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Authors: Ewa Piotrowicz, Michael Pencina, Ilona Kowalik, Piotr Orzechowski, Maciej Banach, Renata Glowczynska, Wojciech Zareba, Grzegorz Opolski, Dominika Szalewska, Sławomir Pluta, Zbigniew Kalarus, Robert Irzmanski, Ryszard Piotrowicz

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Predictors of long-term prognosis based on clinical status and measurements achieved after 9-week Hybrid Comprehensive Telerehabilitation in Heart Failure Patients: A Subanalysis of the TELEREH-HF Randomized Clinical Trial

Short title: Predictors of long-term prognosis in heart failure patients

Ewa Piotrowicz[1], Michael Pencina[2], Ilona Kowalik[3], Piotr Orzechowski[1], Maciej Banach[4], Renata Glowczynska[5], Wojciech Zareba[6], Grzegorz Opolski[5], Dominika Szalewska[7], Sławomir Pluta[8], Zbigniew Kalarus[8], Robert Irzmanski[9], Ryszard Piotrowicz[3, 10]

[1]Telecardiology Center, National Institute of Cardiology, Warszawa, Poland
[2]Duke University's School of Medicine, Durham, NC, United States
[3]Institute of Cardiology, Warszawa, Poland
[4]Department of Hypertension, Medical University of Łódź, Łódź, Poland
[5]1st Chair and Department of Cardiology, Medical University of Warsaw, Warszawa, Poland
[6]University of Rochester Medical Center, Rochester, NY, United States
[7]Department of Rehabilitation Medicine, Medical University of Gdansk, Gdańsk, Poland
[8]Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Silesian Medical University, Silesian Center for Heart Diseases, Zabrze, Poland
[9]Department of Internal Medicine and Cardiac Rehabilitation, Medical University of Lodz, Łódź, Poland
[10]College of Rehabilitation, Warszawa, Poland

Correspondence to:
Ewa Piotrowicz, MD, PhD, FESC,
Telecardiology Center, National Institute of Cardiology,
Alpejska 42, 04–628 Warszawa, Poland,
phone: +48 22 343 46 64,
e-mail: epiotrowicz@ikard.pl

WHAT'S NEW?

This is the first risk stratification model for clinically stable heart failure patients based on demographic data, baseline characteristics, clinical status and measurements achieved after 9-week hybrid comprehensive telerehabilitation as the response to exercise training. This risk stratification model indicated the adherence to treatment as the best predictor of long-term prognosis in heart failure patients.

ABSTRACT

Background: Predicting prognosis in heart failure (HF) is of major importance.

Aims: The aim of the study was to define predictors influencing long-term cardiovascular mortality or HF hospitalization ("composite outcome") based on clinical status and measurements obtained after the 9-week hybrid comprehensive telerehabilitation (HCTR) program.

Methods: This analysis is based on TELEREH-HF (TELEREHabilitation in Heart Failure) multicenter, randomized trial that enrolled 850 HF patients (left ventricular ejection fraction [LVEF] ≤40%). Patients were randomized 1:1 to 9-week HCTR plus usual care (development sample) or usual care only (validation sample) and followed for median (interquartile range [IQR]) 24 (20–24) months for development of the composite outcome.

Results: Over 12–24 months of follow-up 108 (28.1%) patients experienced the composite endpoint. The predictors of our composite outcome were: non-ischaemic etiology of HF, diabetes, higher serum level of: N-terminal prohormone of brain natriuretic peptide, creatinine, and high-sensitivity C-Reactive Protein; low carbon dioxide output at peak exercise, high minute ventilation and breathing frequency at maximum effort in cardiopulmonary exercise test; increase of delta of average heart rate in 24 hour-ECG Holter monitoring, lower LVEF and patients' non-adherence to HCTR. The model discrimination C-index = 0.795 and decreased to 0.755 on validation conducted in the control sample which was not used in derivation. The 2-year risk of the composite outcome was 48% in the top tertile versus 5% in the bottom tertile of the developed risk score.

Conclusion: Risk factors collected at the end of the 9-week telerehabilitation period performed well in stratifying patients based on their 2-year risk of the composite outcome. Patients in the top tertile had an almost ten-fold higher risk compared to patients in the bottom tertile. Adherence to treatment but not peakVO_2 or quality of life were significantly associated with the outcome.

Key words: heart failure, prognosis, risk stratification, telerehabilitation

INTRODUCTION

Heart failure (HF) is a major cause of cardiovascular (CV) mortality and hospitalization [1–4]. Despite the progress in pharmacological and non-pharmacological treatment the prognosis for HF patients remains poor [3, 4]. The ESC-HF (European Society of Cardiology-Heart Failure) pilot survey reported that 12-month all-cause mortality rates for hospitalized and ambulatory clinically stable HF patients were 17% and 7%, respectively, and the 12-month hospitalization rates were 44% and 32%, respectively [4]. Moreover, re-hospitalization affects the half of HF patients within 6 months after discharge [3]. Although most HF patients are treated in accordance with current guidelines, the expected benefits are not always achieved for all patients [5–7]. Therefore, many risk stratification models have been developed to identify high-risk patients who need more aggressive treatment and more frequent control visits in follow-up [8–16]. Unfortunately, the clinical value of risk prediction models for HF prognosis and outcomes is limited. This is due to several factors, including the fact that some models were developed before the era of treatment guidelines [13–16]. Moreover, published data showed, that it is easier to predict mortality than to predict HF hospitalization [1]. This may be partially explained by patient-related factors that can determine the prognosis itself. Re-hospitalization rates might depend on the quality of care and the organization of healthcare in a particular country.

Little is known about association between comprehensive assessments and measurements obtained after cardiac rehabilitation of HF patients and their influence on prognosis and the need for re-hospitalization. Most previous studies created risk stratification models based on HF patients hospitalized due to exacerbation of clinical status or HF patients who participated in clinical research assessment of drug treatment administered [8-16]. Only one study reported risk stratification model based on HF patients who were referred to the cardiac rehabilitation programe [2].

The recently completed TELEREH-HF (TELEREHabilitation in Heart Failure) trial demonstrated that 9-week hybrid comprehensive telerehabilitation (HCTR) significantly improves physical capacity and quality of life (QoL) in patients with HF unlike the usual care (UC) [17]. However, HCTR had no significant impact on mortality and hospitalization rates in a long-term follow-up (i.e., 12–24 months) after the intervention was completed [17]. In this context the questions arose: is it possible to translate the short-term improvement in physical capacity and QoL into the improvement in long-term prognosis? Is it possible to select a subgroup of HF patients with a good versus poor long-term prognosis based on risk factors collected at the end of telerehabilitation period? Therefore, the aim of this study was to define

predictors influencing long-term CV mortality or HF hospitalization based on clinical status and measurements obtained after the 9-week HCTR program.

METHODS

The design and main results of the TELEREH-HF study have been published elsewhere [17–21]. The TELEREH-HF trial was a randomized (1:1), multi-center (5 centers in Poland), prospective, open-label, parallel group, controlled study (Clinical Trials.gov NCT 02523560) which compared HCTR plus usual care (UC) with UC alone in 850 clinically stable HF patients (New York Heart Association [NYHA] class I, II or III) with left ventricular ejection fraction (LVEF) ≤40% after a hospitalization due to worsening HF within 6 months prior to randomization. Patients were randomized between June 8, 2015, and June 28, 2017. The detailed TELEREH-HF inclusion and exclusion criteria were previously published elsewhere [17, 18].

The HCTR intervention was comprehensive and encompassed telecare, tailored home-based telerehabilitation, and remote monitoring of cardiovascular implantable electronic devices. The HCTR group patients underwent a 9-week HCTR program consisting of an initial stage (1 week) in hospital and a basic stage (8 weeks) of HCTR performed at home, five times weekly. Patients underwent endurance aerobic training based on Nordic walking, respiratory muscle training, and light resistance and strength training. The detailed description of the medical team composition, the equipment for telemonitoring and the intervention have been published elsewhere [17, 18].

The study was guided by good clinical practice, in accordance with the Declaration of Helsinki and the regulations applicable in Poland. The trial protocol was approved by the local ethics committee (IK-NP-0021-85/1402/13). Each patient provided written informed consent [17, 18].

All patients underwent the following assessments at entry and after completing the 9-week program: clinical examinations (including NYHA class assessment), lab test (blood count, serum creatinine, electrolites [natrium, potassium], glycaemia, N-terminal prohorone of brain natriuretic peptide [NT-proBNP], high sensitivity C-reactive protein [hs-CRP], aspartate aminotransferase, alanine aminotransferase, thyroid stimulating hormone [TSH], international normalized ratio [INR], urinalysis), echocardiography, six-minute walk test (6-MWT), cardiopulmonary exercise test (CPET), 24-hour ECG Holter monitoring, psychological assessment and the evaluation of the adherence to HCTR. Patients were followed during 12–24 months after the intervention/observation was completed to collect data regarding mortality

and hospitalization. Mortality data were collected during follow-up for a maximum of 24 months with a maximum of two check-up visits within the 12 and 24 months following the end of the preliminary 9-week HCTR and the observation period in UC group. The follow-up was also conducted in the form of a telephone conversation with the patients and/or family member on a monthly basis to accurately collect mortality and hospitalization data.

Echocardiography

Two-dimensional echocardiography was performed using standard parasternal, apical, and subcostal views. LVEF was calculated from conventional apical two-chamber and four-chamber images using the biplane Simpson technique.

Six-minute walk test

The 6-MWT was conducted using a standardized protocol after taking usual medications. Patients were required to perform a six-minute shuttle walk test with markers placed at 25m.

Cardiopulmonary exercise test

The symptom-limited CPET on a treadmill according to a ramp protocol and ESC guidelines was performed using a Schiller MTM-1500 med [22-23]. Oxygen consumption (VO_2) was measured continuously using breath-by-breath analysis. The peak VO_2 value was presented per kilogram of body mass per minute (ml/kg/min). Maximal exercise was defined as the respiratory exchange ratio (RER) $\geq$1.

24-hour Holter ECG monitoring

For 24-hour Holter ECG monitoring we used 12-channel, Holter digital recorder Lifecard CF, Del Mar Reynolds Medical UK/US. 24-hour Holter recordings were assessed with the use of analysis system Pathfinder SL, Spacelabs Healthcare. Rigorous quality control was performed on all Holter ECG studies by trained physicians in one center dedicated to Holter analysis.

Psychological assessment

Health-Related Quality of Life Assessment. The Medical Outcome Survey Short Form 36 Questionnaire (SF-36) was used to assess QoL. The SF-36 consists of two major domains (physical and mental QoL) and various subscales [24]. Higher scores indicate a better QoL.

Depression Assessment. The Beck Depression Inventory II (BDI-II) – a 23-item questionnaire, was administered to assess patients' self-reported depression symptoms. In general terms, BDI II scores range from 0 to 63, and the lower the score, the better the patients' emotional condition. Patients with BDI II scores ≥14 were considered affected by depression [25].

Assessment of efficacy of HCTR

Response for HCTR was assessed by changes - delta (Δ) in all evaluated parameters as a result of comparing measurements from the beginning and the end of the program (0 vs. 9 weeks).

Assessment of the adherence to hybrid comprehensive telerehabilitation

Full adherent patients were those who adhered both to the number of training sessions prescribed and to the duration of the prescribed cycle by at least 80%; the rest was classified as partially or non-adherent [17, 18].

Statistical analysis

Our primary analysis focused on patients randomized to HCTR group, with the usual control arm used as validation sample. Quantitative variables are expressed as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate, and categorical variables are expressed as counts and percentages. Missing data were imputed with the median. The distribution of continuous variables was tested for normality with the Kołmogorov-Smirnov test. The study groups were compared using the chi-square test of independence (unless the number of expected events is less than 5, in which cause Fisher's exact test was used) for categorical variables and two independent t-test or Wilcoxon rank-sum tests for continuous data, as appropriate. The primary outcome for this analysis was HF hospitalization or CV mortality. Follow-up time was calculated from the end of the 9-week HCTR to the final visit at the study end (maximum follow-up of the 24 months) or the time when the first event occurred. Patients who were lost during the follow-up were censored at the time of the last contact. Cox proportional hazards regression was used to identify predictors significantly associated with the primary outcome. Candidate predictors are listed in Table 1**.** All variables with significant prognostic impact in univariate analysis ($P \leq 0.10$) were included in the multivariable model. Then a backward selection was used to creating the final model (model I; adjusted for age and sex). Model II was developed after forcing three other common predictors to Model I. The linear predictor obtained in the final Cox proportional hazards regression model was calculated as the risk score. The proportionality of hazards was verified using the weighted

Schoenfeld residuals. Model discrimination was assessed using Harrell's Concordance Statistics (C-index). We first assessed discrimination on the development sample (HCTR) and then applied the final Model I to the usual control arm (not used in model development) as a validation sample. Kaplan-Meier curves were constructed and log rank test with Tukey-Kramer correction for multiple comparison were calculated summarizing the relationship between the tertiles of the risk score and survival. First, the risk score was calculated for each patient, next the patients were divided into 3 groups according to the value of terciles of the risk score and finally the probabilities of surviving without a composite endpoint estimated with Kaplan-Meier method in these 3 groups were estimated and compared. In all analyses, the tests were two-sided, and the level of significance was set at 0.05. The statistical analysis was performed using SAS version 9.4 (SAS Inc., NC, US).

RESULTS

Of the 850 patients randomized, 425 were assigned to HCTR and 425 to UC. Twenty seven patients did not participate in HCTR program due to: technical difficulties with operating the telerehabilitation set (21), new onset of comorbidities (4), return to work (2) [17]. Finally, 384 patients were included in present analysis. Over 12–24 months of follow-up (Median [IQR], 24 [20–24] months) 27 (7%) patients died of cardiovascular causes, 95 (24.7%) experienced HF hospitalization and 108 (28.1%) experienced the composite endpoint. The baseline characteristics of the entire primary study sample (HCTR group) and by composite event status are presented as Supplementary material.

Association of baseline predictors with composite outcome

The predictors of higher CV mortality or HF hospitalization retained after backwards elimination are presented in Table 2 and included the following variables collected at the end of the 9-week telerehabilitation period: non-ischemic etiology of HF, diabetes, higher serum level of: NT-proBNP, creatinine and hs-CRP; low carbon dioxide output at peak exercise, lower LVEF, high minute ventilation and high breathing frequency at maximum effort in CPET. Moreover, the increase in average heart rate in 24 hour-ECG Holter monitoring between week 0 and week 9 achieved statistical significance. Finally, non-adherence to HCTR more than doubled the risk of the primary composite outcome.

Notably, despite improving during the 9-week telerehabilitation period, peakVO_2 at the end of the 9-week program was not significantly associated with the primary composite outcome (Table 2). The same was true for the SF-36 and BDI-II.

The final model's discrimination C-index was 0.795 (95% CI, 0.754–0.836). When validated on the control sample which was not used in derivation, the C-index decreased to 0.755 (95% CI, 0.708–0.802). The baseline characteristics of the UC sample are presented in Supplementary material.

Risk stratification

When the model-based risk of the composite event was stratified into tertiles, we observed substantial separation of the observed 2-year risk of CV mortality or hospitalization. Figure 1 shows the Kaplan-Meier curves for the three ranges of model-based risk: (1) good prognosis (risk score <0.0): 2-year risk of outcome 95% CI, 0.047 (0.010–0.084); (2) moderate prognosis (risk score from 0.0 to 1.1): 2-year risk of outcome 95% CI, 0.260 (0.182–0.338); (3) poor prognosis (risk score >1.1): 2-year risk of outcome 95% CI, 0.481 (0.395–0.567).

DISCUSSION

This analysis from the TELEREH-HF randomized controlled trial database was the basis for the development of the risk stratification model for CV mortality or HF hospitalization occurrence based on the comprehensive non-invasive assessment of HF patients who completed the 9-week HCTR program. To our knowledge, this is the first risk stratification model for clinically stable HF patients based not only on demographic data and baseline characteristics, but also on measurements achieved after 9-week HCTR and response to exercise training assessed by changes (delta [Δ]) in parameters as a result of comparing values from the beginning and the end of the telerehabilitation program.

Based on our data, the score indicated that patients' non-adherence to HCTR, non-ischemic etiology of HF, diabetes, lower LVEF, higher serum level of: NT-proBNP, creatinine and hs-CRP; low peak VCO_2, high VE and high BF at maximum effort in CPET and increase of difference (Δ) in average heart rate in 24h-ECG Holter monitoring between baseline and after 9-week HCTR examinations, each had independent predictive power.

It should be emphasized that in our model patients fully adherent to HCTR were associated with more than twice lower risk of CV death and HF hospitalization. This is in line with published meta-analysis of controlled trials by Ruppar et al., who demonstrated that among HF patients, intervention to improve medication adherence has significant impact on decreasing readmissions and reducing mortality [26]. Hybrid telerehabilitation is a comprehensive procedure which supports adherence to both medical treatment and to the exercise training.

Moreover, daily contact with the telemonitoring center helped patients to develop healthy habits for the future.

The non-ischemic etiology of HF was associated with our composite endpoint. This result is in contrast with data from the Seattle Heart Failure Model, which indicated that ischemic etiology with others predictors (NYHA class, diuretic dose, LVEF, systolic blood pressure, sodium, hemoglobin, percent lymphocytes, uric acid and cholesterol) had independent predictive power [13,14]. However, results from the DANISH study (Danish Study to Assess the Efficacy of ICDs in Patients With Non-Ischemic Systolic Heat Failure on Mortality) reported that for many patients with dilated cardiomyopathy, ICDs do not increase longevity, which indicates that this subgroup of patients had a high risk of CV death [27]. Our analysis confirms these findings. This may be related to myocardial fibrosis as a substrate for malignant ventricular arrhythmias, specific genetic mutations affected arrhythmic risk, not homogenous etiology, and the natural aggressive course of the disease in some cases [27].

Comorbidities are of great importance in the stratification of CV risk. In our model diabetes was associated with higher risk of CV mortality or HF hospitalization in long-term follow up. However, hypertension, stroke, chronic kidney disease and hyperlipidemia were not predictive of prognosis and readmissions. Diabetes is a common comorbidity and ranges from 10 to 30% in HF with reduced LVEF. Additionally, it has a significant negative impact on prognosis [28]. Moreover, diabetic patients more frequently suffered from HF. According to the Swedish Heart Failure Registry, in patients with HF and diabetes mortality was 37% [29]. In the REACH (Reduction of Atherothrombosis for Continued Health) Registry, diabetes was associated with a 33% greater risk of HF hospitalization, moreover the presence of HF at baseline was independently associated with CV death and hospitalization for HF [30]. Diabetes was also the predictor of fatal outcomes in the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial [12]. In the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) model, diabetes with older age and lower LVEF were the most prognostic variables predicting either the composite end point of CV death or HF hospitalization, or the all-cause mortality [15]. Diabetes was associated with around a doubling of risk of either death or the composite outcome when insulin-treated, and 50% increase in risk non-insulin-treated diabetes [15]. In our model, diabetes increased the risk of a composite endpoint one and a half times. In the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) model similarly as in ours, the presence of hyperlipidemia was not predictive of post discharge mortality in HF patients [11]. In contrast

to our results, reactive airway disease, depression, and liver disease were associated with higher risk of post discharge mortality.

LVEF is generally considered a strong predictor of poor prognosis, which was confirmed in the Seattle HF, CHARM and CORONA models as well as in our model [12–15].

Only a few models incorporated biochemical data and biomarkers for risk stratification. This is due, inter alia, to the fact that when the CHARM and Seattle models were developed, biomarkers were not routinely used [13–15].

Renal function is an important predictor of prognosis. In our model the serum creatinine level was a strong predictor of outcome. This result is consistent with the CORONA model [12]. The plasma concentration of NT-proBNP level is commonly used as an initial test in the diagnosis of HF [5, 6]. In the CORONA model, NT-proBNP was the most important prognostic variable for each outcome (CV, HF, sudden cardiac death; CV, HF hospitalization; all-cause mortality or HF hospitalization as well as atherothrombotic and coronary endpoint) which is in line with our results in terms of predicting CV mortality or HF hospitalization [12]. It is worth noticing that although it may be considered that NT-proBNP reflect the cardiac and renal function, both creatinine and LVEF remained in the final models of CORONA and TELEREH-HF. Many inflammatory markers are elevated in HF. In our model hs-CRP was a significant predictor of the composite outcome. Meanwhile, in the CORONA model, hs-CRP was an independent predictor of the atherothrombotic endpoint [12].

Data from CPET are commonly used to determine the prognosis in HF patients. Keteyian et al. evaluated multiple CPET-derived variables for their association with prognosis in patients with HF with reduced LVEF. This analysis showed that the relationship for all variables, except for RER, was highly significant [31]. Published data indicated that peak VO_2, percent predictive VO_2, CPET duration and the VE/VCO_2 slope have the strongest ability to predict prognosis in HF patients [31, 32]. In the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise TraiNing) risk stratification model, the most important predictor for the composite of death or all-cause hospitalization end point was exercise duration in CPET [2]. In our model breathing frequency (BF), maximal minute ventilation (VE) and carbon dioxide production (VCO_2) during CPET were stronger predictors of CV death or HF hospitalization than peak VO_2 and VE/VCO_2 slope. This led to these two last variables not making it into the final multivariable model. Advanced HF is associated with an increase in VE (due to increased dead space ventilation) and an increase in VCO_2 relative to VO_2 (because of bicarbonate buffering of lactic acid), which are in line with our results. Therefore, the association between BF, VE, CO_2 and VE/VCO_2 is very strong and supports these findings.

Another variable which affects prognosis is heart rate. Published data reported an association between increase heart rate over time and cardiovascular and all-cause mortality [32]. This was confirmed in our analysis, where the increase of difference (Δ) in average heart rate in 24h-ECG Holter monitoring between baseline and after 9-week HCTR examinations was a predictor of poor prognosis. Similarly, in the CHARM and CORONA studies heart rate was included in the risk stratification models [12, 15].

It is worth noting that the TELEREH-HF population included a fairly homogeneous group of stable patients with HF with reduced LVEF treated in accordance with the current guidelines (what was included in the study inclusion/exclusion criteria). Ninety-six percent of patients were treated with β-blockers, 93% with an ACEI or ARB, 82% with aldosterone antagonists; 79% had CIEDs, and 62% ICD. Similarly, patients enrolled in the HF-ACTION study were treated according to the evidence-based therapy (95% of them took β-blockers, 74% used ACEI, and 40% had an ICD). The determinants of higher mortality in HF-ACTION trial were male sex, lower body mass index (BMI), higher serum urea nitrogen and shorter CPET duration. The corresponding C-index was 0.73, suggesting moderately good capacity of the model of indicating patients at greater risk of death [2]. For the second predictive model of primary composite end point of death or hospitalization from any cause the same variables were included with one exception — the KCCQ symptom stability statement score was incorporated instead of BMI [2]. The defined models from the HF-ACTION are not consistent with ours. However, the models deal with different aspects of prognosis: in the HF-ACTION death or hospitalization from any cause vs CV mortality or HF hospitalization in the TELEREH-HF study.

In the context of published data, it is worth noting the good C-index of our model, (0.795 in development, 0.755 in validation sample), especially if we consider the fact that the study was randomized. According to the results of the study by Ouwerkerk et al. “cohort and prospective studies produced higher C-statistics than models on the basis of data of randomized trial”[1]. The reason for the lower C-statistic in the other randomized controlled trials may be that these studies were not primarily created for risk stratification model development and the population was more homogenous due to preselection according to inclusion and exclusion criteria.

Identifying a strong model for predicting both prognosis and rehospitalization should allow for a more personalized treatment and holistic management of patients with HF who completed the home-based telerehabilitation program. This is in line with the current recommendations that support multidisciplinary tailored management of HF patients to maintain short-term improvement after hospitalization or other interventions such as cardiac rehabilitation [5, 6].

Strenghts and limitations

The TELEREH-HF model refers to a homogeneous population of patients with HF with reduced LVEF ≤40% treated according to the current standards, which on the one hand is an advantage and on the other hand is a limitation, as the results may not be simply translated into other populations, e.g., HF with preserved LVEF, different racial or ethnic groups. The advantage of this analysis is the comprehensive patient evaluation based on non-invasive examinations recommended by the guidelines achievable in HF and cardiac rehabilitation departments [5, 6]. Notably, our model did not take into account the socioeconomic status of patients, which may also affect prognosis.

The presented results refer only to the Polish population, where diagnostic, treatment options and the organization of healthcare differ in comparison to other European countries [33]. Moreover, the use of new therapies in HF changes the prognosis of the current HF patients in Poland and other countries which might affect the presented results from the perspective of 2023 and current clinical practice.

CONCLUSION

Based on data from the TELEREH-HF randomized trial we were able to show that it is possible to use risk factors collected at the end of the 9-week telerehabilitation period to stratify patients based on their 2-year risk of CV mortality or HF hospitalization. In our model patients in the top tertile had an almost ten-fold higher risk compared to patients in the bottom tertile. Adherence to treatment but not peakVO_2 or quality of life were significantly associated with the outcome.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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Table 1. The baseline characteristics of HCTR group depending on the occurrence of the event; and candidate predictor variables for event (cardiovascular death or heart failure hospitalization)

Baseline	HCTR group with event (n = 108)	HCTR group without event (n = 276)	*P*-value
Male sex, n (%)	94 (87.0)	250 (90.6)	0.31
Age, years, mean (SD)	63.1 (11.3)	61.6 (10.6)	0.20
BMI, kg/m^2, mean (SD)	28.9 (5.1)	28.9 (5.1)	0.99
LVEF, %, mean (SD)	28.5 (7.1)	32.0 (6.6)	**<0.001**
Duration of heart failure, years, median (IQR)	8.0 (3.3–13.7)	5.1 (1.4–10.0)	**0.001**
Etiology of heart failure, n (%)			
Ischemic, n (%)	62 (57.4)	189 (68.5)	**0.04**
Non ischemic, n (%)	46 (42.6)	87 (31.5)	
Past medical history, n (%)			
Atrial fibrillation or atrial flutter, n (%)	29 (26.8)	44 (15.9)	**0.01**
Hypertension, n (%)	54 (50.0)	174 (63.0)	**0.02**
Stroke, n (%)	9 (8.3)	14 (5.1)	0.23
Diabetes mellitus, n (%)	48 (44.4)	82 (29.7)	**0.006**
Chronic kidney disease, n (%)	39 (36.1)	31 (11.2)	**<0.001**
Hyperlipidemia, n (%)	55 (49.5)	135 (48.9)	0.72

Implantable devices, n (%)			
Cardiovascular implantable electronic device, n (%)	91 (84.3)	214 (77.5)	0.14
Implantable cardioverter-defibrilator, n (%)	51 (47.2)	139 (50.4)	0.12
Cardiac resynchronization therapy (CRT-P/CRT-D), n (%)	39 (36.1)	73 (26.4)	
Lab parameters			
NT-proBNP, median (IQR)	1946 (843–813)	669 (261–1307)	**<0.001**
NT-proBNP in patients with sinus rhythm, median (IQR)	1349 (865–2172)	536 (231–1114)	**<0.001**
NT-proBNP in patients with atrial fibrillation or atrial flutter, median (IQR)	2419 (1342–4300)	1349 (865–2172)	**0.01**
Cardiopulmonary exercise test			
pVO2, ml/kg/min, mean (SD)	14.3 (4.4)	18.2 (5.6)	**<0.001**
Minute ventillation at peak effort, l/min, mean (SD)	43.6 (14.4)	51.7 (19.0)	**<0.001**
Breathing frequency at peak effort, /min, mean (SD)	29.5 (6.4)	29.3 (6.3)	0.81
Pharmacotherapy, n (%) the number of patients taking the drug is written in brackets			
β-blocker, n (%)	104 (96.3)	265 (96.0)	>0.99
Bisoprolol (n = 39, n = 120), dose (mg), median (IQR)	5 (5–10)	5 (5–10)	0.55
Carvedilol (n = 31, n = 66), dose (mg), median (IQR)	25 (12.5–50)	25 (12.5–50)	0.85
Metoprolol (n = 21, n = 59), dose (mg), median (IQR)	100 (100–175)	100 (50–175)	0.36
Nebivolol (n = 11, n = 19), dose (mg), median (IQR)	5 (2.5–5)	5 (2.5–5)	0.82
Atenolol, Betaxolol, (n=2, n=1)			

ACEIs/ARBs, n (%)	100 (92.6)	258 (93.5)	0.76
ACEIs, n (%)	86 (79.6)	220 (79.7)	0.99
Ramipril (n = 68, n = 182), dose (mg), median (IQR)	2.5 (2.5–5)	5 (2.5–5)	0.06
Perindopril (n = 10, n = 16), dose (mg), median (IQR)	5 (5–5)	5 (5–5)	0.97
Enalapril (n = 2, n = 6), dose (mg), median (IQR)	20 (10–30)	20 (15–40)	0.73
Cilazapril, Lisinopril, Trandolapril (n = 6, n = 16)			
ARBs n (%)	14 (13.0)	38 (13.8)	0.84
Losartan (n = 5, n = 15), dose (mg), median (IQR)	50 (50–50)	50 (50–50)	0.70
Candesartan (n = 5, n = 6), dose (mg), median (IQR)	8 (4–8)	12 (8–32)	0.12
Valsartan (n = 4, n = 8), dose (mg), median (IQR)	80 (60–120)	80 (80–160)	0.58
Telmisartan (n = 0, n = 9), dose (mg), median (IQR)		80 (40–80)	
Ivabradine, n (%)	7 (6.5)	21 (7.6)	0.70
Ivabradine dose (mg), median (IQR)	7.5 (5–10)	10 (7.5–10)	0.14
Aldosterone antagonists, n (%)	95 (88.0)	228 (82.6)	0.20
Eplerenone (n = 59, n = 153), dose (mg), median (IQR)	25 (25–50)	25 (25–50)	**0.01**
Spironolactone (n = 36, n = 75), dose (mg), median (IQR)	25 (25–25)	25 (25–25)	0.61
After 9 weeks of HCTR			
Functional status by NYHA class, n (%)			
I	17 (15.7)	81 (29.3)	**<0.001**
II	65 (60.2)	169 (61.2)	
III	26 (24.1)	26 (9.4)	
Clinical finding, n (%)			

Lower limb swelling, n (%)	13 (12.0)	17 (6.2)	0.054
Anamnesis, n (%)			
Active smoking, n (%)	6 (5.6)	18 (6.5)	0.72
Alcohol abuse, n (%)	2 (1.8)	9 (3.3)	0.73
Lab parameters			
Sodium, mmol/l, mean (SD)	140.3 (2.9)	140.7 (2.7)	0.14
Potassium, mmol/l, mean (SD)	4.47 (0.47)	4.52 (0.43)	0.33
Hemoglobin, g/dl, mean (SD)	13.8 (1.5)	14.3 (1.3)	**0.005**
eGFR, ml/min/1.73 m^2, mean (SD)	56.8 (18.3)	72.3 (20.6)	**<0.001**
NT-proBNP, pg/ml, median (IQR)	1958 (987–3660)	698 (257–1204)	**<0.001**
Creatinine, mg/dl, median (IQR)	1.34 (1.12–1.79)	1.05 (0.90–1.22)	0.06
hs-CRP, mg/dl, median (IQR)	2.50 (1.32–4.90)	1.60 (0.90–3.01)	**<0.001**
SBP, mm Hg, mean (SD)	116.9 (21.9)	122.9 (17.9)	**0.002**
DBP, mm Hg, mean (SD)	72.2 (10.4)	75.5 (10.6)	**0.006**
Six-minute walk test			
Distance, m, mean (SD)	424 (101)	475 (99.5)	**<0.001**
Cardiopulmonary exercise test			
Exercise time, s, mean (SD)	357 (149)	474 (187)	**<0.001**
Maximal heart rate, bpm, mean (SD)	116 (22)	124 (22)	**<0.001**
Sinus rhythm, bpm, mean (SD)	114 (20.5)	123 (20.7)	**0.002**
Atrial fibrillation or atrial flutter, bpm, mean (SD)	120 (25.2)	132 (25.0)	**0.045**
$pVCO_2$, ml/kg/min, mean (SD)	1.27 (0.46)	1.71 (0.71)	**<0.001**
Minute ventillation at rest, l/min, mean (SD)	13.8 (5.5)	13.3 (5.3)	0.40
Minute ventillation at peak effort, l/min, mean (SD)	47.8 (15.1)	54.6 (20.0)	**<0.001**
Breathing frequency at rest, /min, mean (SD)	19.7 (5.4)	19.0 (4.6)	0.19
Breathing frequency at peak effort, /min, mean (SD)	31.2 (6.3)	30.0 (6.2)	0.09
RER, mean (SD)	0.98 (0.13)	0.99 (0.12)	0.24

VE/VO_2 slope, mean (SD)	33.4 (13.3)	29.6 (8.8)	**0.007**
VE/VCO_2 slope, mean (SD)	33.3 (11.4)	29.3 (8.8)	**0.001**
Echocardiography			
LVsD, mm, mean (SD)	57.2 (10.2)	52.6 (9.6)	**<0.001**
LVdD, mm, mean (SD)	66.2 (8.7)	62.3 (8.5)	**<0.001**
LVsV, ml, mean (SD)	166.1 (76.1)	136.3 (65.5)	**<0.001**
LVdV, ml, mean (SD)	227.1 (87.5)	197.6 (81.1)	**0.002**
LVEF (%), mean (SD)	29.7 (7.8)	34.1 (7.4)	**<0.001**
24-hour ECG Holter monitoring			
Average heart rate, bpm, mean (SD)	69.9 (8.7)	68.3 (8.0)	0.09
Sinus rhythm, bpm, mean (SD)	68.2 (7.7)	67.2 (7.5)	0.31
Atrial fibrillation or atrial flutter, bpm, mean (SD)	74.5 (10.0)	74.0 (8.6)	0.83
Maximal heart rate, bpm, mean (SD)	102.4 (16.3)	103.7 (16.6)	0.51
Sinus rhythm, bpm, mean (SD)	100.8 (16.0)	102.2 (15.1)	0.48
Atrial fibrillation or atrial flutter, bpm, mean (SD)	106.8 (17.1)	111.3 (22.3)	0.36
Minimal heart rate, bpm, mean (SD)	59.7 (9.4)	56.9 (9.0)	**0.006**
Sinus rhythm, bpm, mean (SD)	57.8 (7.8)	55.6 (7.8)	**0.03**
Atrial fibrillation or atrial flutter, bpm) mean (SD)	65.0 (11.5)	63.1 (13.0)	0.53
Quality of life			
SF-36, score, mean (SD)	88.4 (13.1)	93.1 (12.1)	**<0.001**
BDI-II, score, mean (SD)	10.2 (6.8)	8.6 (6.2)	**0.03**
Changes 0 – 9 week			
Lab parameters			
Sodium, mmol/l, mean (SD)	–0.12 (2.93)	0.03 (2.81)	0.63
Potassium, mmol/l, mean (SD)	0.01 (0.41)	0.04 (0.45)	0.46
Hemoglobin, g/dl, mean (SD)	0.04 (1.00)	0.00 (1.3)	0.75

eGFR, ml/min/1.73 m^2, mean (SD)	0.12 (11.2)	1.16 (13.73)	0.49
Creatinine , mg/dl, median (IQR)	0.01 (–0.08–0.16)	0.00 (–0.10–0.09)	0.06
NT-proBNP , pg/ml, median (IQR)	–32.5 (–517–421)	–7.7 (–196–136)	0.43
hs-CRP, median (IQR)	–0.19 (–1.46 to –1.1)	–0.15 (–0.85–0.41)	0.82
Clinical finding			
Improvement in NYHA class, n (%)	23 (21.3)	65 (23.5)	0.61
No change in NYHA, n (%)	75 (69.4)	193 (69.9)	
Worsening of NYHA, n (%)	10 (9.3)	18 (6.5)	
SBP, mm Hg, mean (SD)	–0.78 (17.4)	–1.11 (17.7)	0.87
DBP, mm Hg, mean (SD)	–0.04 (11.0)	–1.12 (11.4)	0.40
Six-minute walk test			
Distance, m, mean (SD)	39.3 (69.2)	31.2 (52.3)	0.24
Cardiopulmonary exercise test			
Exercise time, sec, mean (SD)	40.0 (80.1)	53.5 (89.6)	0.17
Maximal heart rate, bpm, mean (SD)	4.45 (22.8)	0.99 (19.93)	0.14
pVO_2, ml/kg/min, mean (SD)	0.89 (2.96)	1.20 (3.31)	0.40
pVO_2 % pred, %, mean (SD)	3.58 (12.0)	3.66 (12.66)	0.96
$pVCO_2$, ml/kg/min, mean (SD)	0.10 (0.31)	20.13 (0.35)	0.53
RER, mean (SD)	0.03 (0.12)	0.02 (0.14)	0.50
Minute ventillation at rest, l/min, mean (SD)	0.73 (4.28)	0.46 (4.30)	0.58
Minute ventillation at peak effort, l/min, mean (SD)	4.15 (10.2)	2.96 (12.9)	0.34
Breathing frequency at rest, /min, mean (SD)	0.78 (4.51)	0.32 (4.49)	0.37
Breathing frequency at peak effort, /min, mean (SD)	1.74 (4.90)	0.71 (5.14)	0.07
24-hour ECG Holter monitoring			
Average heart rate, bpm, mean (SD)	0.35 (6.31)	–0.99 (6.23)	0.06
Minimal heart rate, bpm, mean (SD)	–0.04 (5.50)	–0.14 (5.84)	0.87

Maximal heart rate, bpm, mean (SD)	4.59 (16.5)	1.29 (14.8)	0.06
Baseline presence of nsVT, 9-week absence of nsVT, n (%)	11 (10.4)	32 (11.8)	0.69
LVsD, mm Hg, mean (SD)	–0.29 (4.50)	–0.87 (5.45)	0.33
LVDd, mm Hg, mean (SD)	–0.36 (4.35)	–0.90 (4.92)	0.32
LVsV, mm Hg, mean (SD)	–11.0 (48.1)	–7.42 (38.6)	0.44
LVdV, mm Hg, mean (SD)	–8.3 (60.1)	–2.78 (47.5)	0.39
LVEF, %, mean (SD)	1.12 (3.80)	2.13 (3.94)	**0.02**
SF-36, score, mean (SD)	1.63 (11.0)	2.00 (9.41)	0.76
Adherence to HCTR, n (%)	93 (86.1)	253 (91.7)	0.10

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BDI-II, Beck Depression Inventory; BF, breathing frequency; BMI, body mass index; CRT-D, cardiac resynchronization therapy and cardioverter- defibrillator; CRT-P, cardiac resynchronization therapy with peacemaker function; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HCTR, hybrid comprehensive telerehabilitation; HR, heart rate; hs-CRP, high sensitivity C-reactive protein; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection Fraction; LVSd, left ventricular systolic diameter; LVdV, left ventricular diastolic volume; LVsV, left ventricular systolic volume; nsVT, nonsustained ventricular tachycardia; NT-proBNT, N-terminal fragments of B-type natiuretic peptide; NYHA, New York Heart Association, $pVCO_2$, carbon dioxide output at peak exercise; pVO_2, oxygen uptake at peak exercise; pVO_2% pred, percentage of predicted peak oxygen uptake; RER, respiratory exchange ratio; SBP, systolic blood pressure; SF-36, Short Form 36 Health Survey Questionnaire; VE/VCO_2-slope, slope of the relationship between minute ventilation and carbon dioxide output; VE/VO_2-slope, slope of the relationship between minute ventilation and oxygen uptake; VE, minute ventilation at peak exercise;

Table 2. Predictors of cardiovascular-mortality and heart failure hospitalization within 2 years (Multivariable Cox proportional hazards model)

	Model I, Harrell's Concordance Statistics (C-index) = **0.795**	**Model II**, Harrell's Concordance Statistics (C-index) = **0.798**

	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	0.982 (0.960–1.004)	0.10	0.981 (0.959-1.004)	0.10
Sex	1.311 (0.655–2.625)	0.44	1.334 (0.662–2.689)	0.42
Non-ischemic etiology of heart failure	2.043 (1.316 - 3.173)	**0.001**	2.073 (1.329–3.231)	**0.001**
Diabetes mellitus	1.564 (1.030–2.373)	**0.04**	1.530 (1.003–2.335)	**0.048**
NT-proBNP 9 week	1.105 (1.027–1.189)	**0.007**	1.102 (1.023–1.187)	**0.01**
Creatinine 9 week	3.038 (2.040–4.523)	<**0.001**	2.987 (1.975 - 4.518)	<**0.001**
hs-CRP 9 week	1.036 (1.005–1.068)	**0.02**	1.039 (1.007 - 1.072)	**0.02**
$pVCO_2$ 9 week	0.088 (0.036–0.216)	<**0.001**	0.090 (0.029 - 0.281)	<**0.001**
VE 9 week	1.057 (1.027–1.088)	<**0.001**	1.056 (1.025 - 1.088)	<**0.001**
BF 9 week	1.034 (1.002–1.068)	**0.04**	1.035 (1.002 - 1.069)	**0.04**
LVEF 9 week	0.973 (0.948–0.999)	**0.04**	0.973 (0.948–0.999)	**0.04**
Average heart rate in HM 9 week – baseline	1.051 (1.019–1.084)	**0.001**	1.050 (1.018 - 1.082)	**0.002**
Adherence to HCTR	0.415 (0.231–0.743)	**0.003**	0.405 (0.225–0.730)	**0.003**
pVO_2 9 week	—	—	1.005 (0.932–1.083)	0.91
SF-36 (score) 9 week	—	—	0.992 (0.973–1.011)	0.39
BDI-II (score) 9 week	—	—	1.001 (0.966–1.036)	0.97

Abbreviations: NT-proBNP, N-terminal fragments of B-type natiuretic peptide; hs-CRP, high sensitivity C-reactive protein; $pVCO_2$, carbon dioxide output at peak exertion; VE, minute ventilation at peak exercise; BF, breathing frequency; LVEF, left ventricular ejection fraction; HR, hazard ratio; HM, 24-h ECG Holter monitoring; pVO_2, oxygen uptake at peak exertion; SF-36, Short Form 36 Health Survey Questionnaire; BDI-II, Beck Depression Inventory

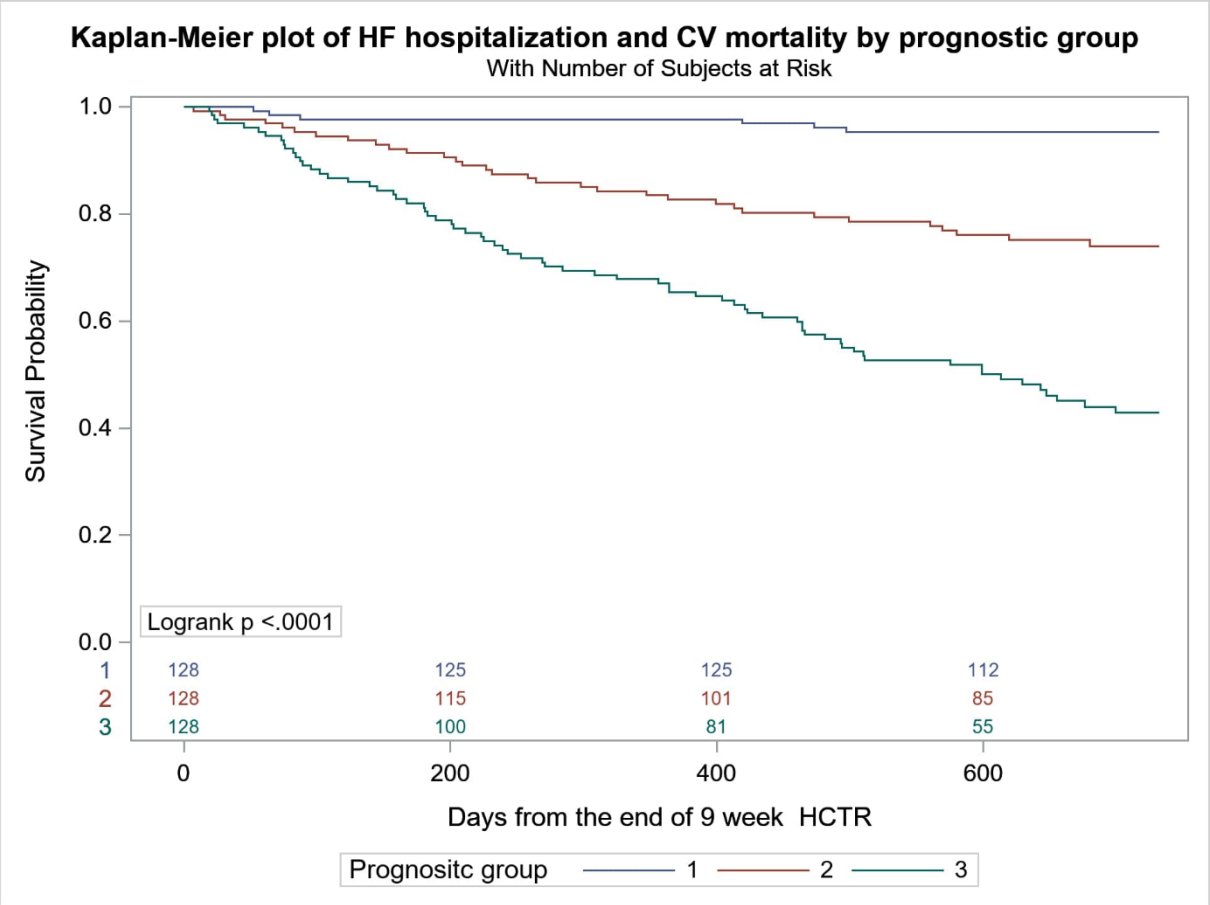

Figure 1. Kaplan-Meier plot, survival of the three prognostic group: good prognosis — risk score <0.0; moderate prognosis — risk score from 0.0 to 1.1; poor prognosis — risk score >1.1