

Predictors of long-term prognosis based on clinical status and measurements obtained in heart failure patients after 9-week hybrid comprehensive telerehabilitation: A subanalysis of the TELEREH-HF randomized clinical trial

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ABSTRACT

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

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

Methods: This analysis is based on the 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 (experimental arm) or usual care only (control arm) 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 outcome. The predictors of our composite outcome were: nonischemic 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 tests; increase in delta of average heart rate in 24-hour Holter ECG monitoring, lower LVEF, and patients' non-adherence to HCTR. The model discrimination C-index was 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. Treatment adherence, but not peak VO₂ or quality of life, was significantly associated with the outcome.

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

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 obtained after 9-week hybrid comprehensive telerehabilitation including exercise training. This risk stratification model indicated that treatment adherence is the best predictor of long-term prognosis in heart failure patients.

INTRODUCTION

Heart failure (HF) is a major cause of cardiovascular (CV) mortality and hospitalization [1–4]. Despite 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 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 by 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 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 organization of healthcare in a particular country.

Little is known about the 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 developed risk stratification models based on HF patients hospitalized for exacerbation of clinical status or HF patients who participated in clinical research assessment of administered drug treatment [8–16]. Only one study reported a risk stratification model based on HF patients who were referred for the cardiac rehabilitation program [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 compared to 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 im-

provement 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 the telerehabilitation period? Therefore, this study aimed 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 (ClinicalTrials.gov NCT 02523560), which compared HCTR plus 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) \leq 40% after hospitalization for worsening HF within 6 months before 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. Patients in the HCTR group underwent a 9-week HCTR program consisting of an initial stage (1 week) in the 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. A detailed description of the medical team composition, equipment for telemonitoring, and intervention has been published elsewhere [17, 18].

The study was guided by good clinical practice and 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 tests (blood count, serum creatinine, electrolytes [sodium, potassium], glycemia, N-terminal pro-hormone 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 (6MWT), cardiopulmonary exercise test (CPET), 24-hour Holter ECG monitoring, psychological assessment, and HCTR adherence evaluation. Patients were followed for 12–24 months after the intervention/observation was completed to collect data on 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 follow-up period in the UC group. The follow-up was also conducted in the form of a telephone conversation with the patients and/or family members 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 6MWT 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 25 m.

Cardiopulmonary exercise test

The symptom-limited CPET on a treadmill according to a ramp protocol and the 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) ≥ 1 .

24-hour Holter ECG monitoring

For 24-hour Holter ECG monitoring, we used a 12-channel Holter digital recorder Lifecard CF, Del Mar Reynolds Medical UK/US. Twenty-four-hour Holter recordings were assessed using the Pathfinder SL analysis system and 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 patients' emotional condition.

Patients with BDI II scores ≥ 14 were considered affected by depression [25].

Assessment of HCTR efficacy

Response to 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 HCTR adherence

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

Statistical analysis

Our primary analysis focused on patients randomized to the HCTR group, with the control arm used as a validation sample. Quantitative variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate, and categorical variables were expressed as counts and percentages. Missing data were imputed with the median. The distribution of continuous variables was tested for normality with the Kolmogorov-Smirnov test. The study groups were compared using the χ^2 test of independence (unless the number of expected events is fewer than 5, in which case Fisher's exact test was used) for categorical variables and two independent t-tests 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 program to the final visit at the study end (maximum follow-up of 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 create 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 final Model I to the control arm (not used in model development) as a validation sample. Kaplan-Meier curves were constructed and log-rank tests with Tukey-Kramer correction for multiple comparisons were calculated summarizing the relationship between the tertiles of the risk score and survival. First, the risk score was calculated for each

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

Baseline	HCTR group with event (n = 108)	HCTR group with-out 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-defibrillator, 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, pmol/l, median (IQR)	1946 (843–813)	669 (261–1307)	<0.001
NT-proBNP in patients with sinus rhythm, pmol/l, median (IQR)	1349 (865–2172)	536 (231–1114)	<0.001
NT-proBNP in patients with atrial fibrillation or atrial flutter, pmol/l, median (IQR)	2419 (1342–4300)	1349 (865–2172)	0.01
Cardiopulmonary exercise test			
pVO ₂ , ml/kg/min, mean (SD)	14.3 (4.4)	18.2 (5.6)	<0.001
Minute ventilation 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 given in parentheses			
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

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

Baseline	HCTR group with event (n = 108)	HCTR group with-out event (n = 276)	P-value
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 ventilation at rest, l/min, mean (SD)	13.8 (5.5)	13.3 (5.3)	0.40
Minute ventilation 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, mg/dl, 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 class, n (%)	75 (69.4)	193 (69.9)	
Worsening of NYHA class, 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



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

Baseline	HCTR group with event (n = 108)	HCTR group with-out event (n = 276)	P-value
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 ventilation at rest, l/min, mean (SD)	0.73 (4.28)	0.46 (4.30)	0.58
Minute ventilation 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-proBNP, N-terminal fragments of B-type natriuretic peptide; NYHA, New York Heart Association, pVCO₂, carbon dioxide output at peak exercise; pVO₂, oxygen uptake at peak exercise; pVO₂, % pred, percentage of predicted peak oxygen uptake; RER, respiratory exchange ratio; SBP, systolic blood pressure; SF-36, Short Form 36 Health Survey Questionnaire; VE/VCO₂-slope, slope of the relationship between minute ventilation and carbon dioxide output; VE/VO₂-slope, slope of the relationship between minute ventilation and oxygen uptake; VE, minute ventilation at peak exercise

patient, next the patients were assigned into 3 groups according to the value of terciles of the risk score, and finally the probabilities of surviving without a composite endpoint in these 3 groups were estimated and compared with the Kaplan-Meier method. 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 randomized patients, 425 were assigned to HCTR and 425 to UC. Twenty-seven patients did not participate in the HCTR program due to technical difficulties with operating the telerehabilitation set (21), new onset of comorbidities (4), and return to work (2) [17]. Finally, 384 patients were included in the 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 composite event status are presented as Supplementary material.

Association between baseline predictors and the composite outcome

The predictors of higher CV mortality or HF hospitalization retained after backward elimination are presented in **Table 2** and included the following variables collected at the end of the 9-week telerehabilitation period: nonischemic 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 the CPET. Moreover, an increase in the 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, peak VO₂ 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 in the control sample which was not used in derivation, the C-index decreased

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, years	0.982 (0.960–1.004)	0.10	0.981 (0.959–1.004)	0.10
Sex, male	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 natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; pVCO₂, 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; pVO₂, oxygen uptake at peak exertion; SF-36, Short Form 36 Health Survey Questionnaire; BDI-II, Beck Depression Inventory

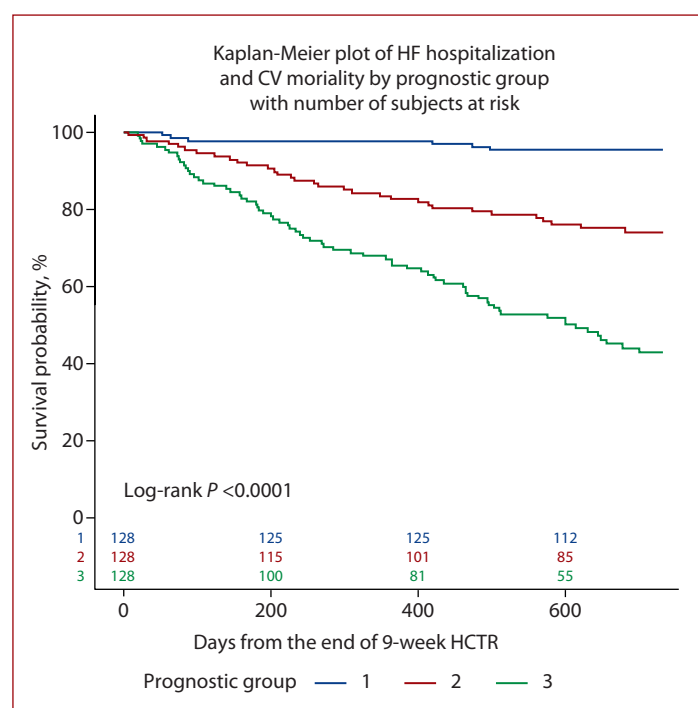


Figure 1. Kaplan-Meier plot, survival of the three prognostic group: good prognosis — risk score <0.0; moderate prognosis — risk score from 0.0 to 1.1; poor prognosis — risk score >1.1

to 0.755 (95% CI, 0.708–0.802). The baseline characteristics of the UC sample are presented in the 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 noninvasive 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 obtained after 9-week HCTR and response to exercise training assessed by changes (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 each of the following factors had independent predictive power: patients' non-adherence to HCTR, nonischemic 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 the CPET and an increase in difference (Δ) in the average heart rate in 24-hour-ECG Holter monitoring between baseline and after 9-week HCTR examinations.

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 a published meta-analysis of controlled trials by Ruppert et al., who demonstrated that among HF patients, intervention to improve medication adherence has a significant impact on decreasing readmissions and reducing mortality [26]. Hybrid telerehabilitation is a comprehensive procedure that supports adherence to both medical treatment and exercise training. Moreover, daily contact with the telemonitoring center helped patients to develop healthy habits for the future.

The nonischemic 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 other 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 Heart 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 affecting arrhythmic risk, nonhomogeneous etiology, and the naturally 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 in older age and with lower LVEF were the most prognostic variables predicting either the composite endpoint of CV death or HF hospitalization, or all-cause mortality [15]. Diabetes was associated with a doubling of risk of either death or the composite outcome when insulin-treated, and a 50% increase in the risk of 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, like 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 NT-proBNP may be considered to reflect 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 CPETs 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 the 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 endpoint was exercise duration in the CPET [2]. In our model breathing frequency (BF), maximal minute ventilation (VE), and carbon dioxide production (VCO_2) during the 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 being included in 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), 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 that affects prognosis is heart rate. Published data reported an association between increased heart rate over time and cardiovascular and all-cause mortality [32]. This was confirmed in our analysis, where an increase in difference (Δ) in the average heart rate in 24-hour 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 (which 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% ICDs. Similarly, patients enrolled in the HF-ACTION study were treated according to evidence-based therapy (95% of them took β -blockers, 74% used ACEI, and 40% had an ICD). The determinants of higher mortality in the 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 a moderately good capacity of the model to indicate patients at greater risk of death [2]. For the second predictive model of the primary composite endpoint of death or hospitalization from any cause, the same variables were included with one exception — the Kansas City Cardiomyopathy Questionnaire 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 the validation sample), especially given 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 the development of the risk stratification model, 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 more personalized treatment and holistic management of HF patients 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].

Strengths and limitations

The TELEREH-HF model refers to a homogeneous population of HF patients with reduced LVEF $\leq 40\%$ treated according to the current standards, which, on the one hand, is an advantage and, on the other hand, 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 noninvasive examinations recommended by the guidelines and 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 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. Treatment adherence, but not peak VO_2 or quality of life, was significantly associated with the outcome.

Supplementary material

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

Article information

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