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ORIGINAL PAPER

Application of survival classification and regression tree analysis for identification of subgroups of risk in patients with heart failure and reduced left ventricular ejection fraction

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Abstract

The aim of this study was to identify by classification and regression tree (CART) analysis groups of patients with different survival patterns in a population of patients with heart failure and reduced left ventricular ejection fraction (HFrEF) by using standard methods of heart function assessment, as well as well as utilizing non-traditional approaches for determining hydration and nutritional status in HF patients—lung ultrasonography (LUS) and bioimpedance spectroscopy (BIS) analysis. Eligible patients with a left ventricular ejection fraction (LVEF) below 45% were identified via the daily echocardiography assessments. LUS was performed with patients in the supine position, for a total of 28 sites per complete examination. The hydration state and the body composition were assessed using a portable whole-body BIS device. Our study included 151 patients (69.2% males) with a mean age of 67.1 years. During the follow-up 53 (35.1%) patients died. Using the CART algorithm, we identified five groups based on serum sodium, the severity of NYHA class, serum urea and systolic blood pressure. When comparing the two models, the model derived from the CART analysis showed better predictive power than the conventional Cox model (c-index 0.790, 95% CI 0.723–0.857 vs. 0.736, 95%CI 0.664–0.807, $p < 0.05$). The application of CART analysis allowed us to identify different groups of risk for all-cause mortality in patients with HFrEF. The use of this type of modelling showed better prediction capabilities over that of using more conventional statistical approach. ClinicalTrials.gov Identifier: NCT02764073.

Keywords Lung ultrasonography · Bioimpedance spectroscopy · Heart failure · Prognostic score · Mortality

Introduction

Chronic heart failure (HF) represents a major global public health problem, being a primary cause of death and disability throughout the world. The epidemiological data regarding the magnitude of the issue is not entirely reliable due to the lack of case reports in underdeveloped countries and

Dimitrie Siriopol and Raluca Popa have equally contributed to this work.

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the variability of methods in assessing the presence of the condition, but it is considered there are approximately 26 million cases of heart failure worldwide [1]. However, it is considered that as population ages, the problem will become more and more prominent [2], simultaneously increasing the economic burden it brings [3].

Despite the broadening of the therapeutic possibilities in the last decades, such as the introduction of β-blockers, mineralocorticoid receptor antagonists, ivabradine, and more recently sacubitril/valsartan and SGLT-2 inhibitors, as well as devices such as implantable defibrillators, the mortality rates in patients with HF remain relatively similar to early 2000′s—around 50% at 5 years and 70% at 10 years [4, 5]. To statistically predict the risk of complications associated with HF, there have been a number of risk prediction models published. However, the application of these models in clinical daily practice is limited, due to the difficulty in individualizing at the patient bedside [6].

The aim of this study was to identify by classification and regression tree (CART) analysis groups of patients with different survival patterns in a population of patients with heart failure and reduced left ventricular ejection fraction (HFrEF) by using standard methods of heart function assessment, as well as well as utilizing non-traditional approaches for determining hydration and nutritional status in HF patients—lung ultrasonography (LUS) and bioimpedance spectroscopy (BIS) analysis. We also compared the prognostic value of this novel approach with that of conventional Cox survival analysis.

Methods

Patients and study design

Details about this study were previously published [7]. Briefly, this was a prospective observational study of outpatient adults referred for clinically indicated transthoracic echocardiograms at an academic hospital between 2016 and 2018. Eligible patients with a left ventricular ejection fraction (LVEF) below 45% were identified via the daily echocardiography assessments. From a total number of 321 eligible patients, we excluded 153 patients because of limb amputation (N = 3), metallic joint prostheses (N = 11), cardiac pacemakers or stents (N = 94), decompensated cirrhosis (N = 7), prior diagnosis of pulmonary fibrosis (N = 5), pneumectomy (N = 1), massive pleural effusion (N = 7), end-stage renal disease (N = 3), active systemic infections (N = 5) and terminal illnesses (N = 17). There were an additional 17 patients that didn't want to sign the informed consent form and were not included in the study. As a result, 151 patients were included in the final analysis.

The investigation was performed in accordance with the principles outlined in the Declaration of Helsinki [8]. The trial registered at ClinicalTrials.gov (NCT02764073), was approved by the Research Ethics Committee of the "Grigore T. Popa" University of Medicine and Pharmacy Iasi; an informed consent was obtained from all included patients and also from the Legally authorized representative/next of kin of died participants.

Demographic and clinical parameters

As previously described, the following demographic parameters were recorded at baseline: age, gender, weight, height, comorbidities [diabetes, coronary artery disease, hypertension, atrial fibrillation, chronic kidney disease (CKD)] and smoking status. Arterial blood pressure was determined in the morning in all patients by a physician by three consecutive measurements, after a 15-min resting period, with the mean values calculated for systolic (SBP) and diastolic blood pressure (DBP), using an automatic BP measuring device certified by Association for the Advancement of Medical Instrumentation, European Society of Hypertension, and British Society of Hypertension—model OMRON M6 with an adjustable cuff for arm circumferences from 24 to 42 cm, respecting the current guideline recommendations [9]. Hypertension was defined as a SBP of at least 140 mmHg and/or DBP of at least 90 mmHg or previously diagnosed hypertension under treatment during the previous 2 weeks, regardless of BP values. We considered that a patient had coronary artery disease if in the medical records there was a diagnosis of coronary artery/heart disease, angina or angina pectoris, or myocardial infarction.

We also assessed diuresis, the presence of peripheral edema (slight pitting of at least 2 mm depth with no visible distortion) [10], the NYHA functional class and the medication.

Biochemical analysis

As already described, all blood samples were obtained from patients in the morning, after 12 h of fasting, for measurement of serum creatinine, hemoglobin, glucose, total cholesterol, triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol, C-reactive protein (CRP), uric acid and sodium levels. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [11].

All laboratory tests were performed by standard procedures with certified methods on the day of the lung ultrasonography and BIS assessments.

Echocardiographic assessment

Echocardiographic measurements were performed before (the same day or maximum a day before) LUS and BIS evaluations by two trained echocardiographers according to the recommendations of the American Society of Echocardiography [12].

B-lines assessment

LUS was performed with patients in the supine position, for a total of 28 sites per complete examination, as previously described [13]; the total number of B-lines was recorded for each zone (from a minimum of 0 to a maximum of 10) and the extent of lung congestion was obtained by summing the scores from all the 28 zones—see Fig. 1 with two assessments performed from two different patients from our study. Two trained physicians blinded to the echocardiography assessment performed all measurements.

Bioimpedance analysis

The hydration state and the body composition were assessed immediately after the LUS evaluation using a portable whole-body BIS device (BCM—Fresenius Medical Care D GmbH [14]). By attaching electrodes to the patient's forearm and ipsilateral ankle, this device measures the impedance spectroscopy at 50 frequencies. The extracellular water (ECW), intracellular water (ICW) and TBW were determined as previously described [15].

The device expresses body composition as a three-compartment model, being able to provide information about overhydration, lean and tissue mass. For overhydration description we used both absolute fluid overload (AFO), defined as the difference between the expected patient's ECW under normal physiological conditions and the actual ECW, and relative fluid overload (RFO), defined as the AFO to ECW ratio. For lean and tissue mass presentation, we used the lean tissue index (LTI) and fat tissue index (FTI), where LTI and FTI are the respective tissue masses normalized to height squared. In patients with limb amputation, metallic joint prostheses, cardiac pacemakers or stents, or decompensated cirrhosis, this method could provide unreliable results [16] and as such, these patients were excluded from the study (see above).

Outcome

The main outcome was all-cause mortality. Death was confirmed through patient follow-up phone calls, hospital's electronic medical records or the social security death index.

Statistical analysis

Variables were expressed as medan with interquartile range (IQR), mean ± standard deviation (SD), or as percentage of frequency, as appropriate. For the categorical variables, the between-group comparisons were performed using the Chi-square test and for the continuous variables using the Mann–Whitney U test or the independent T-test, as appropriate. The Shapiro–Wilk test was used for assessing the normality of the distribution and logarithmic conversion was performed for non-normally distributed variables.

To identify subgroups of risk for all-cause mortality, as well as cut-off values for the factors identified as significant risk predictors, we used we used the CART analysis. CART analysis was used to identify which categories of these variables, when considered simultaneously, place a patient at a

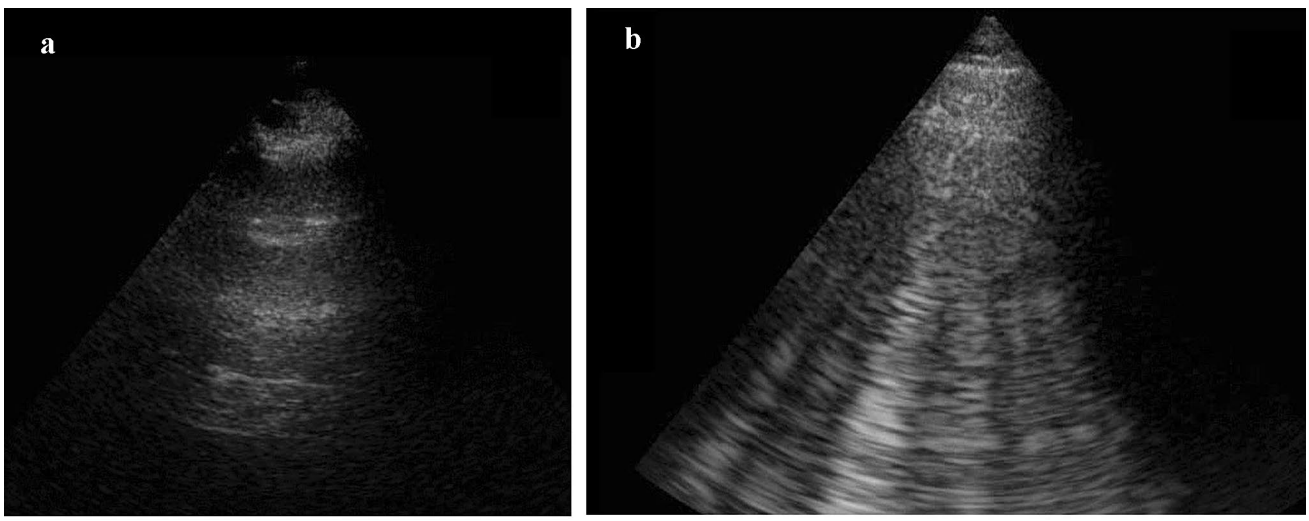

Fig. 1 Images from the lung ultrasound from two different sites from patients from our study, showing 0 (**a**) and 10 B-lines (**b**)

higher risk for death. In theory, CART is a form of binary recursive partitioning and is of help in identifying particular categories from a population that are most related to the outcome variable based on numerous shared characteristics. CART is preferable to parametric approaches for identifying homogenous subgroups due to greater resistance to the effects of multicollinearity, outliers, as well as its ability to examine higher-order interactions among predictors [17]. CART begins by partitioning data into smaller sections to provide a clearer view of interactions among variables. These interactions begin as a single group ('parent node') and are subsequently split into two groups ('child nodes'). In the CART analysis for failure time data, the martingale residuals of a Cox model are used to calculate chi-square values for all possible splitting points on all the CART covariates. Splitting continues until predetermined stopping criteria are met (we used a maximum p-value for a split of 0.05).

To assess whether the use of CART analysis provides superior predictive performance over conventional Cox survival analysis we compared the results of two Cox proportional hazard models: the first one a conventional Cox model and the second one using only the subgroups identified by the CART analysis.

For the conventional Cox analysis, a backward stepwise elimination procedure was used in order to select the model with the best predictive performance (we used a removal probability of 0.05). All the variables associated with mortality in the univariable Cox analysis were included in the initial analysis. For the CART analysis, all the available variables were included in the initial step.

Data is presented in the form of Hazard ratios (HR) and 95% confidence intervals (CI). We performed bootstrapping validation when needed in order to avoid the problem of overfitting due to the low number of incident outcomes. We compared the two Cox models using the concordance index (c-index), a measure equivalent to the area under the receiver operating characteristic curve in logistic regression. The Bayesian information criterion (BIC) and the Akaike information criterion (AIC) were also calculated for each Cox model; there is no statistical test that compares different BIC or AIC estimations, and a lower value indicates a better fitted model.

All analyses were performed using Stata SE software, version 13 (StatCorp, College Station, TX, USA). A p value < 0.05 was considered to be statistically significant.

Results

We analyzed data from 151 patients (69.2% males) with a mean age of 67.1 ± 12.1 years. The most frequent causes of HF were dilated and ischemic cardiomyopathy with 56 (37.1%) and 47 (31.1%) patients, respectively. Overall demographic, biological, bioimpedance, echocardiographic and treatment characteristics of the population are presented in Tables 1 and 2 and Supplementary Table 1.

During the follow-up 53 (35.1%) patients died. Patients who died had a higher prevalence of peripheral edema and of severe baseline NYHA class. When compared to the survivors, they also had a significantly higher number of B-lines (median 21 vs. median 7.5, $p < 0.001$) and urea, CRP, soluble ST2 and galectin-3 levels (see Table 1). However, these patients showed significantly lower eGFR (61.1 ± 25.3 vs. 69.4 ± 23.7 ml/min/1.73 m^2, $p = 0.04$), hemoglobin (12.6 ± 2.1 vs. 13.8 ± 2.0 g/dL, $p = 0.001$), serum sodium (135.5 ± 5.3 vs. 138.2 ± 4.3, $p < 0.001$) and leptin (median 13.5 vs. median 24.8 ng/mL, $p = 0.01$) values.

When analyzing the differences in regard with the bioimpedance analysis, we noticed that those patients who died had higher values for ECW (19.1 ± 2.7 vs. 17.4 ± 3.4 L, $p = 0.001$), AFO (2.0 ± 2.3 vs. 0.6 ± 2.9 L, $p = 0.002$) and RFO (10.2 ± 11.9 vs. $1.9 \pm 13.6\%$, $p < 0.001$), but lower values for ICW (17.4 ± 3.3 vs. 18.7 ± 3.6 L, $p = 0.04$) and LTI (10.5 ± 2.3 vs. 11.6 ± 2.6 kg/m^2, $p = 0.01$) than those who survived. Nevertheless, there were no differences between these patients in regard to TBW and FTI (see Table 2).

Survival and prognostic analysis

The mean and median follow-up time were 18.8 and 20.4 months, respectively.

As shown in Table 3 age, the severity of NYHA class, the number of B-lines and urea, CRP, NT-proBNP, LVMI, LAVI, AFO and RFO values were positively associated with all-cause mortality, while hemoglobin, serum sodium, leptin, ICW and LTI levels were negatively associated with the outcome.

A crucial point of our analysis was to determine if CART analysis could provide a superior predictive performance over conventional Cox survival analysis.

Using a backward stepwise Cox survival analysis, and including all the univariable associates of the outcome, only age, the severity of NYHA class, hemoglobin, serum sodium and LTI were retained in the final model (see Supplementary Table 2). Using the CART algorithm, and including all the available variables in the initial step, we identified five groups based on serum sodium, the severity of NYHA class, serum urea and systolic blood pressure (see Fig. 2 and Supplementary Table 3). The best survival was observed in patients with serum sodium of at least 136 mmol/L and NYHA class I or II (Group 1 in Fig. 2 and Supplementary Table 3), while a significant worse prognosis was seen in patients with serum sodium ≥ 136 mmol/L, NYHA class III or IV and serum urea ≥ 70 mg/dL (Group 3 in Fig. 2 and Supplementary

Table 1 Baseline demographic, clinical and biological characteristics of the study population

	All (N = 151)	All-cause death NO (N = 98)	All-cause death YES (N = 53)	p value
Age, years	67.1 ± 12.1	65.6 ± 12.1	69.8 ± 11.7	**0.03**
BMI, kg/m^2	28.9 ± 4.7	29.2 ± 4.6	28.4 ± 4.8	0.33
Male, n (%)	105 (69.5)	70 (71.4)	35 (66.0)	0.49
SBP, mmHg	124.6 ± 18.3	124.5 ± 16.9	124.8 ± 20.8	0.90
DBP, mmHg	75.4 ± 11.3	76.1 ± 10.5	74.0 ± 12.6	0.28
Smoking, n (%)	60 (39.7)	37 (37.8)	23 (43.4)	0.49
Diuresis, L/day	1.4 ± 0.5	1.4 ± 0.5	1.5 ± 0.5	0.09
Edema, n (%)	75 (49.7)	36 (36.7)	39 (73.6)	**< 0.001**
III/IV NYHA class, n (%)	73 (48.3)	41 (41.8)	32 (60.4)	**0.03**
B-lines	12.0 (3.0–32.0)	7.5 (2.0–26.0)	21.0 (10.0–48.0)	**< 0.001**
Comorbidities				
Diabetes, n (%)	53 (35.1)	31 (31.6)	22 (41.5)	0.23
CAD, n (%)	89 (58.9)	63 (64.3)	26 (49.1)	0.07
Hypertension, n (%)	93 (61.6)	57 (58.2)	36 (67.9)	0.24
Atrial fibrillation, n (%)	80 (53.3)	50 (51.6)	30 (56.6)	0.55
Biological parameters				
Serum creatinine, mg/dL	1.1 (0.9–1.4)	1.1 (0.9–1.3)	1.2 (0.9–1.4)	0.12
eGFR, ml/min/1.73m^2	66.5 ± 24.5	69.4 ± 23.7	61.1 ± 25.3	**0.04**
Urea, mg/dL	47.0 (35.0–69.0)	43.5 (33.0–62.0)	58.0 (41.0–80.0)	**< 0.001**
Hemoglobin, g/dL	13.4 ± 2.1	13.8 ± 2.0	12.6 ± 2.1	**0.001**
Serum glucose, mg/dL	107.0 (96.0–131.0)	107.5 (95.0–131.0)	106.0 (98.0–128.0)	0.52
Total Cholesterol, mg/dL	151.0 (127.0–187.0)	153.0 (132.1–187.0)	144.0 (123.0–184.0)	0.32
LDL cholesterol, mg/dL	91.0 (75.0–117.4)	93.5 (77.0–116.0)	87.0 (74.0–124.0)	0.68
HDL cholesterol, mg/dL	38.0 (30.0–46.0)	37.0 (31.0–47.0)	40.0 (30.0–45.0)	0.84
Serum triglycerides, mg/dL	121.0 (96.0–148.0)	121.0 (97.0–148.0)	123.0 (81.0–147.0)	0.35
CRP, mg/L	25.6 (9.0–56.4)	19.9 (7.8–46.9)	35.1 (15.8–89.7)	**0.01**
Uric acid, mg/dL	7.5 (6.2–8.8)	7.5 (6.1–8.4)	7.8 (6.5–9.1)	0.29
Serum sodium, mmol/L	137.2 ± 4.9	138.2 ± 4.3	135.5 ± 5.3	**< 0.001**
Soluble CD146, ng/mL	236.00 (189.60–329.20)	221.4 (190.2–338.0)	236.8 (188.8–314.0)	0.48
NT-proBNP, pg/mL	800.0 (400.0–1500.0)	795.0 (300.0–1500.0)	910.0 (500.0–1320.0)	0.26
ST2, pg/mL	8.17 (4.61–14.35)	6.47 (3.67–11.93)	10.32 (5.77–14.85)	**0.02**
Galectin-3, ng/mL	26.40 (18.30–35.80)	24.3 (17.0–35.4)	29.2 (22.4–37.0)	**0.04**
CT-1, pg/mL	1.40 (0.30–10.20)	2.7 (0.4–10.9)	1.2 (0.3–6.7)	0.26
Acylated ghrelin, pg/mL	10.30 (1.30–41.5)	11.6 (2.0–41.6)	6.1 (1.0–40.9)	0.32
Leptin, ng/mL	21.90 (7.70–49.10)	24.8 (10.8–49.7)	13.5 (6.2–29.7)	**0.01**

Data are expressed as mean ± SD, or median with IR, or percent frequency, as appropriate. Significant values are indicated in bold

BMI body mass index, *CAD* coronary artery disease, *CKD* chronic kidney disease, *CRP* C-reactive protein, *CD146* cluster of differentiation 146, *CT-1* cardiotrophin-1, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *NT-proBNP* N-terminal brain natriuretic peptide, *SBP* systolic blood pressure, *ST2* soluble suppression of tumorigenesis 2

Table 3), in those with serum sodium < 136 mmol/L and SBP < 120 mmHg (Group 4 in Fig. 2 and Supplementary Table 3) and in those with serum sodium < 136 mmol/L and SBP ≥ 120 mmHg (Group 5 in Fig. 2 and Supplementary Table 3). A trend towards a worse survival was also observed in patients with serum sodium ≥ 136 mmol/L, NYHA class III or IV and serum urea < 70 mg/dL; (Group 2 in Fig. 2 and Supplementary Table 3), but it didn't reach statistical significance.

When comparing the two models, the model derived from the CART analysis showed better predictive power than the conventional Cox model (c-index 0.790, 95% CI 0.723–0.857 vs. 0.736, 95%CI 0.664–0.807, p < 0.05—see Table 4).

Table 2 Echocardiographic and bioimpedance characteristics of the study population

	All (N = 151)	All-cause death NO (N = 98)	All-cause death YES (N = 53)	p value
Echocardiography				
LV EDVi, mL/m^2	85.1 (70.3–107.8)	81.3 (68.2–103.8)	97.8 (79.4–111.1)	**0.01**
LV ESVi, mL/m^2	54.2 (31.3–80.8)	46.6 (29.5–79.9)	61.9 (38.1–82.9)	0.13
Septal wall thickness, mm	12.5 ± 2.2	12.5 ± 2.1	12.5 ± 2.5	0.99
Posterior wall thickness, mm	11.8 ± 1.8	11.7 ± 1.7	11.9 ± 1.9	0.53
LVMI, g/m^2	152.9 (126.9–187.3)	144.7 (121.1–179.3)	168.0 (139.4–200.8)	**0.004**
LAVI, mL/m^2	40.7 (32.4–62.9)	36.4 27.6–50.9)	57.3 (41.0–74.0)	**< 0.001**
LVEF, %	32.5 ± 10.2	32.7 ± 10.5	32.0 ± 9.8	0.68
Bioimpedance				
TBW, L	36.5 ± 5.8	36.4 ± 5.9	36.6 ± 5.8	0.85
ECW, L	18.3 ± 2.9	17.4 ± 3.0	19.1 ± 2.7	**0.001**
ICW, L	18.0 ± 3.4	18.7 ± 3.6	17.4 ± 3.3	**0.04**
AFO, L	1.1 ± 2.8	0.6 ± 2.9	2.0 ± 2.3	**0.002**
RFO, %	4.8 ± 13.5	1.9 ± 13.6	10.2 ± 11.9	**< 0.001**
LTI, Kg/m^2	11.2 ± 2.6	11.6 ± 2.6	10.5 ± 2.3	**0.01**
FTI, Kg/m^2	16.8 ± 5.2	17.0 ± 5.3	16.5 ± 4.9	0.52

Data are expressed as mean ± SD, or median with IQR, as appropriate. Significant values are indicated in bold

AFO absolute fluid overload, *ECW* extracellular water, *FTI* fat tissue index, *ICW* intracellular water, *LAVI* left atrial volume index, *LVEF* left ventricular ejection fraction, *LV EDD* LV end diastolic diameter, *LV EDVi* left ventricular end diastolic volume index, *LV ESD* LV end systolic diameter, *LV ESVi* left ventricular end systolic volume index, *LVMI* left ventricular mass index, *LTI* lean tissue index, *RFO* relative fluid overload, *TBW* total body water

Table 3 Univariable Cox survival analysis

	HR	IC 95%	p value
Age, years	1.03	1.00–1.05	**0.03**
NYHA class, (reference Class I-II)	3.27	1.78–6.01	**< 0.001**
Log B-lines	1.50	1.18–1.92	**0.001**
Hemoglobin, g/dL	0.82	0.72–0.93	**0.002**
Log Urea, mg/dL	1.84	1.06–3.20	**0.03**
Log CRP, mg/L	1.27	1.05–1.53	**0.01**
Serum sodium, mmol/L	0.92	0.88–0.96	**< 0.001**
Log NT-proBNP, pg/mL	1.26	1.01–1.59	**0.04**
Log Leptin, ng/mL	0.76	0.62–0.94	**0.01**
Log LVMI, g/m^2, g/m^2	2.58	1.02–6.55	**0.04**
Log LAVI, mL/m^2	2.49	1.29–4.79	**0.006**
ICW, L	0.92	0.85–0.99	**0.04**
AFO, L	1.11	1.02–1.19	**0.01**
RFO, %	1.02	1.01–1.04	**0.004**
LTI, Kg/m^2	0.88	0.78–0.98	**0.03**

Significant values are indicated in bold

AFO absolute fluid overload, *CI* confidence interval, *CRP* C-reactive protein, *HR* hazard ratio, *ICW* intracellular water, *LAVI* left atrial volume index, *LVMI* left ventricular mass index, *LTI* lean tissue index, *NT-proBNP* N-terminal brain natriuretic peptide, *RFO* relative fluid overload

Table 4 Performance comparison of Cox models using only patient data and only CART subgroups

	c-index (95% CI)	AIC	BIC
Conventional model[a]	0.736 (0.664–0.807)	447.81	462.89
CART model[b]	0.790 (0.723–0.857)*	428.59	440.66

AIC akaike information criterion, *BIC* Bayesian information criterion, *CART* classification and regression tree, *LTI* lean tissue index

[a]Conventional model includes age, NYHA Class, hemoglobin, serum sodium and LTI

[b]CART model includes the 5 groups identified by CART analysis

*$p < 0.05$ versus conventional model

Discussion

The application of CART analysis allowed us to identify different groups of risk for all-cause mortality in patients with HFrEF. The use of this type of modelling showed better prediction capabilities over that of using more conventional statistical approach.

Prognostic stratification has been widely used for prediction of future outcomes in HF, but their acceptance in clinical practice is difficult [6], most probably secondary to a low reliability at patient level, the variety of approaches to choose from or the complexity of statistical methodologies used [18]. A recent systematic review identified 40

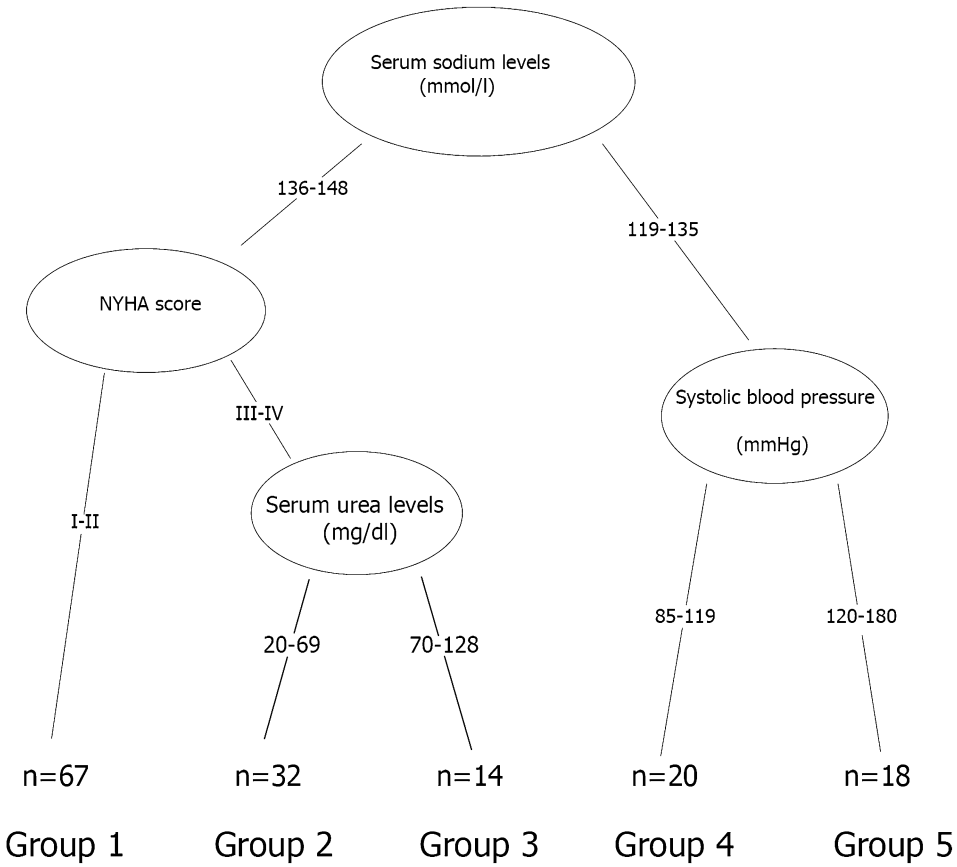

Fig. 2 Tree for classification of survival subgroups

studies with 58 risk prediction models and 105 distinct predictors [19], underlying the complex physiopathological mechanisms that render HF as a major clinical and public health condition. Using conventional statistical prognosis analysis, the most frequent variables included in the prognostic models were NT-proBNP, age, diabetes and sex, but also sodium and NYHA class [19]. Although in our similar analysis (Model from Supplementary Table 2) NT-proBNP levels were not retained in the final model, age, the severity of NYHA class and serum sodium were included in the model. Interestingly, in our conventional Cox analysis hemoglobin and LTI were also independently associated with all-cause mortality. As hemoglobin levels could be a surrogate of fluid control/a marker of extracellular water [20], its association with the outcome is expected. Although an increase in BMI is considered a risk factor for the development of HF, a higher BMI in those with established HF is associated with better outcomes [21, 22]. In the context of this now called "obesity paradox", our newly identified negative association between LTI and the outcome of interest could explain, at least in part, the aforementioned paradox (eg. a higher BMI with an increase in LTI, and not FTI, could be protective).

An important advantage of the CART analysis is represented by its ability to identify predictive cut-off values for continuous, and even related, variables. Previous studies have used arbitrary cut-off values based on subjective evaluations or on the distribution of data in their sample [23, 24]. Using the CART algorithm enables an exploratory subgrouping of patients based only on the outcome and its respective prognosis.

Another major characteristic of the phenotypes identified by the CART analysis is related to its simplicity and ease of use. Although serum sodium, NYHA class, SBP and even serum urea levels could be used as indirect markers of fluid status/overhydration, it is important to notice that these variables were retained in the final model, while other, more related to body fluid compartments (like LUS and BIS related characteristics), were not. Although BIS is not a validated tool in HF patients (as opposed to hemodialysis patients [16, 25–27]), LUS, through the B-lines assessment, is a well-established diagnostical and prognostic method used in acute and chronic HF patients [28–32]. The fact that in our population of chronic HF patients, the number of B-lines was not retained as a prognostic variable in neither of the two prognostic models could be related to the differences in the included populations (without pacemakers or stents, all patients with a LVEF below 45%), in the LUS protocol, but also to the differences in the adjusting factors (we included both serum

sodium and serum urea levels, while in the other studies these variables were not) [29, 32].

Finally, using the tree classification, we identified joint effects between different factors, expressing also the importance of such factors in the context of others. For example, in our CART analysis, the importance of SBP values is limited only in patient who are hyponatremic and, similarly, serum urea levels only in the context of severe HF. Since in HF patients a lower serum sodium level usually indicates poor water excretion (linked to a cardio-renal syndrome) or the use of diuretics, the level of SBP used in this context of further classification could represent a surrogate of fluid status, renal function or activation of the renin–angiotensin–aldosterone (RAA) or sympathetic systems. Similarly, in the context of severe HF, the levels of serum urea levels could represent a worse renal function or an increase in the activation of the RAA system.

Limitations and strengths

Our study has limitations and strengths. We included a relatively small sample size of selected HF patients from a single-center unit and we weren't able to provide the exact cause of death. However, we used a special automated survival tree algorithm that has provided different advantages over conventional statistical approach. Our population of HF patients is a particular one, as we excluded those patients with different comorbidities that could interfere with our volume assessment techniques, and as such, the generalizability of the results to the entire HF population could be limited. Furthermore, since we didn't have a validation cohort, these results should be validated in other HF populations, including larger samples.

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Data availability If needed.

Code availability Stata 13.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Research Ethics Committee of the "Grigore T. Popa" University of Medicine and Pharmacy Iasi (No. 10618).

Consent to participate All patients signed an informed consent.

Consent for publication All authors approved the manuscript.

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