Survival, months	154/154	66 (43)		33	<0.001
GTN dose, mg	151/154	2.4 [1.6–3.2]	2.4 [1.2–3.2]	2.4 [1.6–3.2]	0.324[a]
Female sex[#]	154/154	60 (39)	28 (42)	29 (35)	0.400
Age[#], years	154/154	71.0 [62.0–76.0]	73.0 [63.3–77.0]	68.0 [59.0–75.0]	0.095[a]
Body mass index[#], kg/m^2	154/154	28.9 [25.3–33.4]	31.0 [27.2–34.3]	27.8 [24.1–32.4]	0.003[a]
Smoker[#] (current or within last 6 months)	154/154	12 (7.8)	6 (9.1)	6 (7.3)	0.767
Hypertension[#]	154/154	125 (81.2)	55 (83.3)	65 (79.3)	0.673
Coronary artery disease	154/154	69 (44.8)	26 (39.4)	42 (51.2)	0.185
Atrial fibrillation/flutter	154/154	113 (73.4)	45 (68.2)	62 (75.6)	0.358
Diabetes mellitus[#]	154/154	56 (36.4)	19 (28.8)	35 (42.7)	0.089
Diagnosis of CHF ≥ 18 months[#]	154/154	83 (53.9)	29 (43.9)	53 (64.6)	0.013
COPD[#]	154/154	25 (16.2)	16 (24.2)	9 (11.0)	0.046
Device therapy (ICD or pacemaker)	154/154	78 (50.7)	23 (34.9)	54 (65.9)	<0.001
Aldosterone blocker use	153/154	82 (53.6)	28 (42.4)	48 (59.3)	0.069
ß-Blocker use[#]	153/154	132 (86.3)	59 (89.4)	69 (85.2)	0.470
ACE inhibitor/ARB use[#]	153/154	136 (88.9)	57 (86.4)	73 (90.1)	0.624
Calcium channel blocker use	153/154	27 (17.7)	12 (18.2)	13 (16.1)	0.826
Cardiac glycoside use	153/154	34 (22.2)	8 (12.1)	26 (32.1)	0.006
Diuretic use	153/154	144 (94.1)	63 (95.5)	76 (93.8)	0.732
NYHA class[#]	153/154				
I		4 (2.6)	3 (4.5)	1 (1.2)	
II		27 (17.5)	13 (19.7)	10 (12.2)	
III		114 (74.0)	47 (71.2)	65 (79.3)	0.337
IV		8 (5.2)	2 (3.0)	6 (7.3)	
V'O_2 peak, ml/min/kg	78/154	11.0 [9.6–13.2]	11.9 [10.7–14.3]	9.9 [8.9–12.5]	0.002[a]
Maximum workload, W	78/154	50 [40–60]	60 [40–70]	40 [30–50]	<0.001[a]
GFR[#], ml/min/1.73 m^2	145/154	62.0 [48.1–81.0]	68.6 [53.8–94.7]	58 [44.5–72.0]	0.009[a]
Urea, mg/dl	126/154	54.0 [38.0–78.5]	42.0 [34.8–66.8]	59.0 [44.0–81.0]	0.005[a]
Sodium, mmol/l	145/154	139 [136–141]	140 [138–141]	138 [135–140]	0.008[a]
NT-proBNP, pg/ml	141/154	1,890 [973–4182]	1,137 [602–2405]	3,281 [1732–5165]	<0.001[a]
LVEF[#], %	154/154	45 [25–55]	55 [39–55]	35 [20–55]	<0.001[a]
TAPSE, mm	109/154	15 [12–19]	18 [16–20]	13 [11–16]	<0.001[a]
RVSP, mmHg	131/154	54 [43–66]	49 [39–60]	58 [47–70]	0.004[a]

Data are displayed as count (percentage), or median [interquartile range] except where otherwise indicated. GTN, glycerol trinitrate; HTX, heart transplantation; LVAD, left ventricular assist device; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; ICD, implantable cardiac defibrillator; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NYHA, New York Heart Association; V'O_2 peak, oxygen uptake measured by cardiopulmonary exercise testing; GFR, glomerular filtration rate; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; RVSP, right ventricular systolic pressure derived from tricuspid regurgitation velocity. `PAC-GTN > 2.55 vs. PAC-GTN ≤ 2.55. §Stroke volume and thus PAC after GTN administration was not available in 6 patients. [a]Mann–Whitney U test. All categorical variables were compared using Fisher's exact test. [#]Tagging of the variables used for the MAGGIC-Score.

predictive information of the difference between baseline PAC and PAC-GTN (delta PAC), and established parameters such as PAC (baseline) and the presence of CpcPH (defined by PVR >3 WU and/or DPG ≥ 7 mmHg). In this multivariable analysis, considering several clinical important factors, PAC-GTN was the only independent significant factor associated with survival (**Figure 2**).

Correlation analyses were performed additionally to demonstrate independence of PAC-GTN related to known risk markers. In patients with PAC-GTN >2.55 ml/mmHg, there were the following correlations of PAC-GTN: vs. NT-pro BNP: $r = -0.10$; vs. LVEF: $r = 0.08$; vs. TAPSE: $r = 0.17$ (all p-values > 0.05); and in patients with PAC-GTN ≤ 2.55 ml/mmHg: vs. NT-pro BNP: $r = -0.16$; vs. LVEF: $r = -0.09$; vs. TAPSE: $r = 0.22$; all p-values > 0.05.

This significant finding was the basis for further analyses. PAC-GTN was able to improve the AUC in the ROC analysis of the MAGGIC score to differentiate patients with an unfavorable outcome (**Figure 3**). PAC-GTN and delta PAC were not correlated to the GTN dose administered (Spearman r

TABLE 2 | Hemodynamics at baseline and after GTN administration.

	BASELINE					GTN				
Data availability (D.a.)	**D.a.**	**PAC-GTN > 2.55** ***n* = 66**[§]	**D.a.**	**PAC-GTN ≤ 2.55** ***n* = 82**[§]	***p*-Value***	**D.a.**	**PAC-GTN > 2.55** ***n* = 66**[§]	**D.a.**	**PAC-GTN ≤ 2.55** ***n* = 82**[§]	***p*-Value***
Systolic BP, mmHg	66	134.0 (±25.0)	82	119 [106-136]	0.006[a]	66	124.0 (±22.0)	82	112 [101-128]	0.003[a]
Mean BP, mmHg	66	93 [84–106]	81	88 [80–97]	0.016[a]	65	88.0 (±14.0)	81	82.0 (±12.0)	0.003[b]
Heart rate, beats/min	66	67.0 (±10.0)	82	70.0 (±9.5)	0.098[b]	66	67 [61–73]	82	69 [62–75]	*0.286*[a]
PAWP, mmHg	66	21.0 [18–24]	82	26.0 (±5.0)	<0.0001[a]	66	13.0 [9.0–18.0]	82	20.0 [16.0–24.0]	<0.0001[a]
sPAP, mmHg	66	51.0 (±11.0)	82	68.0 [56–73]	<0.0001[a]	66	35.0 [29–45]	82	55.0 (±13.0)	<0.0001[a]
mPAP, mmHg	66	33.0 (±6.3)	82	41.0 (±6.7)	<0.0001[b]	66	23.0 (±6.0)	82	32.0 (±7.3)	<0.0001[b]
dPAP, mmHg	66	20.0 (±4.8)	82	25.0 (±5.6)	<0.0001[b]	66	*15.0 (±4.7)*	82	19.0 (±5.8)	<0.0001[b]
PP, mmHg	66	30.0 [25.0–37.0]	82	40.0 [32.0–47.0]	<0.0001[a]	66	20.0 [17.0–25.0]	82	36.0 [29.0–42.0]	<0.0001[a]
RAP, mmHg	66	11.0 [7.0–13.0]	82	12.0 [9.0–17.0]	0.009[a]	63	7.0 [5.0–10.0]	71	9.0 (±4.9)	0.056[a]
TPG, mmHg	66	11.0 [8.0–14.0]	81	15.0 [11.0–19.0]	<0.0001[a]	66	9.6 (±3.7)	81	14.0 (±5.3)	<0.0001[b]
DPG, mmHg	66	−0.92 (±4.1)	81	−1.0 [−4.0-3.0]	0.572[a]	66	1.4 (±3.9)	81	0.28 (±5.3)	0.169[b]
CO-TD, l/min	66	5.0 [4.1–5.9]	82	3.7 [3.1–4.5]	<0.0001[a]	66	5.4 (±1.3)	82	4.2 [3.5–5.1]	<0.0001[a]
CI-TD, l/min/m^2	66	2.5 [2.2–2.8]	82	2.0 [1.7–2.3]	<0.0001[a]	66	2.7 (±0.63)	82	2.2 [2.0–2.6]	<0.0001[a]
SV-TD, mL	66	72.0 [62.0–92.0]	82	54.0 [45.0–69.0]	<0.0001[a]	66	77.0 [64.0–91.0]	82	61.0 [49.0–77.0]	<0.0001[a]
PVR, WU	66	2.3 (±0.9)	81	3.6 [2.9–5.4]	<0.0001[a]	66	1.9 (±0.74)	81	3.0 [2.2–4.2]	<0.0001[a]
SVR, WU	66	19.0 [16.0–22.0]	82	24 (±6.5)	<0.0001[a]	66	17.0 [13.0–20.0]	81	20 (±5.3)	0.002[a]
PVR/SVR	66	0.12 [0.08–0.16]	80	0.16 [0.13–0.22]	<0.0001[a]	65	0.11 (±0.05)	80	0.17 (±0.07)	<0.0001[b]
TPR, WU	66	6.6 (±1.5)	82	11.0 [8.8–13.0]	<0.0001[a]	66	4.5 (±1.2)	82	7.6 [6.0–8.9]	<0.0001[a]
PAC, mL/mmHg	66	2.4 [2.1–3.0]	82	1.4 [1.1–1.7]	<0.0001[a]	66	3.5 [3.0–4.5]	82	1.9 [1.4–2.2]	<0.0001[a]
Ea, mmHg/mL	66	0.63 (±0.18)	82	1.0 [0.89–1.4]	<0.0001[a]	66	0.40 (±0.14)	82	0.73 [0.57–0.87]	<0.0001[a]
PAPi	66	3.0 [2.2–4.0]	82	3.3 [2.2–4.8]	0.263[a]	63	3.0 [2.3-4.2]	71	4.3 [3.2–6.3]	<0.0001[a]
RAP/PAWP	66	0.53 [0.40–0.64]	80	0.53 [0.36–0.62]	0.906[a]	63	0.56 [0.42–0.65]	74	0.43 (±0.21)	0.006[a]
RV $power_{oscill}$, W	66	0.11 [0.08–0.13]	82	0.10 [0.08–0.13]	0.524[a]	66	0.08 [0.06–0.11]	82	0.09 [0.07–0.12]	0.093[a]

*Data are displayed as median [interquartile range] or mean (± standard deviation) except where otherwise indicated. GTN, glycerol trinitrate; BP, blood pressure; PAWP, pulmonary arterial wedge pressure; sPAP, systolic pulmonary arterial pressure; mPAP, mean PAP; dPAP, diastolic PAP; PP, pulse pressure; RAP: mean right atrial pressure; TPG, transpulmonary gradient; DPG, diastolic pulmonary gradient; CO, cardiac output; TD, Thermodilution method; CI, cardiac index; SV, stroke volume; PVR, pulmonary vascular resistance; WU, Wood units; SVR, systemic vascular resistance; TPR, total pulmonary resistance; PAC, pulmonary arterial compliance; Ea, pulmonary effective arterial elastance (calculated); PAPi, pulmonary artery pulsatility index; RV, right ventricle; oscill, oscillatory; W, watt. *PAC-GTN > 2.55 vs. PAC-GTN ≤ 2.55. [§]Stroke volume and thus PAC after GTN administration was not available in 6 patients. [a]Mann–Whitney U test. [b]Student's t-test.*

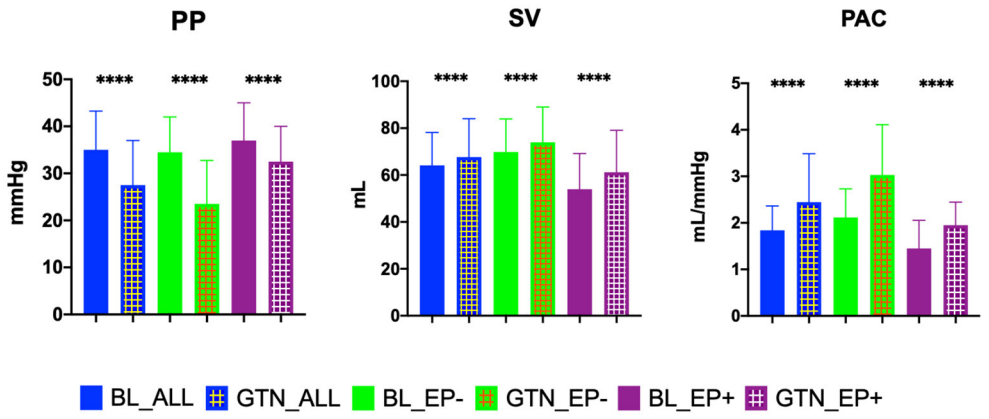


FIGURE 1 | Key hemodynamic parameters at baseline and after glyceryl trinitrate (GTN) application in all patients, in patients who did not reach the endpoint transplant/LVAD free survival (EP-), and in patients reaching the endpoint (EP+). PP, pulse pressure; SV, stroke volume; PAC, pulmonary arterial compliance; BL, baseline. $^{****}P < 0.00001$.

$= -0.14$; $p = 0.09$, and $r = -0.04$; $p = 0.60$). Kaplan-Meier survival analyses confirmed the prognostic power of PAC-GTN. Although presence of CpcPH and baseline PAC were both associated with survival, PAC-GTN was superior in prognostication (**Figure 4**). Kaplan-Meier subgroup analysis in patients with HFpEF and in patients with HFmrEF/HFrEF demonstrated that PAC-GTN was associated with survival in both groups, and the association appeared stronger in HFpEF patients (**Supplementary Figures 2**, **3**). Delta PAC and percentage increase in PAC after GTN administration were also significantly associated with survival (delta PAC: cutoff 0.52 ml/mmHg, $p < 0.0001$; percentage increase in PAC: cutoff 0.23%, $p < 0.0001$; **Supplementary Figures 4**, **5**).

Interestingly, reduction of RV oscillatory power and thus oscillatory load was more pronounced in PAC-GTN >2.55 than ≤2.55 ml/mmHg (median −0.025 vs. −0.010 W; $p < 0.0001$), whereas the extent of PVR reduction was even smaller in PAC-GTN >2.55 than ≤2.55 ml/mmHg (-0.39 vs.−0.78 WU; $p = 0.031$).

To explore whether classification according to PAC-GTN instead of CpcPH would lead to a significant change in prognostication, we performed a reclassification analysis. Seventy-one patients were classified as high risk according to CpcPH criteria; they all had PVR >3 WU, and 8 of them additionally had DPG ≥ 7 mmHg. Hence, DPG did not influence risk stratification. Fourteen of those patients with PVR >3 WU had PAC-GTN > 2.55 ml/mmHg (thus changing from high to low risk), and 24 patients with PVR ≤3 WU had PAC-GTN ≤2.55 ml/mmHg (thus changing from low to high risk). All in all, 38 patients (25%) had different hemodynamic prognostication by either PVR (CpcPH) or PAC-GTN (cut-off).

DISCUSSION

Here we present a comprehensive analysis of the prognostic value of invasive hemodynamics at baseline and after challenge with sublingual GTN in HF patients with post-capillary PH. The relevant findings of our study are as follows: (i) three hemodynamic parameters (PAC, Ea, TPR) obtained after administration of GTN, all of them derived from pressure/flow relationships, showed significant prognostic value; (ii) PAC-GTN was the best prognostic marker, which was superior to established parameters such as PAC (19) and the presence of CpcPH; (iii) PAC-GTN may be a surrogate for a successful reduction of RV oscillatory load.

There are few reports available concerning prognostic implications of VRT in pre-capillary PH (20, 21). In candidates for cardiac transplantation, reversibility of post-capillary PH and thus a better outcome post-transplantation is assumed if TPG decreases to <15 mmHg and/or pulmonary vascular resistance decreases to <3 WU. In other heart failure patients, VRT is currently not recommended, and a consistent protocol is lacking as well as the definition of a positive test result (22, 23). Ghio et al. (24) conducted VRT using intravenous nitrates in 156 heart failure patients with a reduced LVEF and PH and found that survival was significantly reduced in non-responders in contrast to responders. In a study by Al-Naamani et al. (25) VRT did not predict outcome in 73 patients with PH and heart failure with preserved LVEF. Lim et al. (26) described an association of PVR reduction (at least 20%) with survival, and baseline PAC was associated with survival in 98 patients with "mixed" PH. To the best of our knowledge, however, our study is the first to demonstrate a prognostic value of VRT in post-capillary PH independent of the "CpcPH" definition and a predefined, albeit arbitrary definition of "response."

Three factors may have contributed to these new findings: the vasodilator used and its dosage, the measurement methods, and the most suitable hemodynamic parameter. Most drugs used for VRT are more or less selective pulmonary vasodilators that cause a small decrease or even an increase in PAWP, which is undesired in LHF (but nevertheless may result in PVR reduction). GTN decreases PAP and PAWP markedly by provoking venous and also arterial vasodilation, thus lowering pre- and afterload and indirectly increasing subendocardial blood

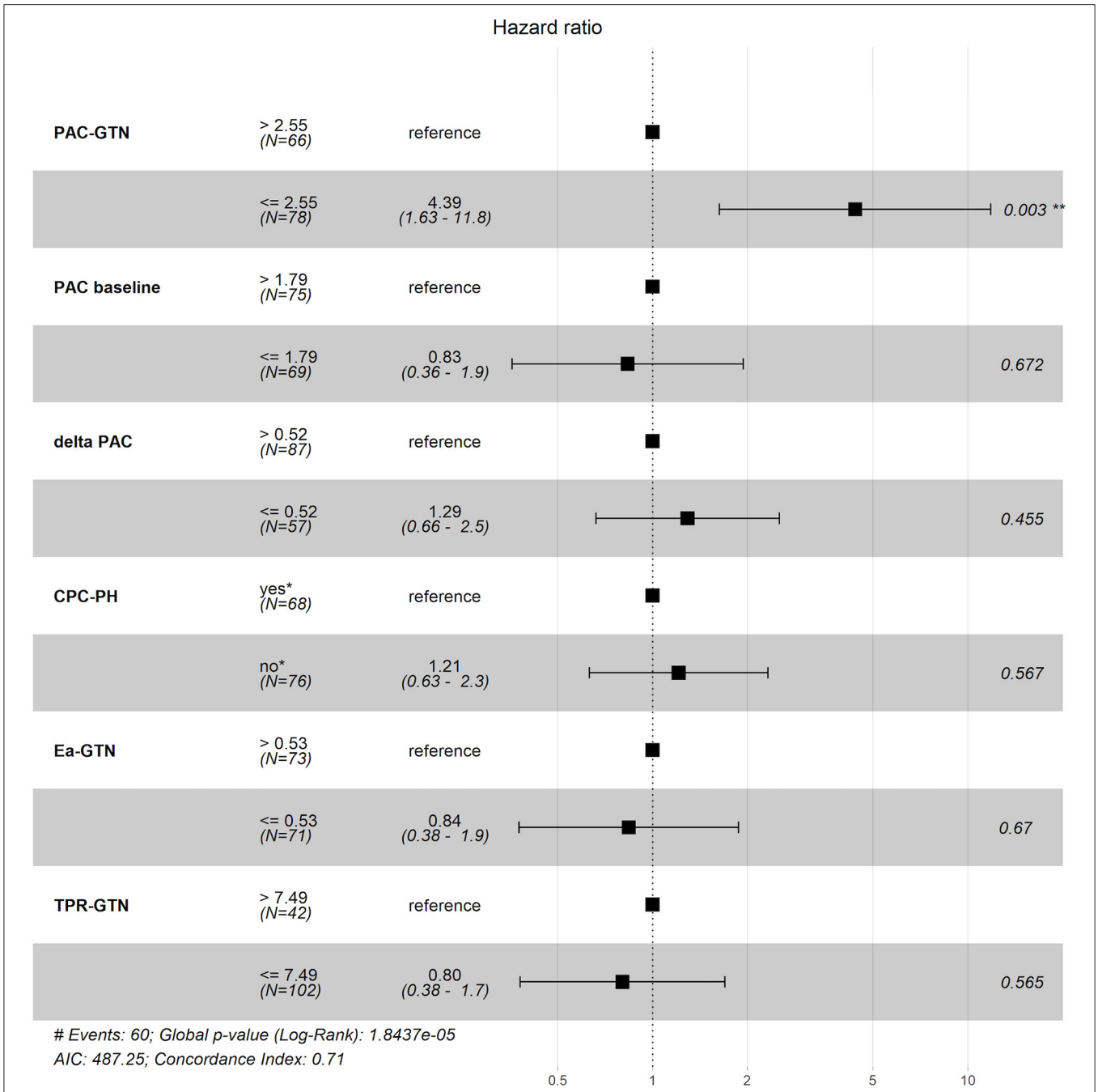


FIGURE 2 | Forest plot of different hemodynamic variables and their impact on prognosis. PAC, pulmonary arterial compliance; CpcPH, combined post- and pre-capillary pulmonary hypertension ("yes," if pulmonary vascular resistance >3 wood units and/or diastolic pulmonary gradient ≥7 mmHg); GTN, glyceryl trinitrate; Ea, pulmonary effective arterial elastance (calculated); TPR, total pulmonary resistance.

flow (11, 27). Therefore, GTN causes much more than pulmonary vasodilation: the whole RV-PA-LV unit is unloaded in a dose-dependent manner. The term "unloading test" would describe these combined effects better than "vasoreactivity test." However, the primary component contributing to improved PAC by GTN in the survivors of our cohort was the decrease in PA pulse pressure rather than an increase in stroke volume. In line with this, PAPi as an index of right ventricular contractility independent of CO measurement (28) did not show prognostic relevance. Pulse pressure after GTN alone was also prognostic, but weaker than PAC-GTN. In our cohort, patients with preserved LVEF showed a larger reduction of pulse pressure in response to GTN than those with reduced LVEF, but a smaller increase of cardiac output.

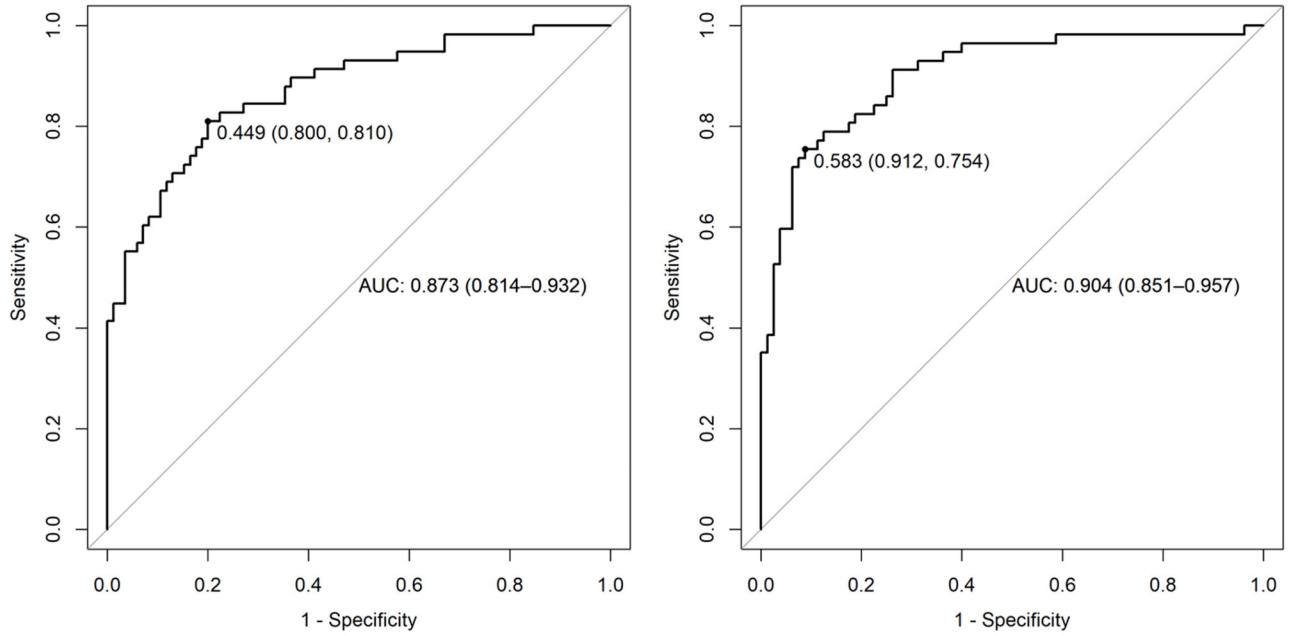


FIGURE 3 | AUC of ROC analysis for prediction of survival. Left panel: variables of the MAGGIC score; right panel: MAGGIC variables and PAC-GTN.

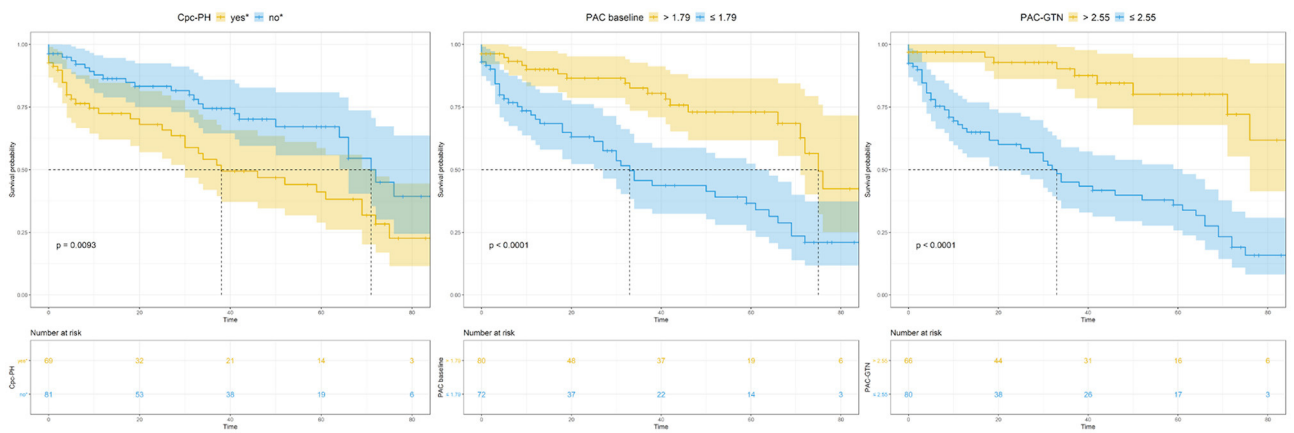


FIGURE 4 | Kaplan-Meier analysis of key variables CpcPH, baseline PAC, and PAC-GTN. CpcPH, combined post- and pre-capillary pulmonary hypertension ("yes," if pulmonary vascular resistance >3 wood units and/or diastolic pulmonary gradient ≥7 mmHg); PAC, pulmonary arterial compliance; GTN, glyceryl trinitrate.

Single hemodynamic measurements may be subject to the bias of situational influences such as vasoconstriction and may mitigate the prognostic power of established hemodynamic indices such as CpcPH. Repeated measurements after vasodilatory challenge and thus ventricular unloading may be advantageous in this context. If unloading does not lead to markedly improved pressure-flow relationships (which are the basis for calculation of the abovementioned three key variables), structural pulmonary vasculopathy may be present.

Our analysis took multiple established prognostic hemodynamic factors into account, and Ea, TPR, and PAC as indicators of RV afterload (29) measured after GTN challenge showed the best associations with prognosis. Among them, PAC-GTN stood out and yielded a clear cut-off value. PAC may be superior to PVR because it "bundles the effects of PVR and left-sided filling pressures on RV afterload." (19) Furthermore, PAC integrates resistive, pulsatile, and passive components of RV afterload and therefore may reflect remodeling of the PA (30). Reduction of the RV oscilllatory load is likely to be the dominant effect of PAC increase in our cohort, for the fall of RV oscilllatory load was markedly more pronounced in the PAC-GTN >2.55 group, and reduction of the steady component of RV load (delta PVR) was relatively weak. RV dysfunction or RV-PA coupling may be better defined by Ea and PAC than by

other parameters (29). However, cut-off values proposed for PAC as a risk marker vary widely (19, 31, 32); repeated measurements after vasodilatory challenge could be a method to obtain a more consistent cut-off value.

Limitations

We included patients with different types of heart failure (HFpEF, HFmrEF and HFrEF), which may be a source of bias. However, the effects of all types are elevated left-sided filling pressures, resulting in post-capillary PH (8). Our analysis of patients with HFpEF vs. HFmrEF/HFrEF confirmed our main results in both groups. Furthermore, 23 patients (12, 5 % of the cohort assessed for eligibility) were lost to follow up, which seems to be within an acceptable range (33).

Conclusions

A hemodynamic unloading test using GTN may improve the prognostic power of PAC in patients with post-capillary PH and should be investigated in further prospective studies. Implications for therapeutic options of patients defined as high risk by this method remain elusive.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Faculty of Medicine at the University of Giessen. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AR, DG, and TK: conception and design, statistical analysis, interpretation of data, and drafting of the manuscript, GZ: acquisition of data. SK, SW, MR, KT, UK, VM, CH, and SR: analysis and interpretation of data and revising the manuscript critically for important intellectual content. All authors: final approval of the manuscript submitted.

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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.2022.838898/full#supplementary-material

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SYSTEMATIC REVIEW
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Comparing Machine Learning Models and Statistical Models for Predicting Heart Failure Events: A Systematic Review and Meta-Analysis

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Objective: To compare the performance, clinical feasibility, and reliability of statistical and machine learning (ML) models in predicting heart failure (HF) events.

Background: Although ML models have been proposed to revolutionize medicine, their promise in predicting HF events has not been investigated in detail.

Methods: A systematic search was performed on Medline, Web of Science, and IEEE Xplore for studies published between January 1, 2011 to July 14, 2021 that developed or validated at least one statistical or ML model that could predict all-cause mortality or all-cause readmission of HF patients. Prediction Model Risk of Bias Assessment Tool was used to assess the risk of bias, and random effect model was used to evaluate the pooled c-statistics of included models.

Result: Two-hundred and two statistical model studies and 78 ML model studies were included from the retrieved papers. The pooled c-index of statistical models in predicting all-cause mortality, ML models in predicting all-cause mortality, statistical models in predicting all-cause readmission, ML models in predicting all-cause readmission were 0.733 (95% confidence interval 0.724–0.742), 0.777 (0.752–0.803), 0.678 (0.651–0.706), and 0.660 (0.633–0.686), respectively, indicating that ML models did not show consistent superiority compared to statistical models. The head-to-head comparison revealed similar results. Meanwhile, the immoderate use of predictors limited the feasibility of ML models. The risk of bias analysis indicated that ML models' technical pitfalls were more serious than statistical models'. Furthermore, the efficacy of ML models among different HF subgroups is still unclear.

Conclusions: ML models did not achieve a significant advantage in predicting events, and their clinical feasibility and reliability were worse.

Keywords: heart failure, prediction model, machine learning, systematic review, statistical model

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INTRODUCTION

Heart failure (HF), as a complex cardiovascular syndrome, causes severe healthcare burdens, and its prevalence continues to increase with the global aging tendency (1). Despite recent improvements in diagnosis and management, HF prognosis remains poor (1, 2), partly because estimating patient risk is difficult (3, 4). Due to this challenge, prediction models are considered a potential tool to help clinicians make informed decisions about treatment initiation and survival estimation to prevent adverse HF events (5).

In recent years, machine learning (ML) models have been suggested to be a revolutionary innovation with the potential to transform the whole healthcare system (6) and have been gradually leveraged to create prognostic prediction models. Concerning this changing trend, existing HF prediction models can be coarsely divided into two categories based on methodologies: statistical and ML models. Although ML models are typically described to have theoretical superiority over statistical models for their ability to fit complex data patterns (7), previous studies arrived at controversial conclusions. Some studies claimed that ML-based methods were indeed better than statistical models (8–10), while others held opposite views (11–13). The conflicting opinions on the superiority of ML models motivated us to review HF prediction models with respect to their methodologies comprehensively to answer two questions. (1) Does ML models obtained better performance in predicting HF events? (2) What are the weaknesses of current ML models?

Of note, previous reviews on HF prediction models generally only focused on their discrimination ability (14–19), while the other factors that may affect model application were usually ignored. In this review, we analyzed two representative prognostic events in HF, all-cause death and all-cause readmission. We compared the c-index of the two types of models and investigated their reliability and clinical feasibility, which may clarify the current position of ML models in the two HF events prediction research and identify directions for future work.

METHODS

We conducted this analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (20) and the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies (CHARMS) (21).

Of note, there is no clear demarcation between the two types of models (7). In this review, statistical models refer to linear models developed by logistic regression or Cox regression or those presented as risk scoring systems. ML models refer to emerging models developed by ML methods only.

Literature Search

We designed a broad literature search strategy to include all articles published in English between 2010 and 2021 by applying a search string to their title, abstract, or keyword sections. Earlier studies were not included due to possible discrepancies in population characteristics and therapy. The search string was "(predict* OR progn* OR "risk assessment" OR "risk calculation") AND "heart failure" AND (model OR algorithm OR score)." ZJS searched Medline, Web of Science, and IEEE Xplore on July 14, 2021, and included 13,301 papers for further analysis.

Selection Procedure

We analyzed two representative prognostic events in HF, all-cause death and all-cause readmission. Articles that reported the development or validation of at least one statistical or ML model for predicting these events with appropriate performance evaluation were included. Models that predicted other outcomes or composite endpoints were excluded. Appropriate performance evaluation indicated that each model should report the c-index in the validation phase. Studies that only reported the c-index of models on the training dataset were excluded. Studies also need to report the 95% confidence interval (CI) of the c-index as well [or sample size and event number such that the 95% CI of the c-index could be calculated approximately (22)]. We excluded models that were not originally designed to predict HF events (e.g., CHA2DS2-VASC) (23). These models may be transferred to predict HF events to highlight associations between other disease processes and HF prognosis.

We conducted a three-phase selection in practice as we have more than 10 thousand papers to review. First, we only reviewed papers via their titles, and the papers whose topic is not predicting the two representative prognostic HF events will be excluded. Then, we reviewed papers according to their abstracts, and the papers which did not report any quantitative metrics will be excluded. Finally, we conducted the full-text review, and only the papers that meet all requirements described above will be reserved. If we cannot identify whether a paper should be included via its title/abstract, we will reserve the paper into the next phase for a more detailed investigation. ZS, HS independently conducted the selection procedure, and the discrepancy was reviewed by HM.

Data Extraction

Three researchers (ZH, WD, and HM) performed data extraction by following recommendations in the CHARMS statement. From all eligible articles, two researchers (ZS, HS) extracted (as applicable) the first author, title, digital object identifier, journal, geographical location, year of publication, study type, model name, data collection manner, patient selection criteria, predictor selection method, missing data processing method, numerical feature processing method, age, gender ratio, sample size, number of events, predicted outcome, follow-up time, c-index, 95% CI of c-index, type of algorithm, and performance validation method. HF subtype was also extracted to take HF heterogeneity into consideration. We also collected the list of predictors to investigate their usage.

Statistical Analysis

We summarized the basic characteristics of the studies with respect to the type of methods and prediction tasks. The summarized characteristics included algorithm, geographical location, admission type (chronic or acute HF), HF type (HF with

reduced ejection fraction, HFrEF, or HF with preserved ejection fraction, HFpEF), publication year, and study type (model development study or validation study). The performances of statistical and ML models were compared from two perspectives: (1) We conducted random effects model based meta-analysis to compare the pooled c-index of the two methodologies for all included studies. The meta-analysis was conducted via MedCalc (24), and I-square is used to evaluate the heterogeneity of meta-analysis. (2) We conducted a "head-to-head" performance comparison for studies that developed both ML models and statistical models, which helped us to explore the performance gain of utilizing ML methods under the same experimental settings.

Risk of Bias Assessment

Three researchers (ZH, WD, and ZH) adopted the Prediction Model Risk of Bias Assessment Tool (PROBAST) to appraise reliability (25). PROBAST evaluates the risk of bias (ROB) of models in four domains: participants, predictors, outcome, and statistical analysis. Each domain contained several ROB signal questions answered with "yes," "probably yes," "no," "probably no," or "no information," and the domains were ranked independently. If answers to all questions in all four domains were "yes" or "probably yes," the model was regarded as "low ROB"; if "yes" to all questions in the four domains, the model was with "high ROB." If a domain contained at least one question that signaled "no information," and no question was answered "no" or "probably no," the domain was graded "unclear ROB." If at least one domain was regarded as unclear and none as high, the model was also graded "unclear ROB."

RESULTS

Characteristics of Models

After screening (**Figure 1**), 280 models from 116 articles were selected, the details of which are shown in **Supplementary Table 1**, **Supplementary Data Sheet**. **Table 1** describes the basic characteristics of the included models, the excluded articles and corresponding reasons were included in the **Supplementary Material** as well. Among all 280 model studies, 68% of the statistical model studies and 95% of the ML model studies were conducted in the last 5 years (2016–2021). The included studies were mainly from North America (41%), Europe (31%), and East Asia (22%). Concerning the outcomes, 205 (73%) models predicted all-cause mortality, and 75 (27%) predicted all-cause readmission. Among the 202 statistical model studies, 101 (50%) studies were model development studies, and 101 (50%) were validation studies of 31 different statistical models, while all ML model studies were model development studies. ML models were grouped into seven types according to the algorithm, where boosting, random forest, and decision tree were the most used methods.

Table 1 also indicates the efficacy of statistical HF models was widely investigated for different patient subgroups, as 33% of statistical models were developed or validated for acute HF patients, 16% for chronic HF patients, 31% for HFrEF patients, 6% for HFpEF patients, 63% for hospitalized patients, and 18% for ambulatory patients. In comparison, most ML models did not consider the heterogeneity of HF. ML models were typically developed using a "general" HF population dataset that identified HF patients by primary diagnoses or international classification of disease (ICD) codes without other inclusion or exclusion criteria. For example, these studies did not take symptoms, left ventricular ejection fraction (LVEF), admission type, and comorbidities into consideration to select a specific HF patient group.

Concerning the predictor usage characteristic, statistical models used significantly fewer predictors than ML models (**Supplementary Figure 1**). Specifically, 93 out of 101 (92%) statistical model development studies reported the number of predictors with the median was 11 (interquartile range, IQR: 6–18), and 76% of studies used less than 20 predictors. All ML model development studies reported the number of predictors; the median was 62 (IQR: 16–516), and 72% of studies used more than 20 predictors. Sixty-six (67%) statistical models reported a detailed list of predictors, while only 36 (46%) ML model development studies reported a detailed list of predictors. The predictor usage details can be found in **Supplementary Figure 2**.

Performance Comparison

Figure 2 describes the performance comparison result of the models. As shown in **Figure 2A**, the pooled c-index of statistical models in predicting all-cause mortality, ML models in predicting all-cause mortality, statistical models in predicting all-cause readmission, ML models in predicting all-cause readmission were 0.733 (95% CI 0.724–0.742), 0.777 (0.752–0.803), 0.678 (0.651–0.706), and 0.660 (0.633–0.686), respectively. The meta-analysis indicated that the ML model only outperformed the statistical model in predicting all-cause mortality. In contrast, their performance in predicting all-cause readmission was worse than the statistical model. Of note, the predictive ability across all studies exhibited substantial heterogeneity. Even when these characteristics were incorporated in the meta-regression model or multi-level meta-analysis model, heterogeneity remained high and essentially unchanged. Since the substantial heterogeneity of the included models did not permit reliable comparison of performance by meta-analysis, the result of meta-analysis can only be interpreted carefully within the context.

Figures 2B,C describe the result of the head-to-head comparison, which compares the performance differences of ML models and statistical models trained by same dataset. We found 60 valid comparison pairs, of which ML models achieved better performance in 39 (65%) pairs, and the superiority reached statistical significance in 22 (37%) pairs. In the task-specific comparison, we observed that ML models had a substantial advantage in predicting all-cause mortality, which accords to the result of the meta-analysis. ML models obtained better performance in two-thirds of the pairs, and the advantage was statistically significant in half of the pairs. ML models achieved similar performance compared to statistical models in predicting all-cause readmission. In the method-specific comparison, deep neural networks, boosting, multi-layer perceptron, support vector machine (SVM), and random forest (RF) were more likely

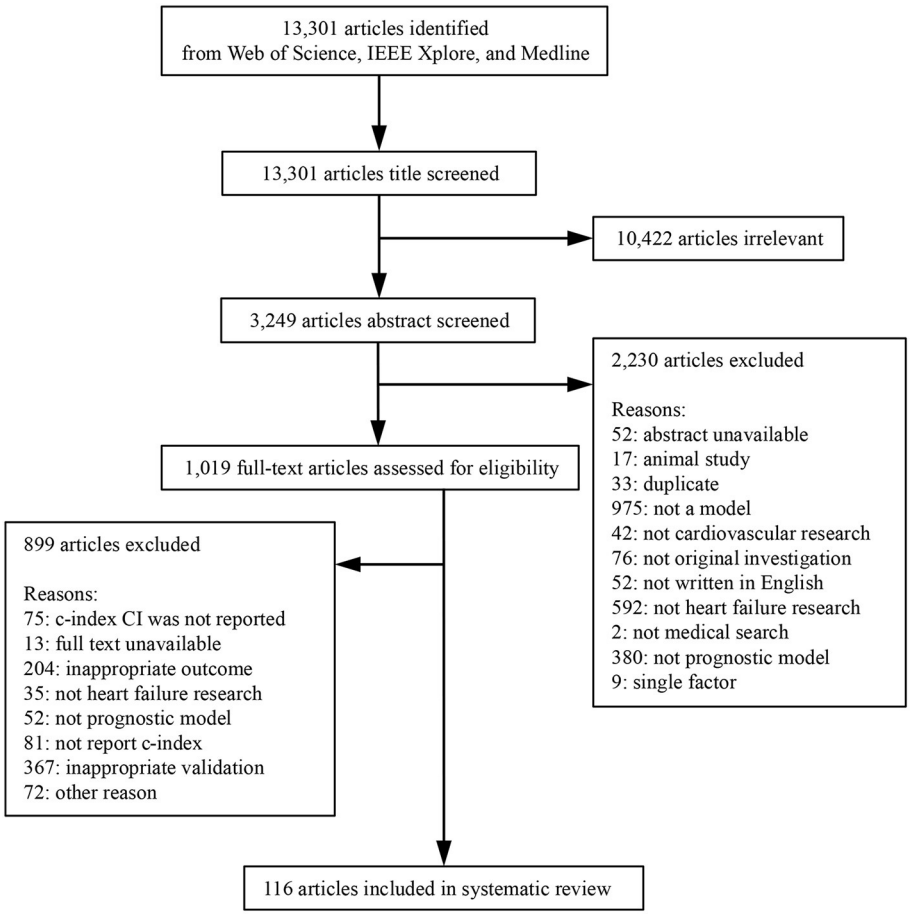

FIGURE 1 | Literature selection procedure.

to achieve better performance than statistical models, while decision tree and other ML algorithms achieved comparable or even worse performance.

Risk of Bias Assessment

Figure 3 describes the ROB of both statistical and ML models. Among 202 statistical models and 78 ML models, only 19 statistical and 2 ML models were graded as low ROB, 18 statistical models were graded as unclear ROB, while all remaining models were graded as high ROB, indicating that most prediction models have technical pitfalls. The measured ROB was mainly from the participant and analysis domains. In PROBAST, models derived from retrospective data were treated as high participants ROB, and 103 (51%) statistical and 55 (70%) ML models were developed or validated with a retrospective dataset. One hundred and sixty-five (82%) statistical and 76 (97%) ML model studies did not conduct appropriate statistical analysis or reported incomplete statistical analysis information. Specifically, 22 (11%) statistical and 54 (69%) ML models were developed or validated from an insufficient number of participants. Thirty-seven (36%) statistical and 21 (27%) ML models categorized continuous predictors, which caused unnecessary loss of information (25). While 52 (26%) statistical and 24 (31%) ML models used high-risk imputation methods, 65 (32%) statistical and 35 (45%) ML models did not report data imputation in detail. To select predictors, 31 (31%) statistical and 9 (12%) ML models used univariate analysis. Although the univariate analysis is a widely adopted method, its use has been discouraged recently (26). One hundred and three (51%) statistical and 62 (80%) ML models did not conduct (or conducted inappropriate) calibration evaluation. Thirty-five (35%) statistical and 34 (44%) ML models used random split or non-random split, rather than more reliable bootstrap and cross-validation, to evaluate the discrimination ability of models.

DISCUSSION

Discrimination Ability

Different from the conclusion of previous reviews (17), our analysis indicated that the performance of ML models is not consistently better than statistical models in predicting HF prognostic events. The superiority of ML models significantly relies on specific experimental environments, i.e., prediction events, population characteristics, and selected algorithms. The

TABLE 1 | Model characteristics.

	Overall	Statistical model		Machine learning model			
	280 models	Overall 202 models	Mortality 158 models	Readmission 44 models	Overall 78 models	Mortality 47 models	Readmission 31 models
HF type							
Acute HF	73 (26%)	66 (33%)	62 (39%)	4 (9%)	7 (9%)	6 (13%)	1 (3%)
Chronic HF	32 (11%)	32 (16%)	25 (16%)	7 (16%)	0 (0%)	0 (0%)	0 (0%)
Not specified	175 (62%)	104 (51%)	71 (44%)	33 (75%)	71 (91%)	41 (87%)	30 (97%)
LVEF							
HFrEF	65 (23%)	62 (31%)	55 (35%)	7 (16%)	3 (4%)	3 (6%)	0 (0%)
HFpEF	23 (8%)	13 (6%)	11 (7%)	2 (5%)	10 (13%)	10 (21%)	0 (0%)
Not specified	192 (69%)	127 (63%)	92 (58%)	35 (80%)	65 (83%)	34 (72%)	31 (100%)
Admission type							
Inpatient	172 (61%)	127 (63)	98 (62%)	29 (66%)	45 (58%)	25 (53%)	20 (65%)
Outpatient	45 (16%)	37 (18%)	32 (20%)	5 (11%)	8 (10%)	8 (17%)	0 (0%)
Other *	63 (22%)	38 (19%)	28 (18%)	10 (23%)	25 (32%)	14 (30%)	11 (35%)
Region							
North America	116 (41%)	72 (36%)	47 (30%)	25 (57%)	44 (56%)	27 (57%)	17 (55%)
Europe	88 (31%)	78 (39%)	67 (42%)	11 (25%)	10 (13%)	2 (4%)	8 (26%)
East Asia	61 (22%)	40 (20%)	35 (22%)	5 (11%)	21 (27%)	18 (38%)	3 (10%)
Others	15 (5%)	12 (6%)	9 (6%)	3 (7%)	3 (4%)	0 (0%)	3 (10%)
Algorithm							
Cox regression	64 (23%)	64 (32%)	58 (37%)	6 (14%)	/	/	/
LR	61 (22%)	61 (30%)	31 (20%)	30 (68%)	/	/	/
Score	77 (28%)	77 (38%)	69 (44%)	8 (18%)	/	/	/
RF	11 (4%)	/	/	/	11 (14%)	7 (15%)	4 (13%)
Boosting	17 (6%)	/	/	/	17 (22%)	11 (23%)	6 (19%)
SVM	7 (3%)	/	/	/	7 (9%)	5 (11%)	2 (6%)
Neural network **		/	/	/			
Multi-layer perceptron	7 (3%)	/	/	/	7 (9%)	5 (11%)	2 (6%)
Deep learning	8 (3%)	/	/	/	8 (10%)	2 (4%)	6 (19%)
Decision tree	10 (4%)	/	/	/	10 (13%)	8 (17%)	2 (6%)
Others	18 (6%)	/	/	/	18 (23%)	9 (19%)	9 (29%)
Year of publication							
2010–2015	69 (25%)	65 (32%)	50 (32%)	15 (34%)	4 (5%)	2 (4%)	2 (6%)
2016–2021	211 (75%)	137 (68%)	108 (68%)	29 (66%)	74 (95%)	45 (96%)	29 (94%)
Study type							
Model development	179 (64%)	101 (50%)	71 (45%)	30 (68%)	78 (100%)	47 (100%)	31 (100%)
Model validation	101 (36%)	101 (50%)	87 (55%)	14 (32%)	0 (0%)	0 (0%)	0 (0%)

Values are presented as numbers.

**"Others" indicates that studies did not specify the origin of patients, or patients have mixed origins.*

***The deep learning model refers to recently proposed neural network-based models (e.g., recurrent neural nets and autoencoder) apart from simple multi-layer perceptron.*

HF, heart failure; HFpEF, heart failure with preserved ejection fraction;HFrEF, heart failure with reduced ejection fraction; LVEF. left ventricular ejection fraction.

meta-analysis result indicated ML models obtained better performance in predicting all-cause mortality, while their performance was worse in predicting all-cause readmission. The head-to-head analysis indicated that ML models achieved similar or worse performance in about one-third of pairwise cases even in exactly the same experimental settings. For the cases where ML models achieved better performance, their superiority is probably not statistically significant. We also found not all ML algorithms were superior to statistical models. Specifically, ensemble learning-based models (boosting and RF) and neural network-based models (multi-layer perceptron and deep learning) achieved better performance, while decision tree and support vector machines generally achieved worse performance than statistical models. This finding is in accordance with the consensus in the computer science community (27, 28).

According to these results, we argue that the expectation of leveraging ML has not yet been fulfilled. ML models were suggested to transfer their computer vision and natural language processing success, thereby transforming medicine (6). Although we cannot precisely summarize the performance of statistical

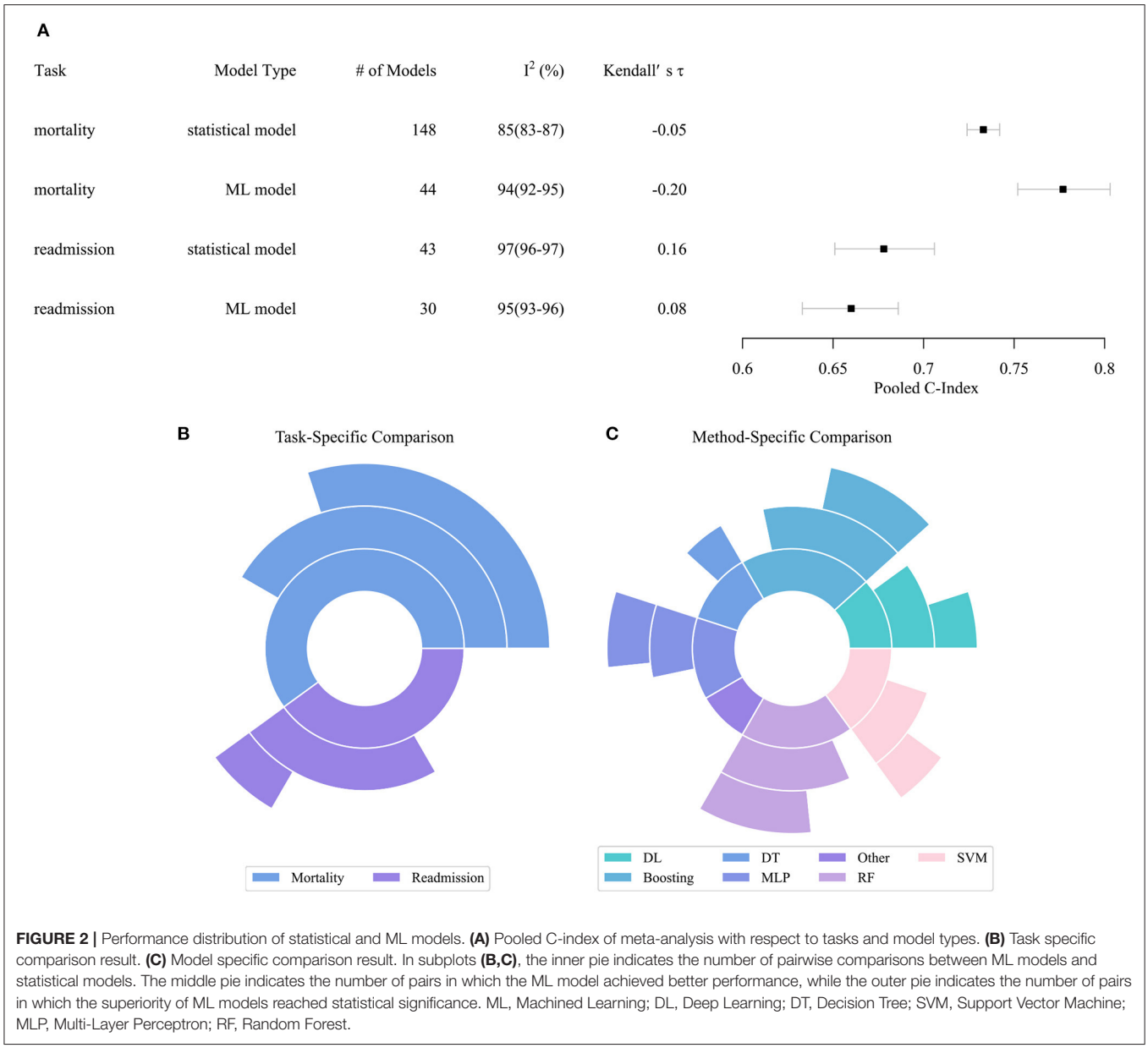

FIGURE 2 | Performance distribution of statistical and ML models. **(A)** Pooled C-index of meta-analysis with respect to tasks and model types. **(B)** Task specific comparison result. **(C)** Model specific comparison result. In subplots **(B,C)**, the inner pie indicates the number of pairwise comparisons between ML models and statistical models. The middle pie indicates the number of pairs in which the ML model achieved better performance, while the outer pie indicates the number of pairs in which the superiority of ML models reached statistical significance. ML, Machined Learning; DL, Deep Learning; DT, Decision Tree; SVM, Support Vector Machine; MLP, Multi-Layer Perceptron; RF, Random Forest.

and ML models in event prediction due to their heterogeneity, ML models clearly achieved at most moderately better or comparable performance compared to statistical models. This degree of improvement is unlikely to trigger a revolution in HF event prediction.

However, the potential of ML models still warrants further investigation for two reasons. First, current ML studies did not take full advantage of the data being analyzed. ML models typically require a large training dataset to become efficient and avoid overfitting. However, our ROB analysis showed about three-quarters of ML models were developed using insufficient numbers of participants, as their event per variable rate was less than 10 (29). ML models were also more likely to be trained by low-quality electronic health record datasets, which also negatively affected their performance. Meanwhile, as HF is a chronic syndrome, longitudinal clinical patient data usually accumulate, including treatment, laboratory tests, and image information generated over the entire HF management process. It is worth investigating how to extract information from longitudinal sequential datasets to achieve better event prediction performance, and only ML algorithms are capable of handling this task (30). Second, the performance of ML models was not sufficiently validated. Notably, about half of the statistical model studies were validation studies, whereas no ML models were externally validated. As model performance typically degenerates upon validation, the performance of current ML models is probably overestimated, but to what degree is unclear.

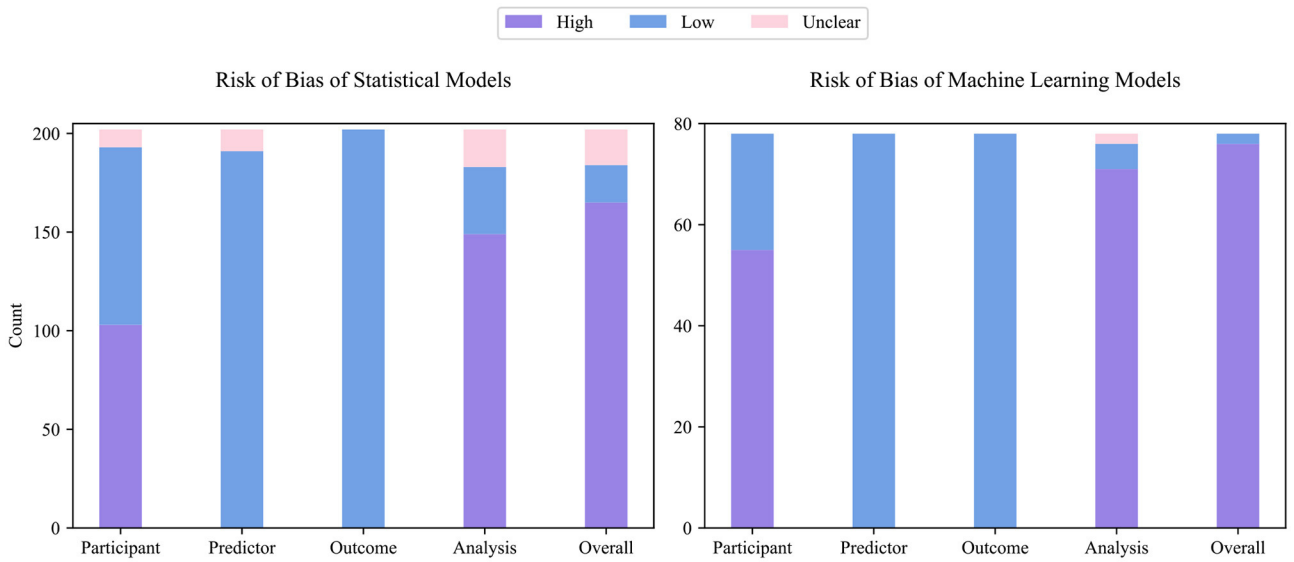

FIGURE 3 | Result of risk of bias analysis.

Model Reliability

This review revealed two reliability issues of ML models, the first being neglect of HF heterogeneity. As a complex syndrome, HF prognosis varies widely among different patient subgroups (19). We observed statistical model studies generally identified this situation and applied a detailed sample inclusion procedure to select the target population before developing or validating a model. Therefore, the efficacy of statistical models in each HF subgroup, e.g., HFrEF, HFpEF, acute HF, and chronic HF, has already been investigated. On the contrary, ML models were typically developed using a "general" HF patient group without clear inclusion criteria and only reported overall performance metrics. The subgroup-specific performance of ML models is currently unclear, which undoubtedly influenced the reliability of ML models in our study. The efficacy of ML models in different HF patient subgroups needs to be investigated in future studies.

Secondly, the PROBAST analysis indicated both types of models have technical flaws. The issues affecting ML models were more serious and can be coarsely summarized to four points. Insufficient information disclosure was the first flaw. PROBAST analysis demonstrated that most statistical and ML models did not report sufficient statistical analysis information, and no ML models reported enough details for model reproduction. Inappropriate statistical analysis was the second flaw. ML models systematically did not perform calibration analysis, which may lead to inaccurate evaluation of event risk. Meanwhile, the training dataset of a large fraction of ML studies was too small to optimize parameters satisfactorily. Third, it is worth noting that adopting ML methods and proposing low ROB models were sometimes controversial. For example, as ML models usually require a large dataset for training, the time cost of imputing missing data via multiple imputation algorithms usually becomes intolerable. In fact, ML studies typically use mean-value imputation or a separate category to tackle the missing data problem, which inevitably brings ROB to ML models and makes them untrustworthy. Lack of external validation was the fourth flaw. More than half of statistical model studies were validation studies, while no ML model was externally validated by independent studies. ROB analyses indicated that the lack of a practical guideline in ML model development and validation is a big challenge. Such a guideline could help tackle a series of tasks in ML model development (i.e., data collection, pre-processing, performance evaluation, and model releasing), and thereafter provide a feasible path for developing reliable ML models, rather than just adopting a particular ML algorithm to fit a clinical dataset.

Clinical Feasibility

Our analysis indicated that the clinical feasibility of ML models was low due to immoderate usage of predictors and lack of computer infrastructure, which may explain why no ML model was externally validated. Current ML development studies usually waived the predictor selection process, which is essential to developing statistical models. As a result, ML models included on average eight times the number of predictors used in statistical models; some even used more than 1,000 predictors. Although the inclusion of more information was regarded as an advantage of ML-based models (31), it makes the model prone to overfit. Furthermore, with more predictors to be evaluated, the inclusion of a large number may limit the clinical utility of models. ML models require a feature selection protocol to effectively utilize more patient information in order to make a precise prediction and determine clinical feasibility.

The complexity of the ML algorithm and the number of used predictors indicated that it is impossible to calculate the model manually. A comprehensive pipeline, including data collection, pre-processing, model invocation, and results display needed to execute a model in real-time. The development of the pipeline

requires mass interdisciplinary collaboration, and the pipeline needs to be elaborately integrated into the current clinical decision support system. As the development and deployment of such a pipeline are obviously beyond the ability of most hospitals, ML models are difficult to be applied in clinical practice. An updated medical decision-making system is required to facilitate the deployment of ML models in the clinical workflow.

Strengths and Limitations of This Study

The major strength of this study was that we analyzed the clinical feasibility and reliability of statistical and ML models, which were not systematically investigated in the previous review (14–19). The large number of studies used to compare different ML and statistical models was another major strength. However, this study also had several limitations. (1) The heterogeneity among studies impeded us from conducting rigorous performance comparisons of the two types of models. (2) We did not conduct an analysis on the calibration of models, as most studies did not report calibration information or conducted inappropriate calibration. (3) We only analyzed for all-cause mortality events, due to the lack of relevant studies examining all-cause readmission. Findings in this review may not be generalizable to other outcomes or settings.

CONCLUSION

In summary, our review indicated ML models did not show the ability to revolutionize the process of predicting prognosis, and due to lack of external validation, their performance is probably overestimated. It seems the increased complexity of ML models did not bring significantly better performance. However, we argue it is still too early to claim that introducing ML technique in heart failure event prediction task is as meaningless. Because applying ML technique in medicine is an emerging research area and pioneer studies may be immature. Substantial effort is required in the future to explore how to utilize ML technology to achieve precise event prediction and overcome the difficulties in deploying ML models in clinical environments.

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

ZS, WD, and ZH were involved in the conception and design of the review, developed the search strategy, and performed the study selection. ZS and HS extracted data from the included studies and were involved in the data analysis. ZS, WD, ZH, LC, and HM were involved in the interpretation and discussion of results. All authors drafted the manuscript, contributed to the drafting of the review, and revised it critically for important intellectual content.

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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.2022.812276/full#supplementary-material

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ORIGINAL RESEARCH
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Mortality Risk Prediction Dynamics After Heart Failure Treatment Optimization: Repeat Risk Assessment Using Online Risk Calculators

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Objectives: Heart failure (HF) management has significantly improved over the past two decades, leading to better survival. This study aimed to assess changes in predicted mortality risk after 12 months of management in a multidisciplinary HF clinic.

Materials and Methods: Out of 1,032 consecutive HF outpatients admitted from March-2012 to November-2018, 357 completed the 12-months follow-up and had N-terminal pro-B-type natriuretic peptide (NTproBNP), high sensitivity troponin T (hs-TnT), and interleukin-1 receptor-like-1 (known as ST2) measurements available both at baseline and follow-up. Three contemporary risk scores were used: MAGGIC-HF, Seattle HF Model (SHFM), and the Barcelona Bio-HF (BCN Bio-HF) calculator, which incorporates the three above mentioned biomarkers. The predicted risk of all-cause death at 1 and 3 years was calculated at baseline and re-evaluated after 12 months.

Results: A significant decline in predicted 1-and 3-year mortality risk was observed at 12 months: MAGGIC ∼16%, SHFM ∼22% and BCN Bio-HF ∼15%. In the HF with reduced ejection fraction (HFrEF) subgroup guideline-directed medical therapy led to a complete normalization of left ventricular ejection fraction (≥50%) in almost a third of the patients and to a partial normalization (41–49%) in 30% of them. Repeated risk assessment after 12 months with SHFM and BCN Bio-HF provided adequate discrimination for all-cause 3-year mortality (C-Index: MAGGIC-HF 0.762, SHFM 0.781 and BCN Bio-HF 0.791).

Conclusion: Mortality risk declines in patients with HF managed for 12 months in a multidisciplinary HF clinic. Repeating the mortality risk assessment after optimizing the HF treatment is recommended, particularly in the HFrEF subgroup.

Keywords: heart failure, mortality, risk models, risk prediction, prognosis

INTRODUCTION

Contemporary management of heart failure (HF) has significantly improved over the past two decades, leading to better prognosis (1). Periodic re-evaluation of the risk of death from HF, which may fluctuate, especially in the first few years of the disease, has become increasingly important for optimal patient care. The addition of biomarkers to clinical scores better reflects the pathophysiological pathways in HF and may improve the detection of changes in mortality risk over time. Consistent evidence has linked N-terminal pro B-type natriuretic peptide (NTproBNP), a marker of myocardial stretch, to increased risk of all-cause mortality in patients with HF (2, 3). High sensitivity troponin T (hs-TnT) is a marker of myocyte injury and a strong and independent predictor of all-cause and cardiovascular mortality in HF (4). Finally, interleukin-1 receptor-like 1, known as ST2 (5), reflects myocardial fibrosis and remodeling and has been strongly associated with worsening left ventricular ejection fraction (LVEF) over time (6). Despite the development of several prognostic risk models for HF in the past few years, only some have been externally validated and few include cardiac biomarkers.

Risk prediction models are used in HF to aid clinicians in assessing patient prognosis. Ultimately, they improve the appropriateness and timing of disease-modifying treatments. Previous studies have mainly focused on a single initial risk evaluation, but HF is a non-stable disease. During the first year of HF management, major medication/device changes occur, which lead to substantial alterations in LVEF, functional class, diuretic dose, biomarkers and ultimately life-time survival. Thus, it may be of particular interest to recalculate mortality risk after an initial period of HF management.

The purpose of this study is to asses changes in the predicted mortality risk after a 12-month management period in a multidisciplinary HF unit.

We used three contemporary web-based risk scores: Meta-Analysis Global Group in Chronic HF (MAGGIC-HF) (7) (http://www.heartfailurerisk.org/) and the Seattle HF Model (SHFM) (8) (https://depts.washington.edu/shfm), which include clinical variables, treatments, and blood tests, and version 2.0 of the Barcelona Bio-HF Risk Calculator (BCN Bio-HF) (9, 10) (http://ww2.bcnbiohfcalculator.org), which also includes NTproBNP, hs-TnT, and ST2.

MATERIALS AND METHODS

Study Population and Follow-Up

All consecutive ambulatory patients with HF of different etiologies who were admitted to a structured multidisciplinary HF clinic at a University Hospital between March 2012 and November 2018 were eligible for this study. Patients who completed a 1-year follow-up and had NTproBNP, hs-TnT, and ST2 measurements available at baseline and 12 months were included in the study. Baseline information was obtained at the first visit in the outpatient HF Unit. Patients were referred to the HF clinic mostly by cardiology or internal medicine departments, and to a lesser extent by emergency or other hospital departments. The criteria for referral to the clinic were HF according to the ESC definition, with at least one hospitalization and/or reduced systolic function, as described previously (11). For follow-up, all patients regularly visited the HF clinic and were treated according to a unified protocol. Follow-up visits comprised a minimum of quarterly visits with a nurse, one visit with a physician (cardiologist, internist, or family physician) every 6 months, and optional visits with specialists in geriatrics, psychiatry, rehabilitation, endocrinology, or nephrology.

During the baseline visit, patients provided written consent for the use of their clinical data for research purposes. Demographic, clinical, echocardiographic, and analytical data were recorded in the REGI-UNIC database. Data that were not routinely recorded in that database were obtained by reviewing electronic patient health records.

Outcomes

Change in the risk of all-cause death was the main endpoint for comparing the different risk calculators. Risk of all-cause death at 1 and 3 years was calculated at baseline and re-evaluated after a 12-month follow-up period. Follow-up was closed on 30 September 2021. Fatal events were identified by reviewing the patient health records from hospital wards, the emergency room, and general practitioners or by contacting their relatives. Data were verified with the databases of the Catalan and Spanish Health Systems and the Spanish National Death Index (INDEF).

The study was performed in compliance with the laws that protect personal data and the international guidelines on clinical investigations from the World Medical Association's Declaration of Helsinki. The local ethics committee approved the study.

Biomarker Assays

All samples were obtained between 9:00 am and 12:00 pm. The three biomarkers were analyzed from the same blood sample: NTproBNP from a fresh plasma sample and hs-TnT and ST2 from serum stored at −80°C without previous freeze-thaw cycles. NTproBNP levels were determined by an immuno-electrochemiluminescence assay on the Modular Analytics E 170 instrument (Roche Diagnostics, Switzerland). This assay had <0.001% cross-reactivity with bioactive BNP. The assay had inter-run coefficients of variation ranging from 0.9 to 5.5%. Since 2016, NTproBNP and hs-TnT have been determined by electrochemiluminescence immunoassays on a Cobas E601 platform (Roche Diagnostics, Switzerland). ST2 was measured by immunoturbidimetry using the SEQUENT-IA reagent kit (Critical Diagnostics, Ireland) and an AU-5800 platform (Bekman Coulter, Ireland).

Statistical Analysis

Categorical variables were expressed as absolute numbers and percentages. Continuous variables were expressed as the mean ± standard deviation (SD) or the median and interquartile range (IQR [Q1–Q3]) according to normal or non-normal data

distributions. Normal distributions were assessed with normal Q–Q plots. Between-group comparisons were performed using McNemar test for paired categorical variables and the paired Student's *t*-test or Mann-Whitney *U* test for continuous variables as appropriate. Missing values were treated by imputing the median values.

Risk of all-cause death at 1 and 3 years year was calculated at baseline with the three online calculators and then re-evaluated after a 12-month follow-up period. The Wilcoxon matched-pairs signed-rank test was used to assess changes in mortality risk due to the much skewed distribution of predicted risks. A meaningful difference in the score was defined as at least a 1% absolute change in the estimated value to enter into the increased or decreased categories. Cohen's kappa coefficient was used to measure inter-score reliability when categorizing patients into the three groups of change in risk of death: one group included patients who presented an increase in mortality risk, another one patients who presented a decrease in mortality risk, and the third patients whose risk did not meaningfully changed.

Statistical analyses were performed using SPSS 24 software (SPSS Inc., Chicago, IL, USA), STATA V.15.1 software (StataCorp, College Station, Texas, USA), and R software (A Language and Environment for Statistical Computing) distributed by the R Core Team (2017; R Foundation for Statistical Computing, Vienna, Austria). A two-sided $p < 0.05$ was considered significant.

RESULTS

A total of 1,032 consecutive patients were admitted to the HF clinic during the inclusion period. Of these patients, 935 were alive after 1 year and 578 patients were excluded because they lacked an NTproBNP, hs-TnT, or ST2 measurement at baseline or 12 months.

Our final cohort included 357 patients. None of the patients included in this study had participated previously in the BCN Bio-HF derivation cohort. **Supplementary Table 1** compares included and excluded patients.

Clinical and Demographic Characteristics of the Study Population

The patients included were predominantly men, aged 65.2 ± 12.3 years, with reduced LVEF (37.8 ± 13.6%), and mostly classified as NYHA class II (75.4%). Ischaemic heart disease was the most prevalent etiology (37.3%). Contemporary HF treatment was optimized according to international guidelines. **Table 1** provides the demographic, clinical, biochemical, and echocardiographic characteristics and treatments of the studied cohort at baseline and after 12 months of follow-up.

Supplementary Table 2 shows the number and management of missing values in the study cohort. The estimated Kaplan-Meier mortality at 1, 2 and 3 years was 4.2, 8.1 and 15.7%.

Left Ventricular Ejection Fraction Trajectories

There was a marked improvement in LVEF after 1 year. The mean LVEF was 37.8 ± 13.6 at baseline and improved to 47.5 ± 13.2 at 1 year ($p < 0.001$). **Figure 1** depicts the percentage of HF patients with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF) and preserved ejection fraction (HFpEF) at baseline and after 12 months.

The relative change in LVEF inversely correlated with changes in the risk of all-cause death estimated by the three calculators (**Table 2**). This was also accompanied by an improvement in the NYHA functional class.

Biomarkers

There was a significant decline in the concentration of NTproBNP and hs-TnT, with median relative reductions of 57.1 and 46.6%, respectively ($p < 0.001$). A modest non-significant 4.8% reduction in the concentration of ST2 ($p = 0.23$) was observed (**Figure 2**). We found a significant correlation between biomarker dynamics and changes in the estimated risk of all-cause death using the three calculators, including MAGGIC-HF and SHFM, which do not include such biomarkers (**Table 2**).

All-Cause Mortality Risk

Supplementary Figure 1 depicts 1- and 3-year predicted all-cause risk of death by every calculator, both at baseline and after 12 months of management. The distribution was extremely skewed, so median values were considered for analyses. A significant global reduction in the predicted risk of all-cause mortality was observed with the three risk scores after a 12-month follow-up (**Figure 3**, **Table 3**), despite the inherent increase in age and HF duration.

Remarkably, the re-calculated risks after 12 months of HF management allowed an accurate identification of the risk of death (**Table 4**, **Figure 4**). Harrell's C statistic for 3-year mortality predictions were 0.762 (95% CI 0.699–0.824), 0.781 (95% CI 0.726–0.836) and 0.791 (95% CI 0.738–0.844) using MAGGIC-HF, SHFM and BCN Bio-HF respectively.

Correlations between the three studied risk scores with regard to the absolute change in risk of all-cause death after a 12-month follow-up were poor (**Supplementary Figure 2**). Although the majority of patients presented with a reduction in mortality risk using the three calculators after 12 months of HF management, a non-negligible proportion of patients presented with a meaningful increase in risk: 20.2% with SHFM, 23.8% with BCN Bio-HF, and 24.4% with MAGGIC-HF. **Supplementary Figure 3** shows correlation between risk estimation at baseline and after 12 months of management. When patients were categorized into three groups according to their change in mortality risk (decrease vs. increase vs. no-change), kappa coefficients between the scores were poor (**Table 5**).

TABLE 1 | Comparison between population characteristics at baseline and after a 12-month management period.

	Baseline (n = 357)	12 months (n = 357)	p-value
Age, years	65.2 ± 12.3	66.2 ± 12.3	–
Male, *n* (%)	255 (71.4)	255 (71.4)	–
BMI (kg/m^2)	28.4 ± 4.9	28.53 ± 5.7	0.98
Ischemic etiology	133 (37.3)	133 (37.3)	–
Heart failure duration, months	4 (1–24)	16 (13–36)	–
Diabetes	144 (40.3)	144 (40.3)	–
COPD	59 (16.5)	59 (16.5)	–
Smoking	68 (19.0)	68 (19.0)	–
Systolic BP	129.1 ± 21.3	127.1 ± 19.9	0.11
NYHA functional class, *n* (%)			
I	43 (12.0)	44 (12.3)	0.89
II	269 (75.4)	275 (77.0)	0.57
III	45 (12.6)	38 (10.6)	0.36
IV	0 (0)	0 (0)	–
LVEF ≤ 40%, *n* (%)	233 (65.2)	107 (30.0)	<0.001
LVEF 41–49%, *n* (%)	62 (17.4)	95 (26.6)	0.003
LVEF ≥ 50%, *n* (%)	62 (17.4)	155 (43.4)	<0.001
Blood tests			
Hemoglobin, g/dL	13.3 ± 1.8	13.4 ± 2.2	0.18
Sodium, mmol/L	137.5 ± 3.4	139.7 ± 2.9	<0.001
Uric acid, umol/L	433.9 ± 93.9	419.5 ± 112.5	0.033
eGFR, mL/min/1.73 m^2	65.0 ± 26.5	62.4 ± 26.3	0.010
Total cholesterol, mmol/L	4.23 ± 0.86	4.27 ± 0.89	0.44
NT-proBNP, pg/mL	1,499 [680–3,434]	643 [233–1,933]	<0.001
ST2, ng/ml	21.0 [15.0–30.0]	20.0 [14.0–29.0]	0.23
hs-TnT, pg/ml	26.3 [14.6–42.8]	18.7 [11.2–32.9]	0.002
Treatments, *n* (%)			
Beta-blocker	300 (84.0)	324 (90.8)	<0.001
ACEI/ARB	262 (73.3)	233 (65.3)	0.003
ARNI	13 (3.6)	39 (10.9)	<0.001
Loop diuretics			
Furosemide >40 mg/d	188 (52.7)	88 (24.6)	<0.001
Furosemide ≤40 mg/d	169 (47.3)	269 (75.4)	<0.001
MRA	65 (18.2)	228 (64.0)	<0.001
CRT	22 (6.2)	33 (9.2)	<0.001
ICD	31 (8.7)	41 (11.5)	<0.001

Values are the mean ± standard deviation, n (%), or median [interquartile range], as indicated.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilisyn inhibitor; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; N/A, not available; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; ST2, interleukin 1 receptor-like 1; hs-TnT, high sensitivity troponin T.

DISCUSSION

In the present study, we aimed to assess changes in the predicted mortality risk after a 12-month management period in a multidisciplinary HF clinic. We used three contemporary web-based risk scores: MAGGIC-HF (6), SHFM (7), and BCN Bio-HF (8, 9).

The most important finding of this study was that despite the inherent increase in age and HF duration, a significant global reduction in the estimated mortality risk occurs with all HF risk scores after a 12-month management period. This reduction in mortality risk reflects the relevance of following guideline recommendations and ensuring that the majority of patients receive evidence-based drugs and cardiac devices when appropriate.

Periodic re-evaluation of the risk of death from HF, which fluctuates in the first few years of the disease, has become increasingly important for optimal patient care. It is vital that patients receive accurate information concerning prognosis in order to make decisions and plans for the future.

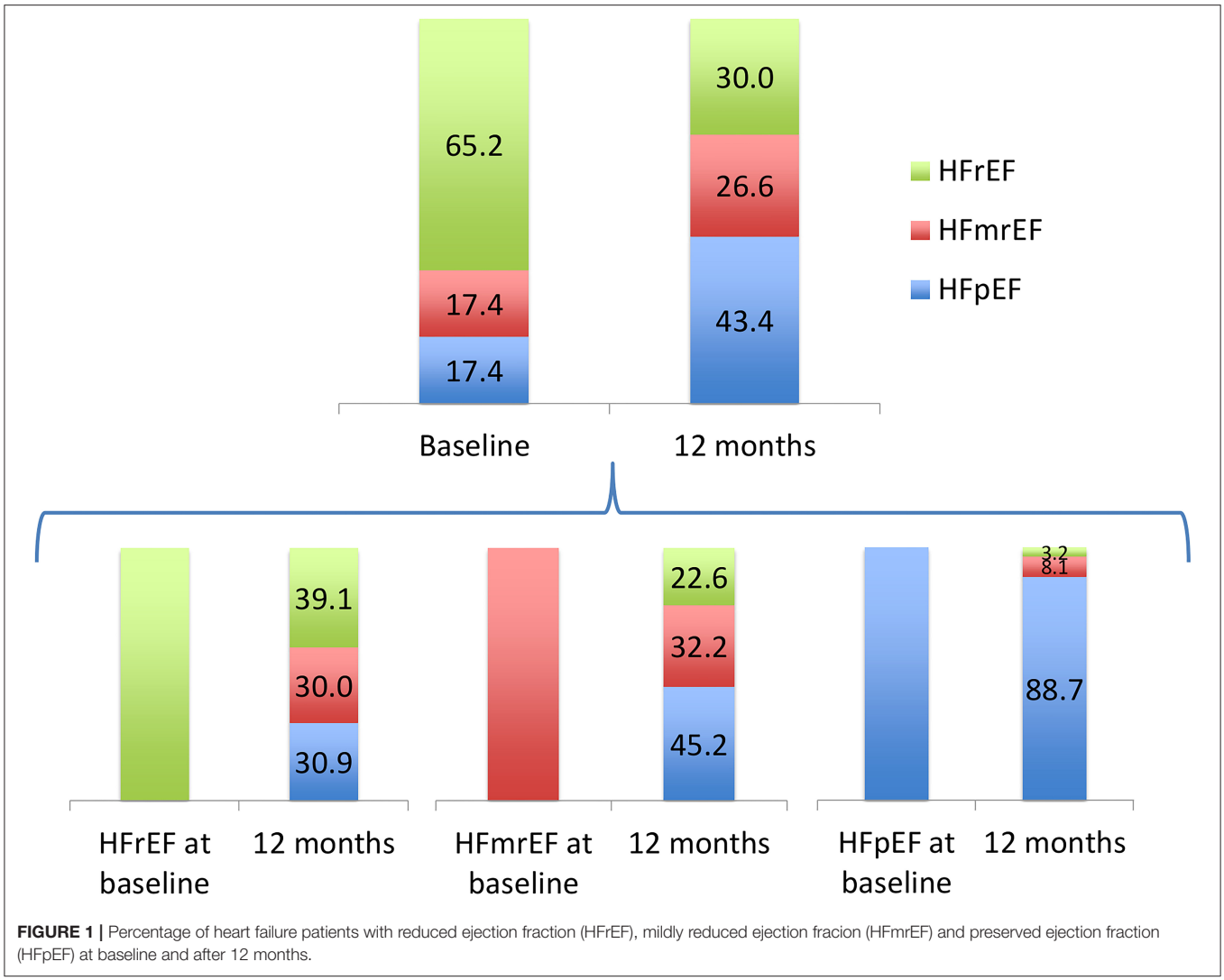

FIGURE 1 | Percentage of heart failure patients with reduced ejection fraction (HFrEF), mildly reduced ejection fracion (HFmrEF) and preserved ejection fraction (HFpEF) at baseline and after 12 months.

TABLE 2 | Correlation between relative changes in all-cause death risk at 1 year for every calculator and relative changes in LVEF and biomarkers.

	SHFM		MAGGIC-HF		BCN-Bio-HF	
	rho	***p*-value**	**rho**	***p*-value**	**rho**	***p*-value**
LVEF	−0.13	0.02	−0.52	<0.001	−0.23	<0.001
NTproBNP	0.18	<0.001	0.37	<0.001	0.43	<0.001
Hs-TnT	0.31	<0.001	0.32	<0.001	0.53	<0.001
ST2	0.12	0.02	0.11	0.04	0.37	<0.001

LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; ST2, interleukin 1 receptor-like 1; hs-TnT, high sensitivity troponin T.

Interestingly, the 1- and 3 year recalculated predicted mortality of BCN Bio-HF and SHFM were closer to the observed mortality than the MAGGIC-HF predicted mortality. The recalculated risks after 1 year of HF management better identified the risk of death than the observed change in the risk, suggesting that it is more accurate to consider the last recalculated risk during patient follow-up in order to better tailor therapeutic options. To the best of our knowledge, this study is the first to assess the dynamics of death risk prediction with these contemporary HF risk scores in a real-life prospective cohort of patients managed at a multidisciplinary HF clinic.

There was a marked increase in LVEF at 1 year, which was accompanied with a significant reduction in the concentration of the three studied biomarkers. Recent evidence indicates that HF includes multiple diverging patient-oriented phenotypes, resulting in a broad spectrum of time-dependent LVEF

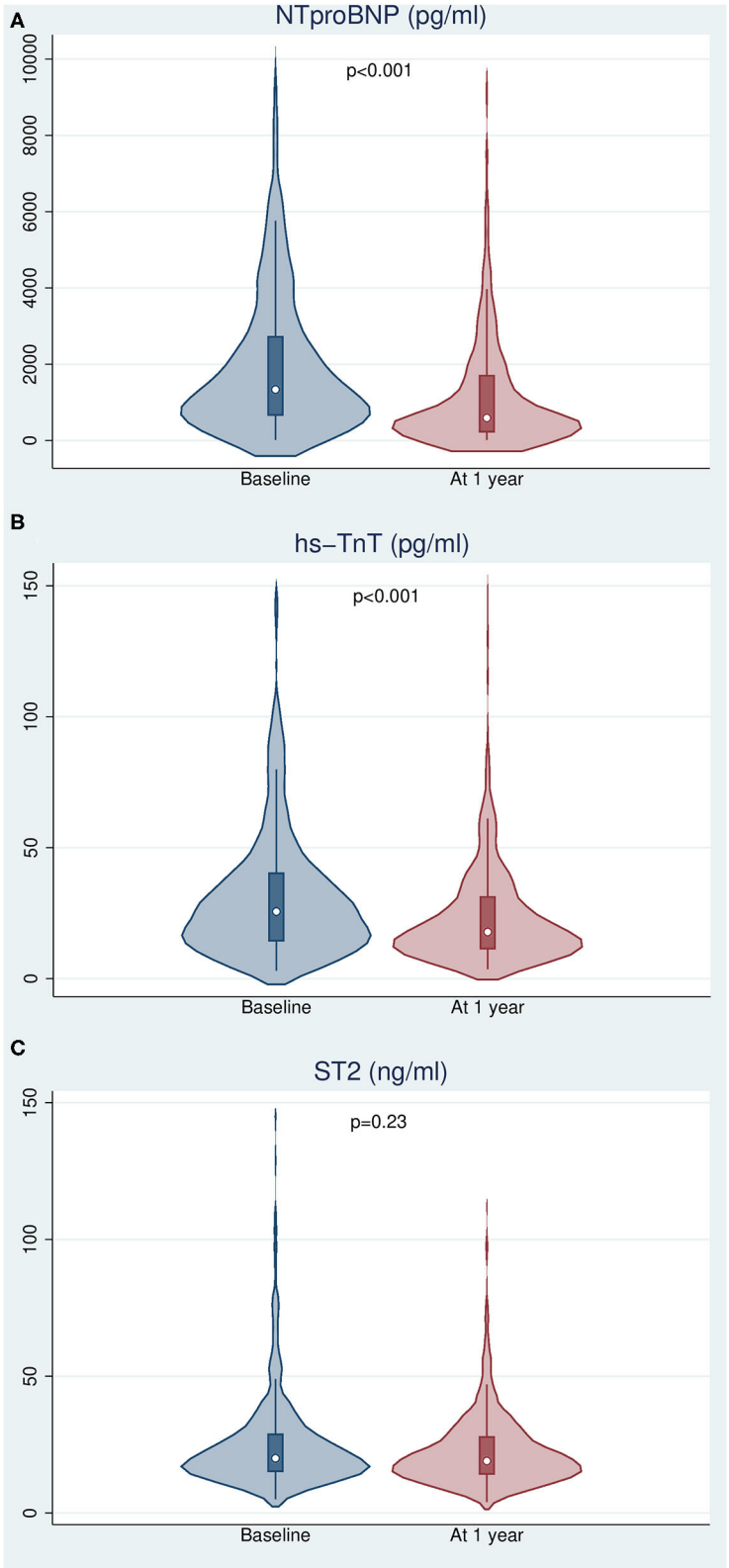

FIGURE 2 | Changes in biomarker levels after 12 months of follow-up. **(A)** N-terminal pro-brain natriuretic peptide. **(B)** High sensitivity troponin T. **(C)** Interleukin 1 receptor-like 1 (ST2).

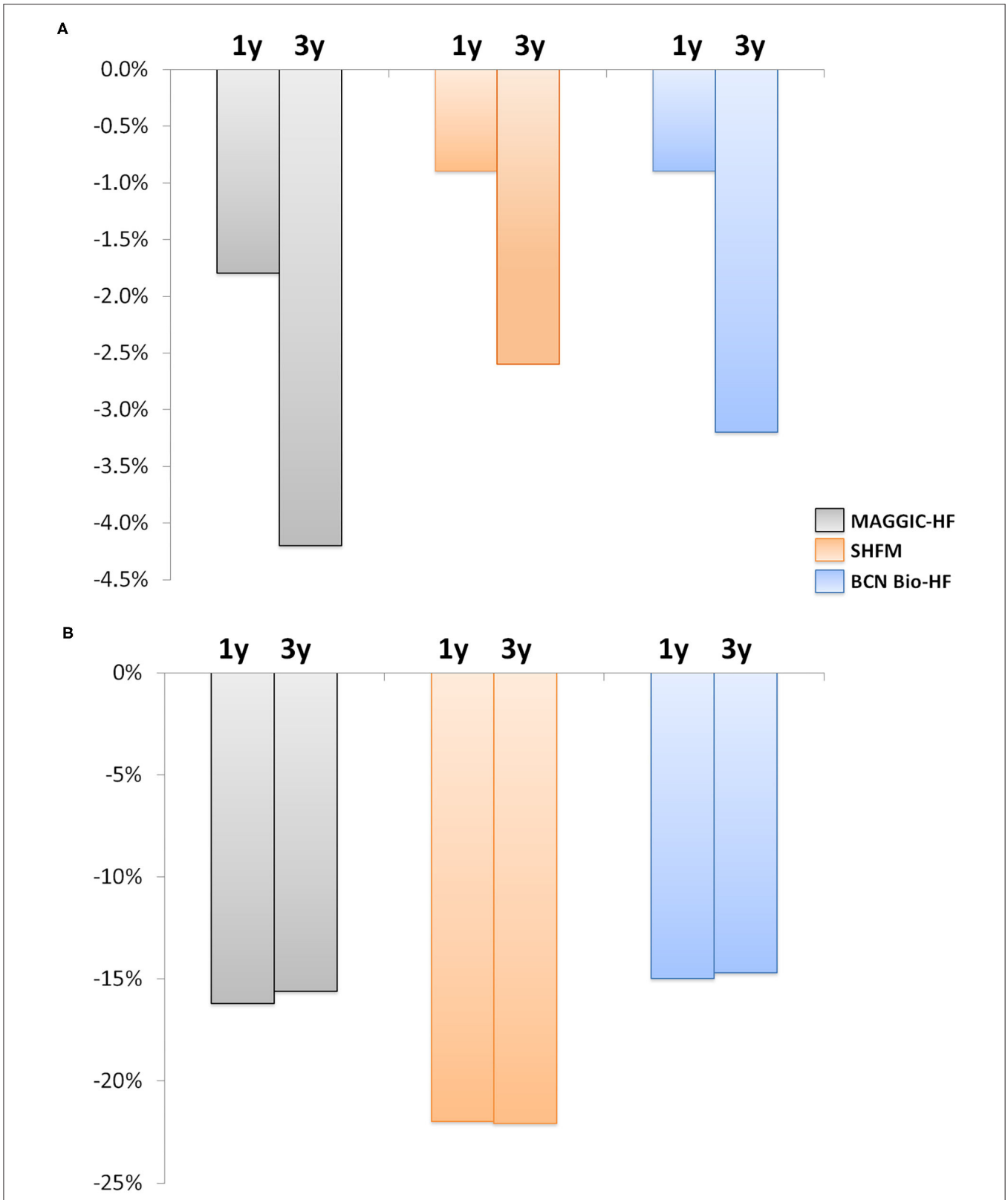

FIGURE 3 | Change in the risk of all-cause death at 1 and 3 years after 12 months of follow-up. **(A)** Absolute risk change. **(B)** Relative risk change. The estimated risk of death decreased significantly with the three calculators (all $p < 0.001$). Gray, MAGGIC; Orange, SHFM; Blue, BCN Bio-HF.

TABLE 3 | 1- and 3-year mortality risk estimation by studied HF calculators at baseline and after 12 months of follow-up.

	Observed#	SHFM		MAGGIC-HF		BCN Bio-HF	
		At baseline*	At 12 months*	At baseline*	At 12 months*	At baseline*	At 12 months*
1 year	4.2%	4.1% (2.5–6.8)	3.2% (2.0–4.8)	11.1% (7.0–17.5)	9.3% (5.2–16.0)	6.0% (2.8–13.2)	5.1% (2.0–11.0)
3 years	15.7%	12.3% (7.8–19.9)	9.7% (6.3–14.3)	26.9% (17.5–39.7)	22.7% (13.4–36.9)	21.8% (10.6–43.1)	18.6% (7.6–37.2)

Statistical comparison: $p < 0.001$ for all risk comparisons.
**Median (IQR). # Kaplan Meyer estimate.*

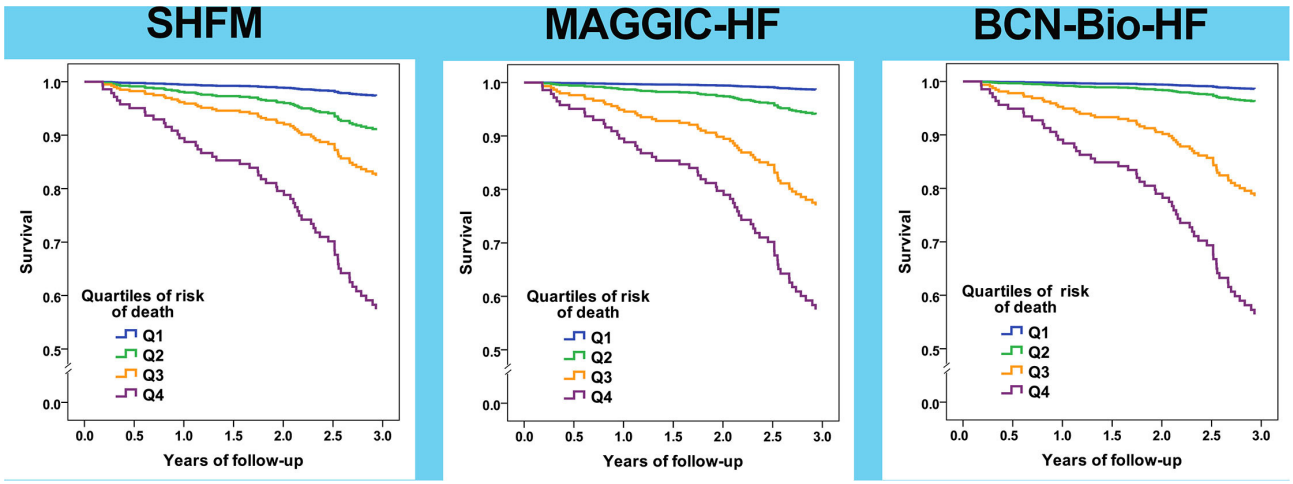

FIGURE 4 | Survival curves based on quartiles of risk of all-cause death for the three calculators based on risk estimated after 12 months of follow-up.

trajectories (12, 13). In the HFrEF subgroup guideline-directed medical therapy led to a complete normalization of LVEF (≥50%) in almost a third of the patients and to a partial normalization (41–49%) in 30% of them. This may explain the lower dose of furosemide needed at 12 months.

On the other hand, only 3.2% of HFpEF patients developed a HFrEF phenotype at the end of the first year. Thus, it might be particularly significant to re-evaluate HF prognostic indicators in the HFrEF subgroup.

Several prognostic risk models of HF have been developed in recent years, but only a few have been externally validated, and even fewer include cardiac biomarkers known to refine death risk prediction in HF patients. A recent head-to-head comparison of contemporary HF risk scores suggested that natriuretic peptides add value to HF risk stratification tools (14). The incorporation of biomarkers in HF scores may not only improve discrimination at baseline, but also reflect changes in mortality risk over time. In the present study, NTproBNP and hs-TNT had a significant reduction in their values, whereas ST2 did not. However, a significant correlation was found between changes observed in the three biomarkers (NTproBNP, hs-TnT, and ST2), together with changes in the LVEF and changes in all-cause death risk assessed by the three calculators. Correlation was higher with the BCN-Bio-HF calculator, likely due to these biomarkers being included as variables in the calculator. Nevertheless, it is remarkable that changes in the three biomarkers also significantly correlated with changes in the estimation of risk by SHFM and MAGGIC-HF at 12 months.

Study Limitations

Our study has some limitations. First, our analysis was performed only for "completers," that is, patients with complete 12-months follow-up and with both baseline and 1-year blood samples available. It is not possible to predict the effect that the "non-completers" may have had on some of the analyses. Nevertheless, in the subgroup of patients who died during first year follow-up, the 1-year average mortality risk estimated by MAGGIC, SHFM and BCNBioHF was 26.8, 10.6 and 55.5%, respectively. Second, only BCNBioHF allows estimating HF related hospitalizations, so we could not compare these events beyond all-cause death. Third, although our sample comprised patients with general HF, most patients had depressed LVEF and were treated at a multidisciplinary HF clinic in a tertiary hospital. In addition, most of the patients were referred from the Cardiology Department. Thus, our cohort was mostly comprised of relatively young men with HF with a significant proportion from ischemic etiology. Consequently, our results may not be generalizable to a global HF population that may include patients with HF with preserved ejection fraction. Although patients with more than three missing values were excluded, we could not rule out the possibility of bias due to the missing variables. Our sample is limited and from a single center over a long

TABLE 4 | Cox regression based on quartiles of the risk estimated at 1 year.

	Risk estimated at 1 year		
	HR	**95% CI**	***p*-value**
SHFM			
Q1	1		
Q2	3.55	0.74–17.1	0.11
Q3	7.23	1.64–31.8	0.009
Q4	20.7	4.96–86.3	<0.001
MAGGIC			
Q1	1		
Q2	4.56	0.53–39.1	0.17
Q3	19.3	2.57–145.1	0.004
Q4	40.9	5.59–298.9	<0.001
BCN Bio-HF			
Q1	1		
Q2	2.72	0.28–26.1	0.38
Q3	17.0	2.26–127.8	0.006
Q4	40.3	5.52–294.3	<0.001

TABLE 5 | Agreement between calculators and Cohen's kappa coefficients regarding increased risk of death after 1 year of follow-up.

	MAGGIC & SHFM	**SHFM & & BCN Bio-HF**	**MAGGIC & & BCN Bio HF**
Agreement (%)	50.2	59.5	50.4
Kappa	0.22	0.37	0.23

time period. A more robust comparison of risk scores should be carried out in a larger multi-center contemporary patient population. Although none of the patients included in the present study had participated previously in the BCN Bio-HF derivation cohort, they were derived from the same clinic as the original BCN-Bio-HF calculator, so we cannot discard potential bias in the analysis.

CONCLUSION

After a 12-month management period in a multidisciplinary HF clinic, the estimated risk of all-cause-mortality was significantly reduced with three contemporary HF risk scores. Therefore, repeat assessment of all-cause death risk in patients with HF is recommended, particularly in the HFrEF subgroup.

In contemporarily treated HF outpatients, recalculated risk with SHFM and BCN Bio-HF after 12 months of management showed closer results to the observed mortality together with better discrimination.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PC, JL, AB-G, and WL drafted the work. EZ, ER-L, AB, GS, GC, MR-C, EC, ES-V, MD, DB, IS, JS, RE, and JN revised it critically. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved and made substantial contributions to the conception of the work and provided approval for publication of the content.

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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.2022.836451/full#supplementary-material

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REVIEW
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Restructuring the Heart From Failure to Success: Role of Structural Interventions in the Realm of Heart Failure

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Heart failure through the spectrum of reduced (HFrEF), mid-range (or mildly reduced or HFmEF), and preserved ejection fraction (HFpEF), continues to plague patients' quality of life through recurrent admissions and high mortality rates. Despite tremendous innovation in medical therapy, patients continue to experience refractory congestive symptoms due to adverse left ventricular remodeling, significant functional mitral regurgitation (FMR), and right-sided failure symptoms due to significant functional tricuspid regurgitation (FTR). As most of these patients are surgically challenging for open cardiac surgery, the past decade has seen the development and evolution of different percutaneous structural interventions targeted at improving FMR and FTR. There is renewed interest in the sphere of left ventricular restorative devices to effect reverse remodeling and thereby improve effective stroke volume and patient outcomes. For patients suffering from HFpEF, there is still a paucity of disease-modifying effective medical therapies, and these patients continue to have recurrent heart failure exacerbations due to impaired left ventricular relaxation and high filling pressures. Structural therapies involving the implantation of inter-atrial shunt devices to decrease left atrial pressure and the development of implantable devices in the pulmonary artery for real-time hemodynamic monitoring would help redefine treatment and outcomes for patients with HFpEF. Lastly, there is pre-clinical data supportive of soft robotic cardiac sleeves that serve to improve cardiac function, can assist contraction as well as relaxation of the heart, and have the potential to be customized for each patient. In this review, we focus on the role of structural interventions in heart failure as it stands in current clinical practice, evaluate the evidence amassed so far, and review promising structural therapies that may transform the future of heart failure management.

Keywords: transcatheter therapies, structural interventions, heart failure, functional valvular regurgitation, robotic sleeves, inter-atrial shunt, ventricular restorative devices

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INTRODUCTION

Despite tremendous advances in medical therapy and revascularization techniques, heart failure continues to be a growing global epidemic– the prevalence of global heart failure doubled from 33.5 million in 1990 to 64.3 million in 2017 (1). According to American Heart Association 2021 statistics, with our aging population, the prevalence of heart failure is projected to increase by

46% from 2012 to 2030 and would affect >8 million Americans or nearly 3% of the population 18 years or older (2). Heart failure continues to be the foremost cause of hospitalization in the elderly that leads to high mortality, morbidity, and economic burden across the spectrum of heart failure with reduced (HFrEF), mid-range (or mildly reduced or HFmEF), and preserved ejection fraction (HFpEF) (3). Regardless of the ejection fraction, hospitalization for heart failure exacerbation has been a reliable predictor of recurrent admissions and cardiovascular death (2). Although sweeping progress has been made in the realm of HFrEF management, the HFpEF domain is yet to meet with similar fortune. In addition, despite optimal medical management of primary cardiac pathology such as ischemic heart disease and/or cardiomyopathy, patients can still experience refractory congestive symptoms due to the progression of secondary valvular disease (tricuspid and/or mitral regurgitation). Tricuspid regurgitation (TR), especially secondary regurgitation, has been a trifled valvular pathology that has gained some attention in recent times as the milieu of chronic venous congestion and its detrimental effect on end-organ function is better understood (4). These patients are not usually favored for surgical valvotomy or valvular replacement due to perceived high surgical risk that is attributed to poor functional status, underlying disease process, recurrent exacerbations, and significant comorbidities. Hence, in the last decade, structural interventions aimed at improving functional valvular regurgitation unlatched new frontiers for those high-risk patients in whom surgery is not feasible. In addition to helping tackle valvular disease percutaneously, novel structural devices are being developed to help monitor pulmonary pressures in a real-time fashion, to effect left ventricular reverse remodeling and improve effective stroke volume, and lastly, there is pre-clinical data supportive of soft robotic cardiac sleeves that serve to improve cardiac function and can have the potential to be customized for an individual patient (**Figure 1**). In this review, we emphasize the role of structural interventions in heart failure as it stands in current clinical practice, evaluate the evidence amassed so far, and review promising structural therapies that may transform the future of heart failure management.

STRUCTURAL INTERVENTIONS TARGETING VALVULAR HEART DISEASE AND HEART FAILURE

Mitral Regurgitation

Moderate or severe functional or secondary MR accompanies heart failure in about one-third of the patients and is mediated by mal-coaptation of the valve leaflets due to left ventricular remodeling and dysfunction secondary to ischemic and/or non-ischemic etiologies or due to annular dilatation in patients with long-standing atrial fibrillation or "atrial FMR" (5, 6).

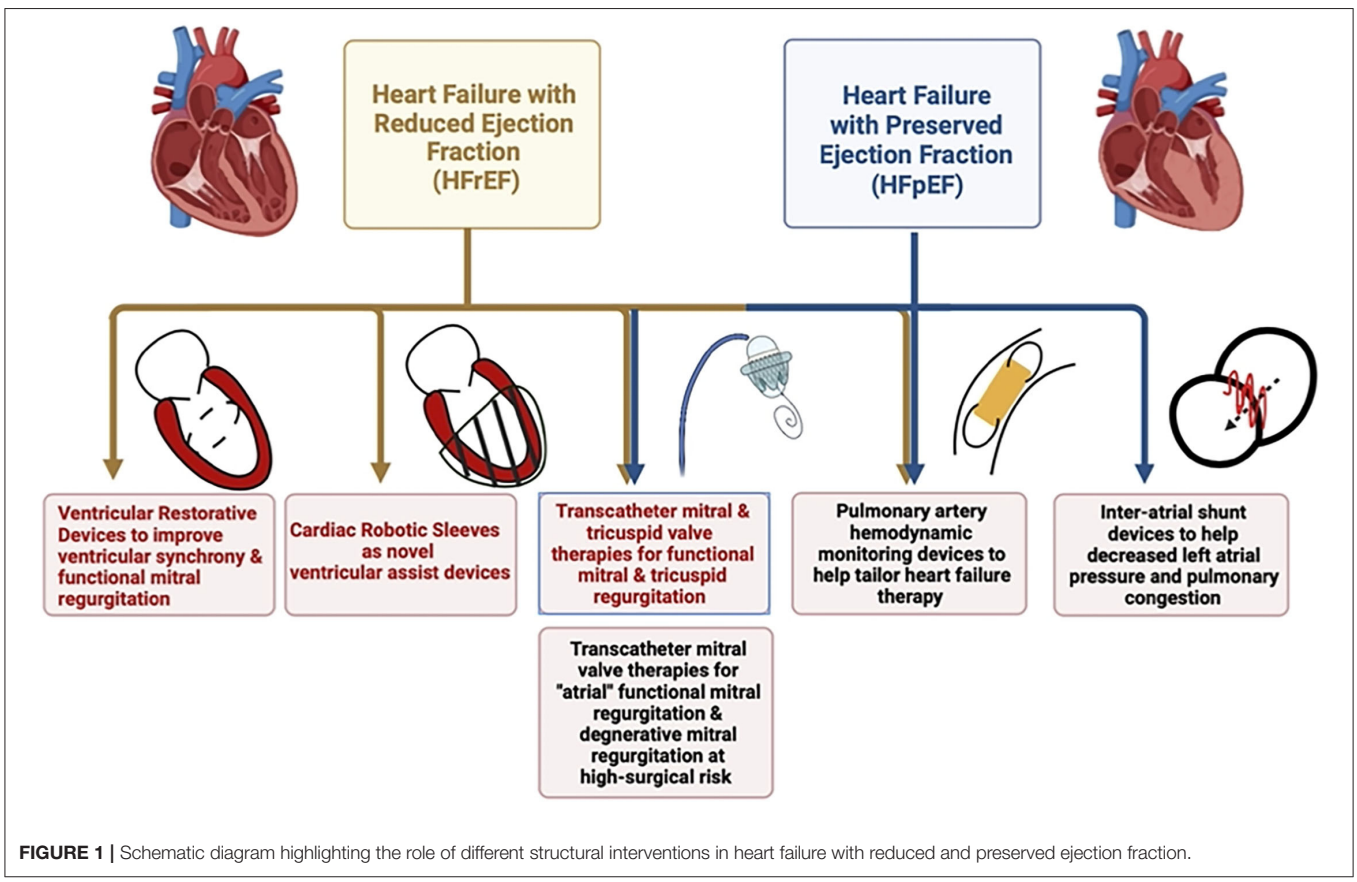

FIGURE 1 | Schematic diagram highlighting the role of different structural interventions in heart failure with reduced and preserved ejection fraction.

Mechanisms causing FMR include an increase in tethering forces causing tenting of the valve due to left ventricular dilation and increased sphericity, displacement of the papillary muscles, and annular dilatation. Further, there is a reduction in mitral valve closure during systole due to impaired contractility and a reduction in mitral annular movement (6). MR further strains the dysfunctional ventricle by causing volume overload and is independently predictive of increased mortality and other adverse heart failure outcomes (7–9). As most of these patients with advanced heart failure are unfavorable or unpropitious surgical candidates, there has been tremendous enthusiasm and research in the management of FMR through minimally invasive or percutaneous strategies. One such method relies on replication of the "Alfieri stitch" that approximates the anterior and posterior leaflets together to reduce mitral regurgitation percutaneously using trans-septal access– Transcatheter Edge-to-Edge Repair (TEER) using the Mitraclip™ (Abbott) or PASCAL™ (Edwards Lifesciences) devices (available only in Europe). Based on the reduction in heart failure hospitalizations and mortality rates with TEER that were noted in the COAPT trial, TEER has been given a class IIA recommendation for patients with HFrEF and chronic, severe FMR with persistent heart failure symptoms [New York Heart Association (NYHA) class II-IV] despite optimization of medical therapy as long as the mitral valve anatomy is conducive for the procedure, LVEF is between 20 and 50%, with left ventricular end-systolic dimension (LVESD) $\leq$70 mm and pulmonary artery systolic pressure is $\leq$70 mm Hg (10, 11). Another contemporary trial that evaluated the role of TEER for secondary mitral regurgitation–MITRA-FR, however, failed to show any difference in clinical outcomes with percutaneous mitral valve repair in a similar population (12). Given subtle differences in the inclusion criteria, patients enrolled in the COAPT trial had more severe valvular heart failure with a lesser degree of dysfunctional/dilated myocardium, better medical and device therapy and better optimization of MR with a larger number of Mitra-clips deployed per patient when compared to patients enrolled in the MITRA-FR trial (13). This discrepancy between the results noted in COAPT and MITRA-FR highlighted the importance of assessment of the severity of mitral regurgitation in proportion to the severity of left ventricular dysfunction and introduces the concept of "proportionate MR as noted in MITRA-FR" and "disproportionate MR as noted in COAPT."

Not all mitral valve anatomies are ideal for performing a TEER and hence alternative mitral valve repair strategies are needed. One such device is a self-expandable nitinol ring that can be implanted in the coronary sinus through the right jugular vein– the Carillon™ Mitral Contour System– this device relies on the close relationship between the coronary sinus and the mitral valve annulus to effect an indirect annuloplasty (14). Advantages of this device include ease of venous access without the requirement of trans-septal puncture and it gives the operators a different mechanism to address FMR by targeting annular dilatation and does not preclude other valvular therapies. Circumflex artery has been shown to cross between the coronary sinus and the mitral valve annulus in about 80% of the patients and depending on the patient's anatomy, it may preclude this procedure in some patients given the inherent risk of impingement or compression of the artery when the annuloplasty band is deployed (15). Multiple trials (AMADEUS, TITAN, and TITAN II) have established the safety and feasibility of successive iterations of the Carillon™ device for FMR (16–18). REDUCE-FMR randomized patients with severe FMR to device therapy compared to a sham control and showed low device failure rates (14%) and complications, with a reduction in regurgitant volume and left ventricular remodeling and improvement in functional outcomes at 1 year (19). The largest sham-controlled trial to evaluate the safety and efficacy of Carillon™ trial in patients with symptomatic FMR (at least mild severity)—the EMPOWER trial– is currently recruiting patients (20). This trial is unique in including patients with mild FMR to assess any difference in clinical and functional outcomes with device therapy.

Another device that targets annular dilatation is a minimally invasive, catheter-delivered direct annuloplasty ring– the Cardioband™ valve reconstruction system (Edwards Lifesciences) (21). This implant is anchored along the posterior mitral valve annulus using steel anchors through a trans-septal approach under fluoroscopic and echocardiographic guidance and involves adjustment of the annular size through a specific size adjustment tool (22). Similar to the TEER devices, an adequate septal length is needed for trans-septal access, and similar to the Carillon devices, specific anatomical issues with the crossing of the circumflex artery can preclude this therapy. A European multi-center study established feasibility with a favorable safety profile for the Cardioband™ device in 31 patients with symptomatic moderate to severe FMR with sustained improvement in annular size, mitral regurgitation, and functional outcomes at 7 months follow-up (23). ACTIVE is an ongoing randomized controlled trial to evaluate the safety and efficacy of the Cardioband™ device compared to medical therapy alone for patients with clinically significant and symptomatic FMR with a long follow-up period of 5 years (24). Mitralign™ (Massachusetts) is another direct annuloplasty device that uses radiofrequency energy to penetrate two pairs of pledget sutures through the mitral annulus tissue from the left ventricular aspect into the left atrium– the annulus and mitral regurgitation are reduced by cinching the sutures. Feasibility study for Mitralign™ in 71 patients with moderate-severe FMR showed technical success in 70% of the patients enrolled with a successful reduction in MR at 6 months in 50% of the patients (25). Mistral™ (Mitralix Ltd.) is a spiral-shaped investigational device that reduces FMR by grasping the chordae tendineae and improving leaflet coaptation– a feasibility study (MERIT) is currently enrolling patients with severe FMR (26).

While these Transcatheter Mitral Valve Repair (TMVr) techniques offer promising results for patients with FMR, some patients have unfavorable mitral valve anatomy (such as calcified mitral annulus) for percutaneous repair and may experience complications or failure with significant residual or recurrent MR despite TMVr (27). Transcatheter Mitral Valve Replacement (TMVR) options are hence being explored aggressively to develop viable alternatives in such patient populations. Owing to the saddle-shaped, dynamic mitral valve annulus and proximity to the left ventricular outflow tract with

TABLE 1 | Descriptive analysis of the different Transcatheter Mitral Valve Replacement devices with human experience.

Valve name	Valve structure	Access for deployment (sheath size)	Level of evidence
CardiAQ™ (Edwards Lifesciences)	Nitinol, self-expanding trileaflet bovine pericardial valve (30-mm) with circumferential anchors on the atrial and ventricular side	Trans-apical, trans-septal (31 Fr)	Early Feasibility Study (RELIEF) has been withdrawn due to high 30-day mortality rates (28). This device has been redesigned as the EVOQUE™.
Intrepid™ (Medtronic)	A self-expanding, nitinol frame with a dual ring design creates a "champagne-cork-like effect" for anchoring. The inner stent frame includes a 27-mm trileaflet bovine pericardium valve.	Trans-apical and Trans-septal (35 Fr)	Early experience of 50 patients- technical success (98%) (29). Ongoing single-arm APOLLO trial for patients with severe, symptomatic MR, including patients with MAC utilizing trans-apical access (30). A feasibility study involving trans-femoral access in 15 patients with severe symptomatic mitral regurgitation (mostly primary MR) at high-surgical risk showed technical success in 93% of the patients with trace/no MR or paravalvular leak, no deaths or strokes at 30 days follow-up (31).
HighLife™ 2-component system (HighLife Medical)	"Valve-in-ring"- Nitinol, self-expanding 31- or 28-mm trileaflet bovine bio-prosthesis is used with a sub-annular implant that is deployed through trans-septal access.	Trans-apical (39 Fr), Trans-septal access for the ring (18 Fr)	Feasibility study for severe, symptomatic MR is ongoing for the 31 mm trans-apical implant−5 patients have been recruited so far (32) and the 28-mm trans-septal TMVR (33).
Tiara™ (Neovasc Inc.)	Self-expanding, nitinol, D-shaped frame, trileaflet, bovine pericardial valve (35- or 40-mm), the frame has three ventricular anchors.	Trans-apical (32/36 Fr)	This device is currently being evaluated in feasibility (TIARA-I) (34) and a safety and performance clinical study (TIARA-II) (35).
Tendyne™ (Abbott Laboratories)	Valve is fully repositionable and retrievable. Trileaflet, a porcine pericardial valve on a self-expanding, nitinol double-frame with an epicardially fixed apical pad. An atrial cuff further helps to anchor the valve.	Trans-apical (34 Fr)	A feasibility study of 100 patients with a 2-year follow-up shows technical success in 97% of the patients. Thirty-nine percent all-cause mortality at 2 years (36). SUMMIT trial to evaluate TEER vs. Tendyne™ and also evaluate Tendyne™ in patients with MAC (37).
AltaValve™ (4C Medical Technologies Inc.)	First TMVR implanted in a supra-annular position to help minimize LVOTO. Trileaflet bovine valve (27 mm) in a self-expanding spherical nitinol stent.	Trans-apical (32 Fr)	Ongoing early feasibility study (38). The trans-septal access system is under development.
EVOQUE™ (Edwards Lifesciences)	Redesigned CardiAQ™ valve (available in 44- and 48-mm sizes) with a lower profile for trans-septal delivery, lower ventricular projection to minimize LVOTO.	Trans-septal (28 Fr)	First-in-human experience (14 patients) with good technical success (93%) (39). Ongoing early feasibility study (40).
SAPEIN M3™ (Edwards Lifesciences)	Balloon-expandable, trileaflet bovine pericardial valve (29-mm) on a nitinol stent, based on the SAPIEN 3 TAVR system. Nitinol dock encircles the chordae tendineae securing the valve in place.	Trans-septal (20 Fr)	First-in-human experience (10 patients) with good technical success (90%) (41). Ongoing early feasibility study (ENCIRCLE) (42).
Cardiovalve™ (Cardiovalve Ltd.)	Trileaflet, 3-scallop shaped bovine pericardial valve (40–50 mm) in a self-expanding nitinol stent with 24 ventricular anchors.	Trans-septal (28 Fr)	Ongoing early feasibility study (AHEAD) (43).

Fr, French; MR, Mitral Regurgitation; MAC, Mitral Annular Calcification; LVOTO, Left Ventricular Outflow Tract Obstruction; TAVR, Transcatheter Aortic Valve Replacement.

potential for obstruction, the development of a prosthesis in this location has its unique challenges. A number of prostheses with different designs have been successfully implanted in humans– the CardiAQ™, the Intrepid™, the HighLife™, the Tiara™, the Tendyne™, the AltaValve™, the EVOQUE™, the SAPIEN M3™, and the Cardiovalve™ (**Table 1**) (44). Because of technical challenges with the positioning of the device and co-axial prosthesis alignment that involves a 90° turn after crossing the interatrial septum, most of the devices were developed to be deployed through trans-apical access except for the EVOQUE™, the SAPIEN M3™, the Intrepid™, and the Cardiovalve™, which have been successfully deployed in patients through a trans-septal approach utilizing transfemoral vascular access. Among these TMVR devices, the longest follow-up data is available for the Tendyne™ valve– in 100 patients with severe, symptomatic FMR at high-surgical risk without significant valvular or annular calcification, deployment of the Tendyne™ valve was associated with procedural success, reduction in heart

failure hospitalizations and persistent reduction in MR without structural degeneration at 2-year follow-up (36). While TMVR offers a more durable reduction in FMR, it does involve a more invasive approach which can lead to increased bleeding complications and a longer hospital course in the frail, elderly population. With the trans-septal approach, the resulting large iatrogenic ASD with TMVR can precipitate volume overload and heart failure decompensations and can cause a right-left shunt with hypoxemia in this high-risk patient population with pulmonary hypertension– the role of closure of this ASD and the timing of the closure is not clear and closure devices can impede access for any future procedures needing trans-septal access. SUMMIT is an ongoing randomized controlled trial comparing TEER with the Tendyne™ valve for patients with symptomatic severe FMR and is also going to evaluate the Tendyne™ valve for patients with significant annular calcification– this trial would help guide patient selection for TMVr vs. TMVR in the future (37).

Tricuspid Regurgitation

In 2005, ∼1,600,000 patients were identified to have moderate-severe TR, however, only <8,000 of these patients underwent tricuspid repair or replacement (45). Primary TR is relatively uncommon (<10%) and is mostly mediated by left-sided valvular disease, pulmonary hypertension, left- and right-sided cardiomyopathies (46). TR has been a neglected pathology; however, it is clear that patients with moderate or higher severity of TR have worse outcomes with higher mortality rates, even after adjusting for pulmonary pressures, right ventricular function, and left ventricular ejection fraction (47, 48). FMR and FTR commonly coexist. In patients undergoing surgery for left-sided valvular disease, it is a class I recommendation to intervene on severe concomitant TR or moderate TR with a dilated annulus, however, no such guidelines exist for transcatheter therapies. A contemporary comparison of two cohorts of patients with concomitant severe functional MR and TR, patients who underwent transcatheter repair of the mitral and tricuspid pathology in the international TriValve registry had improved 1-year survival rates compared to TMVr alone in the German TRAMI registry (49). TMVr has been shown to improve TR in a third of these patients with secondary TR, however, persistent moderate-severe TR is common and is predictive of adverse patient outcomes (50). Persistent significant TR creates volume overload and strains the right ventricle furthering right ventricular dysfunction, tricuspid annular dilatation, which then leads to worsening of TR, thereby creating a vicious downward spiral. If uncorrected, persistent TR can lead to diuretic resistance, and multi-organ failure with renal injury and cirrhosis. Given the high surgical mortality in patients with secondary TR, the development of transcatheter therapies for tricuspid valve repair and replacement has been an area of active research. There is evidence for worse clinical outcomes for tricuspid valve surgery or transcatheter tricuspid valve intervention in patients with evidence of cardio-hepatic syndrome (51, 52). This calls for timely intervention for FTR before organ failure ensues. Patients with FTR are commonly anticoagulated for concomitant atrial fibrillation which makes scoring systems that rely on INR levels like the MELD (Model for End-Stage Liver Disease) score unreliable for assessment of liver dysfunction. Novel scores for assessing liver dysfunction are being actively researched– one such score that factors in patient's age, evidence of renal dysfunction, diuretic resistance and hepatic dysfunction– the TRISCORE– was recently validated as a mortality predictive tool for patients undergoing isolated tricuspid valve surgery (53). The complex anatomy of the tricuspid valve with an asymmetric, large annulus, proximity to important structures like the right coronary artery and AV node and, difficulty in imaging with subjective criteria for grading of TR severity has made the development of these therapies further challenging.

Treatment strategies for Transcatheter Tricuspid Repair (TTVr) include TEER using the Triclip™ (Abbott) and PASCAL™ (Edwards Lifesciences) systems, direct annuloplasty with Cardioband™ (Edwards Lifesciences), Tricinch™ (4Tech Cardio Ltd.), Trialign™ (Mitralign Inc.) and the Mistral™ (Mitralix Ltd.) device which effects a reduction in TR through grasping and inward pulling of the chordae tendineae (**Table 2**). Among these devices, TEER and annuloplasty with Cardioband™ and the Trialign™ devices are based on the known mitral valve repair techniques–owing to ease of use and familiarity, TEER has been the most commonly employed therapy for the tricuspid valve as well (60). TTVr devices were being used initially on a compassionate basis– Triclip™, PASCAL™, and the Cardioband™ devices were recently granted Conformité Européenne (CE) approval. These repair devices can be limited by the valve anatomy in patients with a large coaptation gap. Another mechanism to decrease TR in such patients involves the insertion of spacer devices (like the FORMA™ system) through the annulus over a railing device anchored to the right ventricle (**Table 2**). TriPair™ (Coramaze) is another spacer device that is being tested in the pre-clinical models; a retrievable atraumatic right atrium anchor and absence of a rail distinguish it from the FORMA™ system.

In patients with large coaptation gaps (>6–8 mm), massive/torrential TR, device-related TR, or prior failed repair with single leaflet detachment, TTVr may not be feasible and this has created the niche for Caval Valve Implantation (CAVI) and Transcatheter Tricuspid Valve Replacement (TTVR). CAVI involves placement of a heterotopic valve in the Inferior Vena Cava and possibly the Superior Vena Cava (SVC) to protect the hepatic and renal circulation by redirecting the TR jet and this modality also improves the forward stroke volume ejected through the right ventricle. CAVI is technically easier than other transcatheter tricuspid therapeutic options and can be easily combined with other modalities as the valve or sub-valvular apparatus are intact. While the initial experience with non-dedicated valves showed a high rate of complications related to device thrombosis and dislocation, the novel dedicated bicaval valves are currently undergoing early feasibility studies (**Table 2**) (66). For TTVR, CardioValve™ (CardioValve Ltd.), EVOQUE™ (Edwards Lifesciences), Lux-Valve™ (Jenscare Biotechnology), NaviGate™ (NaviGate Inc.), Trisol™ (Trisol Medical), Intrepid™ (Medtronic), TRiCares™ (TRiCares SAS) are currently being tested in early feasibility trials (69). Most of

TABLE 2 | Descriptive analysis of the different Transcatheter Tricuspid Valve Repair devices with human experience.

Device	Mechanism	Specific characteristics	Level of evidence
TriClip™ (Abbott)	Edge-edge repair	Based on Mitraclip™ technology. Most common repair device used to date. Trans-femoral access.	TRILUMINATE trial- feasibility study of 85 patients in patients with moderate or greater symptomatic TR with poor surgical candidacy– durable reduction in TR (71%) and reverse RV remodeling noted at 1-year (54). A randomized trial comparing TriClip with medical therapy in patients with severe TR at high surgical risk is currently ongoing (TRILUMINATE Pivotal) (55).
PASCAL™ (Edwards Lifesciences)	Edge-edge repair	A similar mechanism to the Triclip™. Trans-femoral access. A unique spacer helps bridge large coaptation gaps and reduces mechanical stress on the leaflets.	CLASP-TR: Feasibility study included 34 patients with severe or greater symptomatic TR at high surgical risk. The device was implanted successfully in 85% of the patients with durable reduction in TR at 30-days in 85% of those patients (56). CLASP-II TR: Ongoing randomized trial comparing tricuspid valve repair (PASCAL) with medical therapy (57).
Cardioband™ (Edwards Lifesciences)	Direct Annuloplasty	Cardioband™ is delivered through transfemoral access into the annulus and is positioned using up to 17 anchors. Once optimally positioned, it is contracted to decrease the tricuspid annulus. The right coronary artery can be affected by device contraction.	Initial European feasibility study (TRI-REPAIR) showed good technical success (100%) in 30 patients with moderate or higher symptomatic TR with favorable results at 2-year follow-up (58). An early feasibility study in the US enrolled 30 patients with severe or greater symptomatic functional TR with technical success in 93% of the patients and promising 30-day outcomes (59).
Tricinch™ (4Tech Cardio Ltd.)	Direct annuloplasty	A two-component device using trans-femoral access– a nitinol corkscrew implant is anchored on the AP tricuspid annulus which is coupled using a Dacron band with a self-expanding nitinol stent that is deployed in the IVC to maintain tension on the system and reduce annular dimensions. Given the valve and sub-valvular apparatus are intact, other therapies can be combined with Tricinch™.	An early feasibility study (PREVENT) in 15 symptomatic patients with moderate-severe TR with annular dilatation was terminated per the sponsor. In the TriValve Registry, 14 patients (4% of the patients) underwent tricuspid valve repair with Tricinch? with procedural success in 62.5% of the patients and no 30-day mortality. Patients with higher regurgitant volume in the registry underwent TTVr with Tricinch™ (60).
Trialign™ (Mitralign Inc.)	Direct annuloplasty	Trans jugular-based suture-based device that reduces tricuspid annular diameter by plication obliterating the posterior leaflet– replicates the surgical "Kay" procedure. Based on the Mitralign? device designed for MR. A guide catheter is used to engage the right coronary artery given its proximity to the annulus.	Early feasibility study (SCOUT) in 15 patients with moderate or greater functional TR showed good technical success (100% at the time of procedure, 80% at 30-days due to single-pledget annular detachments in 3 patients) with safety (61). A larger study to assess the safety and performance of Trialign™ in 60 patients with at least moderate functional TR across the United States and Europe is currently enrolling (62).
Mistral™ (Mitralix Ltd.)	Grasping of the chordae tendineae	Spiral-shaped, nitinol-device delivered transfemorally to grasp the chordae tendineae like a bouquet–this improves leaflet coaptation and improves RV geometry as well– dual mechanisms to decrease functional TR. This device further spares the valve leaflets; hence, other repair devices can still be used in cases of persistent TR.	First-in-human study in 7 patients with severe or greater TR at high surgical risk underwent successful tricuspid repair with the Mistral™ device with good efficacy results and improved RV function at 30-day follow-up (63).
FORMA™ (Edwards Lifesciences)	Spacer device	A foam-filled balloon (spacer- 12/15/18 mm) is positioned across the tricuspid valve over a rail extending from the subclavian vein to the RV apex. The device is anchored to the RV myocardium using a nitinol anchor with six prongs. There is a risk of endocarditis with the implanted device and the subcutaneous pocket. With anchoring of the device in the RV, the risk for perforation exists as well.	First-in-human experience in 19 patients with severe functional TR in Europe and Canada, showed feasibility with sustained TR reduction and functional improvement at 3-year follow-up. Device thrombosis and pulmonary embolism were notable adverse events with sub-therapeutic anticoagulation (64). Similar results were noted with 30-day follow-up in the US with 18 compassionate cases and 29 patients included in the early feasibility study. Two procedural failures in both groups related to perforation and device dislocation (65).
Caval Implantation (CAVI)	Heterotopic valve implantation	Bio-prosthetic valves implanted in the IVC and SVC to allow forward flow into the right atrium but no backflow during TR. The initial experience involved non-dedicated valves (Edwards Sapien™) while novel self-expandable valves dedicated for the bi-caval anatomy include the TricValve™ (P&F Products; CE approval), the Tricento™ (NewValve Technology) and the Trillium™ systems (66). The procedure can be performed without general anesthesia. Device use is limited in patients with severe RV failure, IVC diameter >45 mm, severe pulmonary hypertension, or contraindication to anticoagulation.	TRICAVAL compared medical therapy with CAVI in 28 patients with severe, symptomatic TR at high-surgical risk with Edwards SAPIEN XT balloon-expandable valve (23/26/29 mm). Patient recruitment was stopped early due to four complications within 48 h of the implant– two patients with tamponade due to stent migration and two valve dislocations. Further, no significant difference was noted in the maximal oxygen uptake or functional outcomes between the groups at 3-month follow-up (67). An early feasibility study for TricValve™ (TRICUS) and a CE mark trial (TRICUS-EURO) are currently ongoing (68).

TR, Tricuspid Regurgitation; AP, Anteroposterior; IVC, Inferior Vena Cava; TTVr, Transcatheter Tricuspid Valve Repair; IVC, Inferior Vena Cava; SVC, Superior Vena Cava; CE, Conformité Européenne.

these devices are deployed through transfemoral access except for Trisol™ needing transjugular access and minimally invasive right thoracotomy is needed for Lux-valve™ and Navigate™. Increased risk for prosthetic valve thrombosis due to a low-pressure system within the right heart needing anticoagulation, right-sided heart failure due to near-complete elimination of TR resulting in afterload mismatch, endocarditis, and conduction disturbances are some of the factors to be considered when deciding between transcatheter tricuspid valvular replacement vs. repair in a patient with difficult anatomy and future trials would further help develop an individualized approach for management of functional TR.

Aortic Stenosis

In patients with severe Aortic Stenosis (AS) and left ventricular dysfunction or in patients with Continuous-Flow Left Ventricular-Assist Devices (CF-LVAD) who develop moderate or higher degrees of Aortic Insufficiency (AI), the role of transcatheter aortic valve interventions has been growing. In the TOPAS-TAVI registry, 293 patients with low-flow, low-gradient aortic stenosis and depressed ejection fraction were included and patients with severely depressed EF (<30%) had greater improvements in LVEF at 1-year follow-up after Transcatheter Aortic Valve Replacement (TAVR) compared to patients with moderately reduced EF (<40%), irrespective of the presence of contractile reserve with dobutamine stress (70). Aortic stenosis and left ventricular dysfunction commonly co-exist and it is not surprising to see improvement in cardiomyopathy once the afterload imposed by aortic stenosis is improved with TAVR. TAVR-UNLOAD is an ongoing, randomized controlled trial that would help assess if early TAVR with medical therapy improves outcomes compared to medical therapy alone outcomes in patients with moderate AS and HFrEF (71).

LVAD is increasingly being used as destination therapy in patients with advanced heart failure who are ineligible for heart transplantation. At the time of LVAD implantation, a moderate or higher degree of aortic regurgitation is commonly managed with complete patch closure, central oversewing of the aortic leaflets (Park's stitch), or replacement with a bio-prosthetic valve. Complete valve closure can be fatal in cases of device malfunction and the potential for myocardial recovery should also be weighed in. Surgical Aortic Valve Replacement (SAVR) at the time of VAD surgery would increase the bypass and aortic cross-clamping times and is associated with worse clinical outcomes in patients with INTERMACS 1 and 2 level heart failure (72). There is a role for TAVR in such patients. Further, the altered non-physiological flow profile with LVAD (particularly CF-LVAD) promotes aortic valve closure and commissural fusion leading to the development of *de-novo* AI following LVAD implantation– noted in ∼15–52% of patients at 1-year post-implant (72). Moderate or higher degrees of AI leads to decreased cardiac output due to redundant backflow to the left ventricle and causes persistent heart failure in these patients. Given higher mortality rates from redo surgical repair or replacement due to severe co-morbidities, transcatheter treatment options are being used increasingly in these patients to treat significant post-LVAD AI. Occluder devices (Amplatzer™) have been used successfully in these patients, however, similar to complete surgical closure, these devices make the patient completely dependent on the LVAD (73). In a case series of 9 such patients, TAVR was used successfully with a self-expanding prosthesis resulting in a durable reduction of AI at 6-months. Owing to lack of calcium in pure AI lesions, the prosthesis is prone to migration– 2/9 patients needed implantation of a second valve due to device migration. Dedicated transcatheter valvular designs for AI with a "clasping" mechanism to facilitate anchoring (JenaValve™ and J-valve™) may help bridge this gap (74).

STRUCTURAL INTERVENTIONS THAT ASSIST IN LOWERING LEFT-ATRIAL PRESSURE

Compared to the multitude of medical and device therapy options with a mortality benefit for HFrEF, limited options prevail for the management of patients with HFpEF. Patients with Lutembacher syndrome– congenital or acquired mitral stenosis and an atrial septal defect do not suffer from congestive symptoms. This inspired the development of Transcatheter Interatrial Shunt Devices (IASD)– these devices are implanted through the femoral veins and trans-septal access and aim to lower the left-atrial pressure with activity thereby improving symptoms and outcomes in patients with HFpEF and HFmEF. REDUCE-LAP HF I was a phase-II randomized trial in patients with symptomatic refractory heart failure (wedge pressure ≥25 mm Hg during exercise) with LVEF>40% and a gradient of ≥5 mm Hg between the left and right atria– patients were randomized to treatment with IASD (Corvia® Atrial Shunt) vs. a sham control and significant reduction in pulmonary wedge pressure with exercise was noted in patients treated with device therapy at 1-month follow-up (75). Further, longer follow-up at 1 year showed patency of the shunts with no significant adverse outcomes (76). However, REDUCE-LAP HF II– a randomized controlled trial comparing treatment with IASD (Corvia® Atrial Shunt) vs. a sham control in a similar heart failure population failed to show any improvement in heart failure events or heart failure symptoms at 12–24 months follow-up (77). Patients with right-sided dysfunction, pulmonary hypertension, valvular heart disease, recent deep vein thrombosis or pulmonary embolism, or stroke are not candidates for this device therapy. Interestingly, in REDUCE-LAP HF II trial, the only sub-group that benefited from IASD included patients without evidence of latent pulmonary vascular disease suggesting a possible role of invasive exercise hemodynamics for optimal patient selection (77). While Corvia® Atrial Shunt is a valveless self-expandable device with a double-disc design with an 8-mm opening in the center for an optimal inter-atrial shunt, the V-wave Ventura® IASD is an hourglass-shaped device that included a one-way porcine tissue valve in the initial versions– in the first-in-human study of 38 patients with HFrEF and HFpEF, it was feasible and safe but was associated with poor long-term shunt patency rates (36% at 12-months) (78). A modified valveless version of the V-wave Ventura® IASD with an internal diameter of 5 mm is currently being investigated in a randomized controlled trial including

patients with symptomatic heart failure, irrespective of the LVEF- RELIEVE-HF trial (79). Another device- the Atrial Flow Regulator (AFR, Occlutech)– is a self-expandable nitinol device that needs balloon septal dilation before device deployment and has two different shunt sizes (8 and 10 mm) based on the left-sided filling pressures– the pilot study (AFR-PRELIEVE) showed safety, feasibility and good patency rates at 3-months follow-up (80).

Recently, there has been active research in the development of implant-free Inter-Atrial Shunts– the Alleviant System is one such strategy that creates a shunt using radiofrequency energy-based septectomy that has shown safety and clinical efficacy with patency through 12-months follow-up in the first-in-human clinical study (ALLEVIATE HF-1) (81). The implant-free approach has a unique advantage over implantable IASDs–it does not preclude the use of the inter-atrial septum for any future structural or electrophysiological interventions.

STRUCTURAL INTERVENTIONS FOR HEMODYNAMIC MONITORING

Implantable micro-electromechanical-based sensors in the Pulmonary Artery (PA) have been developed to assist in real-time monitoring of cardiac filling pressures to tailor medical therapy and pre-empt a heart failure exacerbation. This is particularly important for patients with HFpEF, where patients are threading a narrow line between hypervolemia and heart failure and hypovolemia and underfilling of the ventricle resulting in hypotension. CHAMPION was a single-blinded randomized controlled trial that showed a clinically meaningful and significant reduction in HF admissions in patients with moderately symptomatic heart failure (New York Heart Association (NYHA) class III HF with a recent admission in the past 12 months) with the use of the wireless PA pressure monitoring using the CardioMEMS^{TM} HF system (Abbott) compared to medical therapy alone. HF admissions were consistently reduced in patients with HFpEF and HFrEF with a significant change in diuretic dosing across the two arms; this effect was apparent after about 3 months of diuretic titration in the treatment arm and persisted up to 17 months of follow-up (50% relative reduction for HFpEF and 26% for HFrEF) (82). CardioMEMS^{TM} HF system was approved by the Food and Drug Administration for the indications studied in the CHAMPION trial in 2014. Recently, the GUIDE-HF trial studied hemodynamic monitoring-guided management of HF with the CardioMEMS^{TM} HF system compared to medical therapy alone in patients with mild-severe chronic HF (NYHA class II-IV) and patients were not required to have a recent HF admission if they had elevated natriuretic peptides– no significant difference was noted in the primary composite end-point of all-cause mortality and HF events in either HFrEF or HFpEF at 12 months follow-up in this trial (83). It is important to note that the disruptions caused by the Coronavirus Disease 2019 (COVID-19) pandemic may have had a significant impact on this trial results– analyzing the pre-specified pre-COVID-19 sub-group, a benefit was noted with reduced HF admissions in the hemodynamic monitoring-guided management arm, however, it is hypothesis-generating as this analysis lacks adequate power. Another similar micro-electromechanical-based sensor is the Cordella^{TM} (Endotronix Inc.) device that showed promising safety and accuracy data (SIRONA first-in-human study) and is currently being studied in a randomized controlled trial in patients with NYHA class III HF (PROACTIVE-HF) (84, 85). Compared to the CardioMEMS^{TM} HF system that is implanted in the left pulmonary artery, the Cordella^{TM} HF system is implanted in the right PA and the integrated system includes the incorporation of clinical variables in the form of symptoms heart rate, blood pressure, oxygen saturation and weight in addition to the invasive hemodynamic data for HF management. While helpful in monitoring left-sided filling pressures, these devices offer little in terms of right-sided pressure monitoring and use can be limited in patients with recent pulmonary embolism or a predisposition to recurrent pulmonary emboli.

VENTRICULAR RESTORATIVE DEVICES

In HFrEF patients, with disease progression, the left ventricle remodels into a dilated, spherical cavity to compensate and maintain cardiac output based on the Frank-Starling relationship. However, this adverse remodeling results in increased end-diastolic volumes with increased wall stress, more FMR, and drives refractory heart failure symptoms. Ventricular restorative devices are being actively researched to restore the altered LV geometry in patients with refractory heart failure. Parachute® (Cardiokinetix) is a catheter-based, self-expanding, umbrella-shaped, partitioning device, that was intended to separate the aneurysmal portion of the LV and create a new apex in patients with ischemic cardiomyopathy. While the first-in-human study (PARACHUTE) in patients with HFrEF (EF 15–40% and an akinetic of dyskinetic apex) showed safety and feasibility, at 3-year follow-up, a reduction in stroke volume and LVEF were noted. This device was subsequently tested in a randomized, controlled trial (PARACHUTE IV) that enrolled 331 subjects with NYHA class III-IV ischemic cardiomyopathy and wall motion abnormalities (EF 15–35%) with suitable anatomy for the device, however, the trial was terminated prematurely in 2017 and this device is not in use currently (86). Another device designed to help restore the dysfunctional geometry in a failing ventricle is the AccuCinch® (Ancora Heart Inc.) Ventricular Restoration System– a nitinol anchor-based cinching cable positioned in the LV cavity below the mitral valve through a retrograde transventricular approach. This is still being tested in early feasibility trials in patients with HFrEF or moderate or higher degree of FMR with NYHA class III-IV symptoms despite optimal medical therapy (CorCinch) (87). BioVentrix Revivent TC^{TM} is another alternative to surgical left ventricular reconstruction. This device is implanted through a hybrid mini-thoracotomy (left ventricle-septum-right ventricle) and transcatheter approach (neck vein-right ventricle) with its internal anchor implanted into the right ventricle across the anterior septum and the external anchor latched onto the

epicardial surface– it restores left ventricular geometry in patients with ischemic cardiomyopathy through the exclusion of scarred/dyskinetic/aneurysmal myocardium. A single-arm multi-center study of 86 patients with symptomatic ischemic cardiomyopathy (LVEF 15–45%) showed sustained improvement in heart failure symptoms, LVEF and LV volumes at 12 months with this device with >90% survival (4 in-hospital deaths were noted) (88). Based on these promising results, this device has been granted CE approval in Europe and is currently being evaluated against medical therapy in the ongoing pivotal ALIVE trial (89).

CARDIAC SOFT-ROBOTIC SLEEVES

Cardiac sleeves envisage the use of biomimetic implantable robotic devices for ventricular support in heart failure patients. The sleeves have certain benefits compared to current VAD in clinical practice– they can provide bi-ventricular support, no contact with blood reduces the risk for thrombosis, they can be activated to provide support to the heart during systole as well as diastole, and finally, level of support can be weaned as the native function recovers (90). These robotic sleeves are still being tested in pre-clinical animal models. CorInnova Inc has developed such a pneumatically actuated robotic device for biventricular support with a polyurethane membrane on a self-expanding nitinol frame that can be deployed through a mini-thoracotomy with a sutureless pneumatic attachment to the heart– it has shown promising results in pre-clinical ovine models with the first-in-human studies are being planned (91). This device is intended as a short-term cardiac assist device as bridge-to-decision or bridge-to-transplant and for long-term use in patients with advanced heart failure who are ineligible for VADs.

CONCLUSION

In summary, in the last decade, there has been tremendous growth in the development of transcatheter interventions to improve heart failure outcomes. Given the multitude of structural therapies available and the clinical complexity involved in decision-making, the role of team-approach with involvement of the advanced heart failure team, multi-modality cardiac imagers, different medical sub-specialties (intensive care, nephrology and hepatology) and the structural heart team cannot be overstated. Finally, early consideration of structural therapies is paramount to ensure good outcomes before end-organ damage has ensued. The ongoing trials for cardiac robotic sleeves, ventricular restorative devices, implant-free inter-atrial shunts, novel transcatheter mitral and tricuspid valve devices would help shape the future of heart failure management.

AUTHOR CONTRIBUTIONS

DK and MM were involved in the planning, execution, writing, and critical appraisal of this manuscript. All authors contributed to the article and approved the submitted version.

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Readiness of Advance Care Planning Among Patients With Cardiovascular Disease

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Background: Advance care planning (ACP) is a widely advocated strategy to improve outcomes at end-of-life care for patients suffering from heart failure (HF). However, finding the right time to start ACP is challenging for healthcare providers because it is often a sensitive issue for patients with HF and their families. We interviewed patients with cardiovascular diseases regarding ACP readiness and investigated the relationship between the ACP desire and multiple clinical prognostic parameters.

Method: Eighty-one patients (average age 81.8 ± 10.3 years old, 42 men, 62 cases of HF) who introduced cardiac rehabilitation were inquired about previous ACP experience, a desire for ACP, understanding of their cardiovascular diseases, and lifestyle-associated questionnaires. Multiple logistic regression analyses were employed to identify the clinical parameters associated with ACP desire. Patients who desired ACP were also asked about their preferences for medical care at the end-of-life.

Results: Nine patients (11.1%) had previous experience with ACP, and 28 (34.6%) preferred to implement ACP. Patients who did not want to implement ACP were 54.3%. Patients with HF showed a higher acceptance rate of ACP (odds ratio [OR] 5.56, $p = 0.015$). Interestingly, patients harboring skeletal muscle frailty showed lower ACP acceptance, while patients with non-frailty rather positively wanted to implement ACP. Two types of prognosis evaluation scales, such as the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) risk score and the Japanese Version of Supportive and Palliative Care Indicators Tool (SPICT-JP), identified 31 patients (38.3%) needing ACP; however, 19 (61.3%) did not want ACP. The wish not to attempt resuscitation and life-prolonging treatment at the end-of-life reached approximately 70% among patients who requested ACP.

Conclusions: Although patients with HF tended to be ready for implementing ACP, the presence of skeletal muscle frailty was negatively associated with ACP preference. Indeed, patients who should be considered ACP were not carried out and did not desire it. Earlier introduction of ACP into patients before having skeletal muscle frailty may be considered.

Keywords: advance care planning, readiness, cardiovascular disease, predictive factors, end-of-life

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INTRODUCTION

The number of elderly patients with heart failure (HF) repeatedly admitted to hospitals due to acute exacerbations increases with the aging society. In many cases, symptoms during acute exacerbations improve quickly with treatment, so it is known that both patients and healthcare providers have dissociated perceptions of prognosis from reality. It is important to conduct advance care planning (ACP) to prepare for future conditions, such as the terminal stage. The goal is for the patient to lead a satisfying life at the end-of-life. ACP has been reported to improve clinical outcomes (1–5), not to increase anxiety, depression, and hopelessness in patients (6–11), reduce distress in surrogate decision-makers (5, 12), and reduce costs (13). Lack of proper communication about end-of-life preferences leads to lower quality of life, patient anxiety and family distress, the prolonged dying process, unwanted hospitalizations, distrust of medical care, physician burnout, and higher costs (14). However, it is often difficult for patients to face death themselves at the terminal stage, and it is difficult for medical professionals to broach the topic. ACP should be performed when the patient's readiness is in order (15) but it is not easy to confirm this condition.

Therefore, we decided to survey cardiac rehabilitation patients, i.e., relatively healthy patients with cardiovascular disease, about their experience and desire for ACP implementation.

METHODS

Consecutive patients who were introduced to first cardiac rehabilitation at the Tokuyama Medical Association Hospital between July 2019 and August 2021 were assessed for study inclusion. The questionnaire was used to survey patients before cardiac rehabilitation (**Table 1**). Briefly, we asked patients about their previous ACP experience, their desire for ACP, their diagnosis, and lifestyle-associated questionnaires. Patients who had previous experience with ACP or expressed a desire to implement ACP were categorized as the ACP preferred group. Patients who did not want to receive ACP were regarded as the ACP un-preferred group in the following text and tables.

Clinical variables were obtained from the medical records. These include the following variables; i.e., the existence of HF, New York Heart Association (NYHA) classification, left ventricular ejection fraction (LVEF), Controlling Nutrition Status (CONUT) score, Geriatric Nutritional Risk Index (GNRI), body mass index (BMI), Functional Independence Measure (FIM), and Short Physical Performance Battery (SPPB) collected within a week following the initiation of cardiac rehabilitation.

The CONUT score is calculated from serum albumin, total cholesterol concentrations, and total lymphocyte count, and evaluated nutrition status as follows: 0–1 point as normal, 2–4 points as mild, 5–8 points as moderate, and >8 points as severe malnutrition (16, 17). The GNRI is a nutritional risk index published by Bouillanne et al. in 2005 and is calculated by the formula of [1.489 × serum albumin (g/L) + 41.7 × body weight (kg)/ideal weight (kg)] (18). Its prognostic value has been evaluated in elderly patients, hemodialysis patients, and HF patients. From GNRI values, they defined four grades of nutrition-related risk: major risk (GNRI: <82), moderate risk (GNRI: 82 to <92), low risk (GNRI: 92 to <98), and no risk (GNRI: >98) (18). The FIM is an activity of daily life assessment method that includes motor and cognitive items and is scored on a scale of 18–126 (19). The SPPB is an index for evaluating lower limb function in the elderly and is based on a 4-point scale for balance, gait, and standing (20). Eight or fewer points were regarded as frail (19). Personal health records and questionnaires confirmed the coexistence of cancer and chronic obstructive pulmonary disease (COPD), history of aspiration pneumonia, and cerebrovascular disease. The coexistence of dementia was identified as less than 21 points

TABLE 1 | Questionnaire at the time of initiation of cardiac rehabilitation.

Q1. For what disease have you been advised to undergo rehabilitation this time? If you have heart failure, what has been explained by your doctor as the cause of your heart failure? Please describe to the extent you can understand.
Q2. What symptoms are you currently experiencing? Shortness of breath on exertion/chest pain on exertion/leg pain on exertion/palpitations/swelling/Other
Q3. Do you have an exercise habit in your daily life? No/Yes Please specify the type and frequency of your exercise.
Q4. Please check all that apply for your current residence. Home / Institution / Other
Q5. Please check all that apply to your family members who live with you. Husband / Wife / Son / Daughter / Grandson / Other
Q6. In case of an emergency, if you are unable to confirm your intentions, who can you ask to make decisions on your behalf? Name: Relationship: Contact information (phone number)
Q7. Are you currently working? Yes/ No/ On leave and planning to return to work
Q8. Are you currently a cigarette smoker? Yes/No
Q9. If you are a current or former smoker, please tell us how many cigarettes you smoke per day and how long you have smoked. ( ) cigarettes/day, ( ) years
Q10.If you are a drinker, what is your average amount of alcohol consumed per day and days per week? ( )/day, ( )/week
Q11. Do you experience choking when you drink or eat? Often/ Sometimes/ Almost never
Q12. Do you have a heart failure certificate? Yes/No
Q13. Do you have a pacemaker or other device implanted in your body? Yes/No
Q14. If there is a patient class where you can learn about cardiovascular diseases and what you should do in your daily life, would you like to attend? Yes/No
Q15. Do you know what benefits can be expected from cardiovascular rehabilitation? Yes/No
Q16. Have you talked with your doctors or other medical professionals about what kind of treatment you want or do not want to receive, where you want to spend your time, etc. in the end-stage of your illness? With a doctor / With a medical professional other than a doctor / None
Q17. Would you like to discuss the above? Yes/No

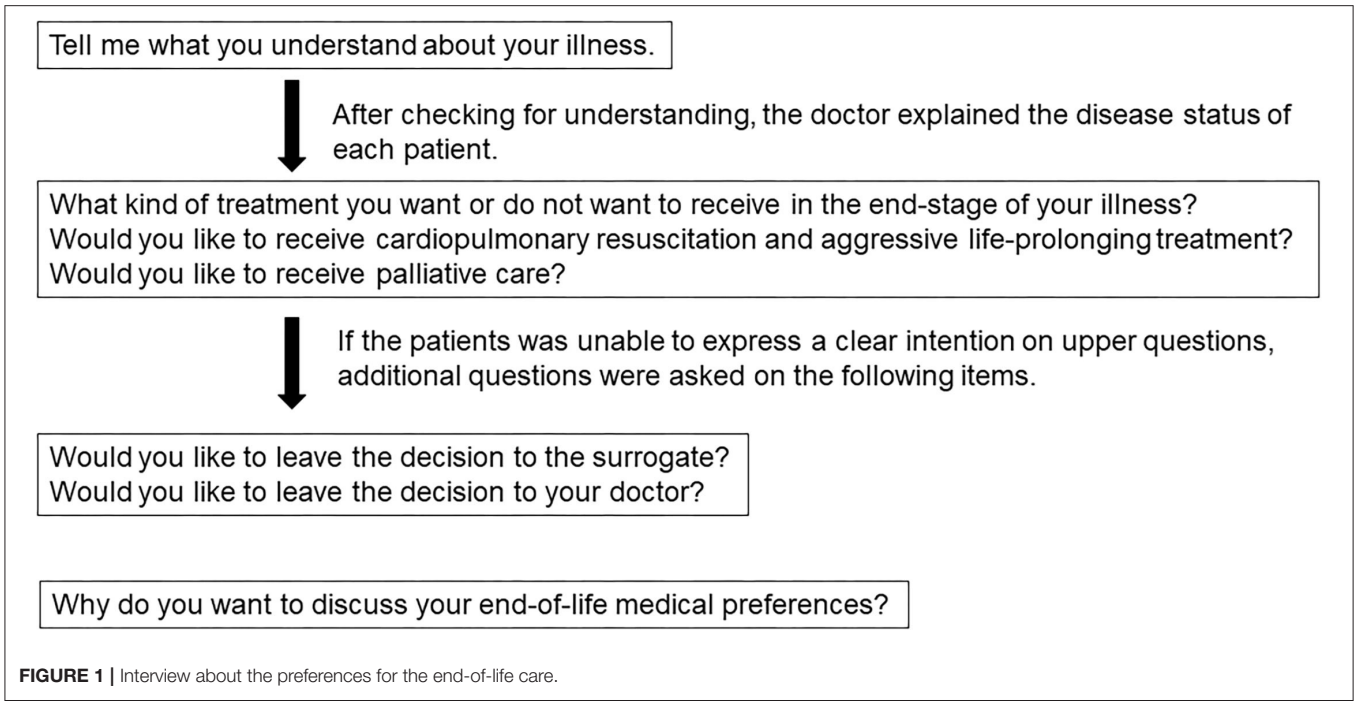

FIGURE 1 | Interview about the preferences for the end-of-life care.

of Mini-Mental State Examination (MMSE) or administration of oral dementia drug.

The Enhanced Feedback for Effective Cardiac Treatment (EFFECT) risk score and the Supportive and Palliative Care Indicators Tool Japanese Version (SPICT-JP) were used as prognostic scales (21–23). The EFFECT risk score predicts 30-day and 1-year mortality by using the following factors: age (year), respiratory rate (breaths/min), systolic blood pressure (mmHg), blood urea nitrogen (mg/dl), presence of sodium concentration <136 mEq/L, cerebrovascular disease, dementia, COPD, hepatic cirrhosis, cancer, and the value of hemoglobin <10.0 g/dl. Patients with very low-risk scores (≤60) had a mortality rate of 0.4% at 30 days and 7.8% at 1 year. Patients with very high-risk scores (>150) had a mortality rate of 59.0% at 30 days and 78.8% at 1 year (21).

The SPICT consists of a combination of general clinical indicators (e.g., poor performance status, unplanned hospital admissions, or persistent symptoms despite optimal treatment of the underlying condition) relevant to patients with any advanced illness and disease-specific indicators for common advanced conditions (e.g., cancer, dementia, and cardiac, pulmonary, or renal disease) (22). It has been reported that four multidisciplinary teams identified 130 patients with advanced kidney, liver, cardiac, or lung disease following an unplanned hospital admission. Hospital clinicians used the SPICT to identify patients at risk of deteriorating and dying. Patients who died had significantly more frequent unplanned admissions, persistent symptoms, and increased care needs. By 12 months, 62 (48%) of the identified patients had died; 69% of them died in hospital, having spent 22% of their last 6 months there (22). One report shows that the SPICT identified patients with palliative care needs better than the surprise questions commonly used in clinical practice. The sensitivity of the surprise question became 69%, of the SPICT 81% regarding predicting 1-year mortality (24). The SPICT-JP is a Japanese version of the SPICT tool (23). The SPICT-JP positive is defined as the presence of two or more of the general indicators of deteriorating health or one or more of the clinical indicators of an advanced state of each disease. Patients who requested ACP in the questionnaire were asked about their preferences for end-of-life care to the extent possible. The dialogue content was prepared regarding previous studies (25, 26). The physicians conducted the interviews following the procedure shown in **Figure 1**.

The experience with ACP was defined as those who answered "With a doctor" or "With a medical professional other than a doctor" to "Q16. Have you talked with your doctors or other medical professionals about what kind of treatment you want or do not want to receive, where you want to spend your time, etc., in the end-stage of your illness?" of the questionnaire. The desire of ACP was defined as those who answered "Yes" to "Q17. Would you like to discuss the above?" of the questionnaires. The end-of-life was defined as a 1-year mortality rate >50%, according to the EFFECT risk score or positive SPICT-JP in this study.

Patients were informed of the publication of the survey results, obtained with the individual's consent. This protocol received approval from the Ethics Committee of Tokuyama Medical Association Hospital (*approval number*: 12), and it conformed to the Declaration of Helsinki provisions.

Statistical Analysis

The patients' backgrounds were compared between the ACP preferred patients and un-preferred patients using the Fisher's exact test for categorical variables, unpaired *t*-test for continuous normative data, and Mann-Whitney U test for non-normative

TABLE 2 | Patient characteristics.

	Total ($n = 81$)
Age(years), mean ± SD	81.8 ± 10.3
Gender	
Male, *n* (%)	42 (51.9)
Female, *n* (%)	39 (48.1)
Inpatients, *n* (%)	58 (71.6)
Outpatients, *n* (%)	23 (28.4)
Living situation	
Cohabitation with family, *n* (%)	45 (55.6)
Separation, *n* (%)	36 (44.4)
Cardiovascular disease	
Heart failure, *n* (%)	62 (76.5)
IHD, *n* (%)	31 (38.3)
Atrial fibrillation, *n* (%)	39 (48.1)
After open heart surgery, *n* (%)	6 (7.4)
Aortic disease, *n* (%)	4 (4.9)
PAD, *n* (%)	23 (28.4)
HT, *n* (%)	57 (70.4)
Non-cardiovascular disease	
CKD	60 (74.1)
Dyslipidemia, *n* (%)	34 (42.0)
DM, *n* (%)	26 (32.1)
Cancer, *n* (%)	5 (6.2)
Dementia, *n* (%)	30 (37.0)
COPD, *n* (%)	7 (8.6)
History of aspiration pneumonia, *n* (%)	3 (3.7)
History of cerebral vascular disease, *n* (%)	15 (18.5)
Evaluation items	
Understanding of the disease	31 (38.3)
NYHA, median (IQR)	3 (2,3)
BMI, mean ± SD	22.1 ± 3.7
LVEF, mean ± SD	51.4 ±15.6
CONUT score, median (IQR)	4 (2,5)
GNRI, mean ± SD	93.6 ± 10.8
SPPB, mean ± SD	6.8 ± 3.8
FIM, median (IQR)	99 (79, 119)

Values were shown as mean ± standard deviation (SD), median (interquartile range (IQR): 25th to 75th percentiles), n (%). IHD, ischemic heart disease; PAD, peripheral artery disease; HT, hypertension; CKD, chronic renal disease; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association classification; BMI, body mass index; LVEF, left ventricular ejection fraction; CONUT score, controlling nutritional status; GNRI, geriatric nutrition risk index; SPPB, Short Physical Performance Battery; FIM, Functional Independence Measure.

continuous data. Univariate and multiple logistic regression analyses were employed to analyze the association between ACP preference and clinical prognostic parameters. Independent variables for multiple logistic analysis were selected from three predictive factors with $p < 0.15$ using univariate analysis, HF, CONUT score as the nutritional status, and SPPB as the degree of frailty. The probabilities of higher EFFECT risk score and SPICT-JP positive group were compared between the ACP preferred group and the unpreferred group using Fisher's extract method.

All statistical analyses were performed with EZR (27). Briefly, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics, and results with a value of $p < 0.05$ were considered statistically significant.

RESULTS

Of the 100 patients initially introduced to cardiac rehabilitation at the Tokuyama Medical Association Hospital, 81 answered the questionnaire. The patient characteristics are shown in **Table 2**. The mean age was 81.8 years, 58 (71.6%) patients were hospitalized, 62 (76.5%) patients had HF with stage C, or more advanced stage, 30 (37.0%) patients had dementia, the mean GNRI was 93.6, and the mean SPPB was 6.8. Nine patients (11.1%) had previous experience with ACP, and 28 (34.6%) patients did not perform but were willing to implement ACP. Comparing patients in the ACP preferred ($n = 37$) and unpreferred groups ($n = 44$), there were significant statistical differences in the CONUT score, SPPB, and FIM groups. Multivariate analysis showed further significant differences in HF (odds ratio [OR] 5.56, $p = 0.015$) and SPPB (OR 1.25, $p = 0.006$; **Table 3**). These data indicate that patients with stage C or advanced HF showed a higher acceptance rate of ACP. In addition, patients harboring lower body skeletal muscle frailty (low SPPB score) showed a lower preference for ACP. In contrast, patients with non-frailty (SPPB score >8) tended to want to implement ACP.

Twenty-nine patients (35.8%) were predicted to have a mortality of ≥50% within 1 year by the EFFECT risk score (poor prognosis group); 32.4 and 38.6% of patients in the ACP preferred and unpreferred groups, respectively (no significant difference between the two groups). In contrast, 13 out of 81 patients (16.0%) were judged to have a poor (positive) prognosis using the SPICT-JP tool. The poor prognosis group was less frequent in the ACP preferred group and more frequent in the ACP unpreferred group ($p = 0.03$). These results indicate that patients who were judged as SPICT-JP positive tended not to prefer ACP (**Table 4**).

At the time of this survey, 31 patients had expressed a preference for ACP, and doctors conducted ACP dialogues with 24 of these patients (2 with previous ACP experience and 22 with no previous ACP experience). **Table 5** examines the 24 patients' wishes regarding their medical care. Do-not-attempt-resuscitation (DNAR) accounted for 70.8% of the patients' end-of-life medical care. There was no significant difference in this medical preference between patients who were judged to be terminal by the EFFECT risk score or SPICT-JP and those who were not judged to be terminal by the EFFECT risk score or SPICT-JP. The reasons for requesting ACP were as follows: old age 10 (41.7%), no specific reason 7 (29.7%), aversion to life-prolonging treatment 5 (20.8%), and living alone 3 (12.5%).

DISCUSSION

The surprise question has been widely used to determine the timing of ACP (28). However, the prognosis of HF is difficult

TABLE 3 | Univariate and multivariate analyses to predict preference of ACP.

	Univariate analysis			Multivariate analysis		
	ACP preferred	**ACP un-preferred**	***P* value**	**OR**	**95%CI**	***P* value**
	(*n* = 37)	(*n* = 44)				
Age (years), mean ± SD	81.4± 12.0	82.0 ± 8.8	0.78			
Male, *n* (%)	22 (59.5)	20 (45.5)	0.27			
Outpatients, *n* (%)	14 (37.8)	9 (20.5)	0.14			
Heart failure, *n* (%)	32 (86.5)	30 (69.8)	0.11	5.56	1.39–22.20	0.015*
Cancer, *n* (%)	2 (5.4)	3 (6.8)	1			
Dementia, *n* (%)	12 (32.4)	18 (40.9)	0.70			
COPD, *n* (%)	2 (11.4)	5 (11.4)	0.45			
History of aspiration pneumonia, *n* (%)	1 (2.7)	2 (4.5)	1			
History of cerebral vascular disease, *n* (%)	7 (18.9)	8 (18.2)	1			
Separation, *n* (%)	16 (43.2)	20 (45.5)	1			
Understanding of the disease, *n* (%)	15 (40.5)	16 (36.4)	0.82			
NYHA, median (IQR)	2 (2,3)	3 (2,3)	0.58			
BMI, mean ± SD	22.1 ± 3.1	22.1 ± 4.2	0.91			
LVEF, mean ± SD	47.7 ± 17.4	54.4 ± 13.5	0.06			
CONUT score, median (IQR)	3 (2,5)	4 (3,6)	0.005*	0.82	0.65–1.03	0.087
GNRI, mean ± SD	95.9 ± 10.7	91.6 ± 10.8	0.07			
SPPB, mean ± SD	8.2± 3.3	5.7 ± 3.8	0.002*	1.25	1.07–1.48	0.006*
FIM, median (IQR)	109(92, 124)	95 (70, 114)	0.009*			

**Indicates $p < 0.05$. In univariate analysis, age, BMI, LVEF, GNRI, and SPPB were compared using an unpaired t-test for continuous normative data. NYHA, CONUT score, and FIM were compared using the Man-Whitney U test for non-normative continuous variables, and others were compared using Fisher's exact test for non-continuous variables. Predictors of preference of ACP were identified by logistic regression analysis. Independent variables were selected from predictive factors with $p < 0.15$ using univariate analysis. OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association classification; BMI, body mass index; LVEF, left ventricular ejection fraction; CONUT score, controlling nutritional status; GNRI, geriatric nutrition risk index; SPPB, Short Physical Performance Battery; FIM, Functional Independence Measure.*

TABLE 4 | Relationship between estimated prognosis and advance care planning (ACP) preference.

	Total	**ACP preferred**	**ACP un-preferred**	***P* value**
	(*n* = 81)	**(*n* = 37)**	**(*n* = 44)**	
1. 1-year mortality rate >50% due to the EFFECT risk score, *n* (%)	29 (35.8)	12 (32.4)	17 (38.6)	0.64
2. SPICT-JP positive, *n* (%)	13 (16.0)	2 (5.4)	11 (25.0)	0.03*
1. and/or 2. positive, *n* (%)	31 (38.3)	12 (32.4)	19 (43.2)	0.37

**Indicates $p < 0.05$. The difference in the experience or desire for ACP between the poor prognosis group and the not poor prognosis group identified by the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) risk score and Japanese Version of Supportive and Palliative Care Indicators Tool (SPICT-JP) was compared using Fisher's exact test for non-continuous variables.*

TABLE 5 | Medical Preferences among patients who requested advance care planning (ACP).

	Total	**End-of-life**	**Not end-of-life**	***P* value**
	(*n* = 24)	**(*n* = 9)**	**(*n* = 15)**	
Aggressive life-prolonging treatment, *n* (%)	0 (0)	0 (0)	0 (0)	
Do not attempt resuscitation and life-prolonging treatment, *n* (%)	17 (70.8)	6 (66.7)	11 (73.3)	1.00
Palliative care, *n* (%)	6 (25.0)	3 (33.3)	3 (20.0)	0.63
Leave the decision to the surrogate, *n* (%)	3 (12.5)	2 (22.2)	1 (6.7)	0.53
Leave the decision to their doctor, *n* (%)	6 (25.0)	3 (33.3)	3 (20.0)	0.63

The differences in medical preferences between the end-of-life and not end-of-life groups were compared using Fisher's exact test for categorical variables. The "end-of-life" group was identified by a 1-year mortality rate >50% according to EFFECT risk score or Japanese Version of Supportive and Palliative Care Indicators Tool (SPICT-JP) positive.

to predict, and advance directives are rarely performed even when the patient is judged to be terminal stage by cardiologists (29). Patients with HF are more optimistic than clinicians in estimating life expectancy (30). Barriers to implementing ACP for healthcare providers include not understanding how to proceed with discussion, a concern that it may cause psychological distress to the patient, the desire to avoid the topic of end-of-life, the desire to avoid dealing with death anxiety, time constraints, difficulty in predicting prognosis, and lack of understanding of how to apply the ACP process to care (14). Factors on the patient's side include anxiety, denial, and a desire not to bother the family (14). Patients facing life-threatening situations tend to avoid discussing end-of-life issues. Other reports have shown

that only 47% of patients with symptomatic HF could complete an advance directive, despite appropriate approaches (31). This study also showed that patients who were identified as having a poor prognosis by HF patients with physical frailty and SPICT-JP did not desire ACP. It was considered difficult to implement ACP for patients in the end-stage of HF, although palliative care is recommended. Investigations in previous studies have been dedicated to topics related to ACP (25, 26, 32, 33). The questionnaire in this study, which asked about lifestyle and social factors, showed that patients involved in ACP discussions were less willing to do so voluntarily. These patients may need to be encouraged and informed about ACP by the medical profession. A study of ACP readiness in patients with advanced lung and colorectal cancer reported that patients did not have to be ready for all ACP topics. They were able to participate in an ACP conversation (26).

On the other hand, such a questionnaire seems to be a good way to pick up ACP wishes in a group of patients who do not yet have a poor prognosis. Patients, who had HF, maintained muscle strength, and had been still far from a poor prognosis, were more willing to perform ACP. Although ACP for patients in situations far from death is considered impractical, initiating dialogue to explore the patient's values at the first ACP can be expected to lower the hurdle of ACP for both the patient and the medical profession. There was no difference in the preference for end-of-life care between the good prognosis group and the poor prognosis group. Moreover, about 70% of the patients in both groups expressed their intention to DNAR. Patients who reported to have an end-of-life conversation were more likely to report peacefulness and desire and received less-invasive care (2).

In a large study of patients older than 60 years, of those who required decisions, 70% did not have decision-making capacity, leaving decisions to surrogates or to previous advance directives (5). Japan has a universal healthcare system. Our healthcare system is oriented toward providing life-sustaining treatment and tends to provide intensive medical care for the elderly. In Japan, there is a tradition of abhorrence of death and a cultural background that makes it difficult to mention death. The HF pandemic is a major problem in Japan's aging society. It has become a vexing issue for medical professionals regarding how far they should go in providing treatment to frail elderly patients (34). In recent years, the ACP has been promoted as a national policy, and in 2018, the ACP was nicknamed the "Life Conference." The number of people interested in ACP increases due to these educational activities, but medical staff cannot conduct ACP. This study suggests that ACP should be administered gradually to patients with the cardiovascular diseases earlier than we had assumed.

LIMITATIONS

This study has several limitations. First, this research was a single-center study and a small sample size. Further studies with larger samples and multicenter enrollment need to be considered. Second, this study was exclusively Japanese and did not include other races, such as African American, White, Pacific, or others.

CONCLUSIONS

Nearly half of patients with cardiovascular diseases introducing cardiac rehabilitation expressed a preference for ACP. Although patients with HF tended to be ready for implementing ACP, skeletal muscle frailty was negatively associated with ACP acceptance. Patients who should be considered ACP were not carried out and did not desire it. Earlier introduction of ACP into patients before having frailty may be considered.

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 Ethics Committee of Tokuyama Association Hospital (Approval Number: 12). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NF was the primary investigator for this study, collected data, and the overall writing of the project. YI supervised the writing of this paper, reviewed all documents, and helped to analyze the data, figures, and tables. EN administered the questionnaire. MK, KO, SS, and AT reviewed the manuscript and offered insights based on their experiences. All authors gave final approval, agreed to be accountable for all aspects of the work, and ensuring integrity and accuracy.

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