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Single-Center Study in Lithuania to Evaluate the Role of Transthoracic Impedance Cardiography in the Diagnosis and Outcome Evaluation of 301 Patients with Chronic Heart Failure Exacerbation

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Manuscript Preparation E
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Background: Scientific data regarding transthoracic impedance cardiography (ICG) parameters and its utility in patients with heart failure (HF) remains controversial. This study from a single center in Lithuania aimed to evaluate the role of ICG in the diagnosis and outcome evaluation of patients who were admitted to the hospital due to HF exacerbation.

Material/Methods: The sample consisted of 301 consecutive patients with a previous chronic HF diagnosis (166 men, 135 women) hospitalized for HF flare-ups. ICG data were compared to other noninvasive HF diagnostic tests. Data about patient outcomes were gathered from the Lithuanian Medical Record Database.

Results: A weak correlation of amino-terminal pro-brain natriuretic peptide (NT-proBNP) with thoracic fluid content (TFC) and thoracic fluid content index (TFCI) was found (r=0.204, *P*<0.001 and r=0.207, *P*<0.001, respectively). There was weak to moderate correlation of 6-min walk distance with main ICG data. There was weak correlation between left ventricular ejection fraction (LVEF) with TFCI (r=-0.163, *P*=0.005), systolic index (r=-0.137, *P*=0.017), and systolic time ratio (r=0.236, *P*<0.001). By multivariate Cox proportional analysis, the following parameters were independently associated with cardiac death (*P*<0.001): NT-proBNP ≥425.5 pmoL/L (hazard ratio (HR), 5.104, 95% confidence interval (CI) 3.326-7.832), TFC ≥36.9 1/kOhm (HR, 4.604, 95% CI 2.701-7.849), LVEF ≤40% (HR, 4.942, 95% CI 2.8256-8.647).

Conclusions: The combination of non-invasively measured TFC, LVEF, and NT-proBNP showed great prognostic value for predicting readmissions and cardiac death in patients with HF.

Keywords: Cardiography, Impedance • Echocardiography • Heart Failure • Pro-Brain Natriuretic Peptide (1-76) • Walk Test

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Background

Heart failure (HF) is a complex clinical syndrome with the main symptoms of breathlessness, peripheral edema, and fatigue. During clinical stages of the disease, this syndrome can be accompanied by main clinical signs such as elevated jugular venous pressure, pulmonary crackles, fluid accumulation in peripheral tissues, and serous cavities [1]. Signs and symptoms are due to a structural or functional abnormality of the heart that results in elevated pressure inside the heart chambers or inadequate cardiac output at rest or during exercise [1]. Traditionally, HF is divided into distinct phenotypes based on the measurement of left ventricular ejection fraction (LVEF) [2]: HF with reduced LVEF (≤40%) is designated as heart failure with reduced ejection fraction, HF with mid-range LVEF (41-49%) is designated as heart failure with mildly reduced ejection fraction, and HF with normal LVEF (≥50%) is designated as heart failure with preserved ejection fraction. According to clinical presentation, HF is usually divided into 2 subgroups: chronic HF (CHF) and acute HF [1]. CHF describes patients who already have an established diagnosis of HF or who have a more gradual onset of symptoms. If CHF deteriorates, either suddenly or slowly, the episode can be described as decompensated HF. This can result in a hospital admission or treatment with intravenous diuretic therapy in the outpatient setting [1]. Currently, the prevalence of HF appears to be 1% to 2% in the adult population [3,4]. The prevalence increases with age, from around 1% in individuals younger than 55 years to >10% in those aged 70 years or older [1]. As researchers usually only include confirmed HF cases, the true prevalence is likely to be higher. The overall survival rate of patients with confirmed HF is slightly more than 56.7% at the 5-year margin and only 34.9% at the 10-year margin [5]. Patients with advanced HF (symptoms persist even with maximal therapy) have even worse prognosis, with a 5-year survival rate as low as 20% [6]. In 2021, the prevalence of HF in Lithuania was 30.15 of 1000 in the general population (84 682 total cases), proportion of patients admitted to hospitals was 3.59 of 1000 (10 076 total cases), mortality rate was 221.41 of 1000 inpatients, and average length of hospital stay was 28 days [7]. The current guidelines recommend the following tests in patients with suspected CHF [1]: a resting 12-lead electrocardiography (ECG), measurement of natriuretic peptides, including amino-terminal pro-brain natriuretic peptide (NT-proBNP), routine blood tests for comorbidities, transthoracic echocardiography (TTE), and chest radiography. If a patient is suspected to have acute HF, additional tests, such as lung ultrasound, mid-regional pro-atrial natriuretic peptide, serum troponin, D-dimer, procalcitonin, lactate, pulse oximetry, and arterial blood gas analysis, are recommended [1]. For the evaluation of patient outcomes and prognostication, the current guidelines [1] recommend the following tests: natriuretic peptides, serum creatinine, serum electrolytes, and iron status (transferrin, ferritin).

To improve the diagnosis of HF, it is important to search for new diagnostic methods or revive the old ones that are inexpensive, widely available, effective, preferably noninvasive, and have reliable prognostic significance. Transthoracic impedance cardiography (ICG) is one such test. It is a safe, noninvasive, and inexpensive diagnostic method based on the detection of changes in thoracic bio-impedance during the cycle of the heart. The cost of a commercially available ICG system is comparable to that of an electrocardiograph, and the technical skill needed to perform an ICG test is equivalent to that needed for recording ECG [8]. The recording procedure of ICG does not require any specially trained technicians (eg, ultrasonographers), it takes up to 10 min, the results are available immediately, and it can register many useful parameters relevant in diagnosis, real time monitoring, prognosis, and decision making in the treatment of patients with HF.

Numerous studies have been carried out in recent years that examine the possibilities of ICG in HF patients in various aspects: diagnosis, monitoring, treatment, and prognosis. Moderately strong to strong correlations between main ICG parameters and natriuretic peptides, cardiac ultrasound, and invasive diagnostic methods were observed in most studies. For example, Galas et al [9] showed that thoracic fluid content (TFC), the marker of chest congestion, had a moderately strong positive correlation with NT-proBNP (r=0.46, P=0.000001), while the systolic index showed a weak negative correlation with NT-proBNP (r=-0.22, P=0.036). In our previous studies conducted with hospitalized HF patients, we also found that the TFC and thoracic fluid content index (TFCI) had a moderately strong correlation with serum brain natriuretic peptide (BNP) concentration, with correlation coefficients of 0.32 (P<0.001) and 0.425 (P=0.001), respectively [10,11]. Other researchers compared TFC applicability in determining lung congestion, comparing B-lines acquired during lung ultrasound with TFC, and found that TFC was a reliable diagnostic method, with a correlation index of 0.58 (P<0.0001). They also compared TFC with estimated systolic pulmonary arterial pressure acquired during TTE and determined a correlation index of 0.51 (P<0.0001) [12]. Kamath et al [13] in a study with 82 participants found that TFC measured by ICG was not a reliable measure of pulmonary capillary wedge pressure (r=0.18 to 0.52 on serial measurements). Conversely, Malfatto et al [14] in their study with 23 patients found that TFC had a strong correlation with pulmonary capillary wedge pressure (r=0.69, P<0.001). In another study, Malfatto et al found a strong correlation between invasive and transthoracic impedance measurements for TFC (r=0.86, P<0.0001) [15]. It was shown that cardiac output measured by the ICG correlates well with the invasively measured cardiac output (eg, thermodilution, right-sided cardiac catheterization), with a correlation coefficient ranging between 0.76 and 0.89 [16]. However, other researchers found only a modest correlation between invasively measured cardiac output

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and cardiac output measured during ICG (r=0.4 to 0.6 on serial measurements) [13]. In our previous research, we also found only a weak correlation between BNP and cardiac output measured during ICG (r=-0.23, *P*=0.012) [11]. ICG parameters have also been extensively researched as possible prognostic indicators in patients with HF. For instance, Malfatto et al [17] in their prospective study with 205 patients found that patients with BNP <450 pg/mL and TFC <40 1/kOhm had a 2.1% 4-year mortality rate, compared with a 46.5% mortality rate in patients having BNP ≥450 pg/mL and TFC ≥40 1/kOhm. They found that a combination of these predictors showed high sensitivity (89%) and specificity (86%) in identifying death in patients at the 1-year follow-up; the same trends were also observed at the 4-year follow-up, with a sensitivity of 91% and specificity of 88%. In a recent study involving 1236 participants evaluated for HF at Stanford University, it was proven that ICG combined with cardiopulmonary exercise tests were reliable predictors of fatal outcomes, with 5 abnormal parameters from ICG and cardiopulmonary exercise resulting in a combined rise of hazard ratio (HR) to 7.11 (95% confidence interval [CI]: 4.8-10.53, *P*<0.001) [18]. In our previous study with 120 patients who were admitted to intensive care units due to HF flare-ups, we also found that some ICG parameters alone or in combination with other diagnostic tests (eg, serum BNP concentration) had a significant prognostic value, increasing the odds ratio (OR) for fatal outcomes within 6 months after discharge: BNP ≥350 pg/mL (OR 4.4), TFC ≥34 1/kOhm (OR 4.3), and systolic time ratio ≥0.55 (OR 2.9), all *P*<0.05. On the other hand, Gilewski et al [19] in their prospective study with 46 patients compared the main ICG parameters with BNP, TTE, and hemodynamic parameters acquired during right-sided cardiac catheterization and did not find any significant prognostic value in ICG parameters. In other research with 170 hospitalized patients with advanced HF (LVEF ≤30%), no ICG variable alone or in combination with right-sided cardiac catheterization was associated with patient outcomes [12]. Current HF guidelines [1] do not include ICG as a diagnostic or prognostic test, but only recommend the use of the bio-impedance function of implanted therapeutic devices for telemonitoring. These guidelines also state that whether wearable technologies for monitoring lung congestion (bio-impedance or lung radar) offer additional benefits to conventional home telemonitoring is unknown [1].

Scientific data regarding ICG parameters and its applicability in patients with HF remain controversial. Our previous research has focused only on severe CHF flare-ups and involved only relatively small samples (60 patients [10] and 120 patients [11]), and patient outcomes were evaluated during short periods of time (6 months) [11]. Therefore, this present study from a single center in Lithuania aimed to evaluate the role of transthoracic impedance cardiography in the diagnosis and outcome evaluation of 301 patients with exacerbation of CHF.

Material and Methods

Studied Sample

All patients provided written informed consent for their participation in this study, the protocol of the study was approved by the local Kaunas Regional Biomedical Research Ethics Committee (approval no. BE-2-17), and all procedures were conducted in accordance with the principles of the Declaration of Helsinki. This prospective study was conducted between 2019 and 2022 in the Hospital of the Lithuanian University of Health Sciences (Lithuania). It was registered in the ClinicalTrials.gov registry, identifier: NCT05480345. The sample consisted of 301 consecutive patients (166 men, 135 women) admitted to the hospital due to CHF flare-ups. All patients at enrollment had a previously confirmed diagnosis of CHF, according to the current guidelines [1]. The following conditions were exclusion criteria: acute HF, acute myocardial infarction, QRS ≥120 ms, mean arterial pressure >130 mmHg, severe aortic regurgitation, severe aortic stenosis, HR >200 beats per min, implantable device measuring intrathoracic impedance, and patients with minute ventilation pacemakers [10,11,20].

Methods of Examination

In accordance with current guidelines [1] the following investigations were performed: interview (anamnesis, symptoms, New York Heart Association [NYHA] class), physical examination (general inspection, lung auscultation), ECG, basic blood tests, NT-proBNP, chest radiography, and TTE. In addition, all patients underwent ICG, and selected patients underwent the 6-min walk test. Patients underwent ICG, blood sample collection for NT-proBNP serum concentration measurement, and 6-min walk test at enrollment and on the day of discharge from the hospital.

ICG parameters were recorded immediately after TTE, using a Niccomo™ transthoracic ICG monitor (Medis Medizinische Messtechnik GmbH, Ilmenau, Germany) [20] and on the last day of patient's in-hospital treatment, except if there was a death during the hospitalization period. All ICG parameters were recorded, although we only evaluated the main parameters, suitable for the diagnosis and prognosis of HF: systolic index, TFC, cardiac output, TFCI, systolic time ratio, left cardiac work, and left cardiac work index [9-11,17].

The 6-min walk test was performed according to the most recent methodology and guidelines [21]. Only selected patients underwent the test (without severe limiting disabilities, such as advanced osteoarthritis) at enrollment and on the day of discharge from the hospital. The total 6-min walk distance (6MWD), as the main diagnostic and prognostic variable, was used for statistical analysis [21].

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The primary endpoint was sudden cardiac death during in-hospital treatment and the secondary endpoint was death due to HF after discharge from the hospital. Data about patient outcomes after discharge from the hospital (readmissions, time to death due to HF) were gathered from an online database, the Lithuanian Medical Record Database (Electronic Information System of Health Services and Cooperation Infrastructure). These data were used to calculate Kaplan-Meier survival curves.

Statistical Analysis

The analysis of the data was performed using IBM Statistical Package for Social Sciences Statistics for Windows, version 27.0 (SPSS, IBM Corp, Armonk, NY, USA). Descriptive statistics are presented as mean values with 95% CIs. Means between 2 independent groups were compared using the *t* test. Correlation between parameters was evaluated using Spearman's correlation coefficient. For categorical variables, the chi-square test was used to compare groups, and variables are shown as numbers and percentages. Two dependent variables were compared with the Wilcoxon signed-ranks test. The influence of confounding factors on patient outcomes was evaluated by multivariate regression analysis. The Kaplan-Meier method with the log-rank test and survival curves was used to calculate survival rates. Univariate and multivariable Cox models were used to predict the risk of death and the chance of survival. HRs were assessed using Cox proportional-hazards models. A *P* value less than 0.05 was considered statistically significant.

Results

In this prospective study, we enrolled 301 consecutive patients with previously diagnosed CHF who were admitted to the hospital due to an HF flare-up; 135 were women (44.9%) and 166 were men (55.1%). The mean age of patients was 71.87 years (95% CI 70.4-73.4). The main characteristics of the patients are present in **Table 1**. The patients' mean NT-proBNP serum level on admission was 283.9 pmoL/L (95% CI 261.26-306.48) and 192.9 pmoL/L (95% CI 160.94-224.87) on the day of discharge. The patients' mean LVEF was 36.04% (95% CI 34.28-37.8). On the day of admission to the hospital, the distribution of patients by the NYHA classes was as follows: NYHA II, 33 patients (10.9%), NYHA III, 207 patients (68.8%), and NYHA IV, 61 patients (20.3%). On the day of discharge, the distribution was as follows: NYHA I, 1 patient (0.3%), NYHA II, 235 patients (78.1%), NYHA III, 56 patients (18.6%), and NYHA IV, 3 patients (1%).

We compared the relationships between NT-proBNP serum concentration, 6MWD, and LVEF with the main ICG parameters. The analysis revealed a weak correlation of NT-proBNP with TFC and TFCI, whereas the correlations between NT-proBNP and other ICG parameters were not significant (**Table 2**). The analysis of relationships between 6MWD and the main ICG parameters showed that there were weak to moderate correlations of 6MWD with systolic index, cardiac output, left cardiac work, left cardiac work index, and TFCI (**Table 3**); while the comparison of LVEF and ICG data showed only weak correlations of LVEF with systolic index, systolic time ratio, and TFC (**Table 4**).

We also compared the differences between main HF and ICG parameters between admission and discharge from the hospital by using the Wilcoxon signed ranks test (**Table 5**). Statistically significant results were obtained when evaluating main ICG parameters, NT-proBNP, and 6MWD.

Table 1. Main characteristics of the studied patients.

Variable	Mean±95% CI
Gender (M/F)	166/135
Age (years)	71.87±6.74
Heart rate (bpm)	79.03±2.5
sBP (mmHg)	132.95±2.95
dBP (mmHg)	80.33±1.8
RR (breaths/minute)	16.75±0.231
SpO_2 (%)	94.71±0.552
NYHA class	3.09±0.0624
6MWD (meters)	271.32±11.7
LVEF (%)	36.04±1.76
LVDd (millimeters)	50.606±1.09
LAD (millimeters)	49.25±1.08
NT-proBNP (pmoL/L)	283.9±22.58
Serum creatinine level (μmoL/L)	111.003±5.09
Bed days	24.66±0.732
Readmissions (at 6 months)	1.3±0.09
Readmissions (at 12 months)	1.99±0.15
Main diagnosis	**%**
Coronary artery disease	60
Arterial hypertension	23
Arrhythmias	10
Valvular heart disease	7

sBP – systolic blood pressure; dBP – diastolic blood pressure; RR – respiratory rate; SpO_2 – noninvasively measured oxygen saturation; NYHA – New York Heart Association; 6MWD – 6-min walk distance; LVEF – left ventricular ejection fraction; LVDd – left ventricular end-diastolic dimension; LAD – left atrial dimension; NT-proBNP – amino-terminal pro-brain natriuretic peptide.

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Table 2. Correlation between NT-proBNP and ICG data.

ICG parameter	Correlation coefficient	P-value
TFC	0.204	**<0.001**
TFCI	0.207	**<0.001**
CO	-0.034	0.559
SI	0.015	0.798
STR	0.1	0.085
LCW	-0.039	0.506
LCWI	-0.028	0.635

NT-proBNP – amino-terminal pro-brain natriuretic peptide; ICG – transthoracic impedance cardiography; TFC – thoracic fluid content; TFCI – thoracic fluid content index; CO – cardiac output; SI – systolic index; STR – systolic time ratio; LCW – left cardiac work; LCWI – left cardiac work index.

Table 3. Correlation between 6MWD and ICG data.

ICG parameter	Correlation coefficient	P-value
TFC	-0.139	0.242
TFCI	-0.322	**0.006**
CO	0.399	**<0.001**
SI	0.253	**0.031**
STR	0.151	0.203
LCW	0.43	**<0.001**
LCWI	0.419	**<0.001**

6MWD – 6-min walk distance; ICG – transthoracic impedance cardiography; TFC – thoracic fluid content; TFCI – thoracic fluid content index; CO – cardiac output; SI – systolic index; STR – systolic time ratio; LCW – left cardiac work; LCWI – left cardiac work index.

Throughout a median follow-up period of 17 months, there were 128 deaths due to cardiac death in total (42.5%). We compared the main physical examination, laboratory, and instrumental test data between deceased and survived patient groups (**Table 6**). As seen in the table, there were significant differences in the main HF parameters, such as NYHA class, 6MWD, TTE parameters, ICG parameters (except cardiac output and left cardiac work index), and NT-proBNP, with patients who died during follow-up period having worse parameters. There were more readmissions in the deceased patient group as well: 1.59±0.789 vs 1.09±0.733 at 6 months (P<0.001) and 2.39±1.41 vs 1.69±1.188 at 12 months (P<0.001), respectively.

To analyze the relationship of ICG data and other HF parameters with fatal outcome, we calculated Kaplan-Meier survival

Table 4. Correlation between LVEF and ICG data.

ICG parameter	Correlation coefficient	P-value
TFC	-0.083	0.151
TFCI	-0.163	**0.005**
CO	0.009	0.877
SI	0.137	**0.017**
STR	0.236	**<0.001**
LCW	0.029	0.619
LCWI	0.098	0.091

LVEF – left ventricular ejection fraction; ICG – transthoracic impedance cardiography; TFC – thoracic fluid content; TFCI – thoracic fluid content index; CO – cardiac output; SI – systolic index; STR – systolic time ratio; LCW – left cardiac work; LCWI – left cardiac work index.

curves (**Figures 1-3**) and used univariate and multivariate Cox proportional-hazards models to calculate HRs for fatal outcome. **Table 7** shows that univariate analysis parameters, such as systolic blood pressure, respiratory rate, LVEF, left ventricular end-diastolic dimension, left atrial dimension, serum creatinine, NT-proBNP, 6MWD, systolic index, TFC, and TFCI, showed a significant association with cardiac death. However, multivariate Cox proportional analysis revealed that only the following baseline variables were independently and significantly associated with cardiac death (P<0.001): NT-proBNP ≥425.5 pmoL/L (HR 5.104, 95% CI 3.326-7.832), TFC ≥36.9 1/kOhm (HR 4.604, 95% CI 2.701-7.849), and LVEF ≤40% (HR 4.942, 95% CI 2.8256-8.647).

For the prediction of cardiac death in patients with HF, TFC ≥36.9 1/kOhm had a sensitivity of 80.5%, specificity of 55.5%, positive predictive value of 57.2%, negative predictive value of 79.3%, and predictive accuracy of 66% (**Table 8**). Adding predictors such as LVEF ≤40% or NT-proBNP ≥425.5 pmoL/L increased the predictive accuracy to 85.2% and 86.8%, respectively.

Patients with HF with reduced ejection fraction had significantly worse outcomes than patients with HF with mildly reduced and preserved ejection fraction (P<0.001). The difference in deaths between the latter patient groups was not significant (P=0.111).

Discussion

The major finding of the present study was that parameters such as TFC ≥36.9 1/kOhm, LVEF ≤40%, and NT-proBNP ≥425.5 pmoL/L were powerful and independent prognostic markers of worsening of HF and increased mortality. This

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Table 5. Difference between main heart failure parameters on admission and at discharge.

HF parameter	Admission (mean, 95% CI)	Discharge (mean, 95% CI)	Wilcoxon test p-value
NT-proBNP (pmoL/L)	283.9 (261.24-306.48)	192.9 (160.94-224.87)	**<0.001**
6MWD (meters)	271.32 (259.62-283.02)	330.04 (309.34-350.74)	**<0.001**
TFC (1/kOhm)	41.951 (9.9362-11.2062)	37.274 (36.204-38.344)	**<0.001**
TFCI (1/kOhm/m^2)	21.280 (20.513-22.047)	18.873 (18.2-19.6)	**<0.001**
CO (mL/m^2)	5.537 (5.307-5.767)	5.879 (5.59-6.17)	**<0.001**
SI (mL/m^2)	36 (34.74-37.26)	40.2 (38.1-42.3)	**<0.001**
STR	0.4167 (0.3991-0.4343)	0.3932 (0.373-0.414)	**0.06**
LCW (kg×m)	6.688 (6.35-7.026)	6.987 (6.85-7.39)	0.767
LCWI (kg×m/m^2)	3.282 (3.14-3.42)	3.388 (3.23-3.54)	**0.001**

NT-proBNP – amino-terminal pro-brain natriuretic peptide; 6MWD – 6-min walk distance; TFC – thoracic fluid content; TFCI – thoracic fluid content index; CO – cardiac output; SI – systolic index; STR – systolic time ratio; LCW – left cardiac work; LCWI – left cardiac work index.

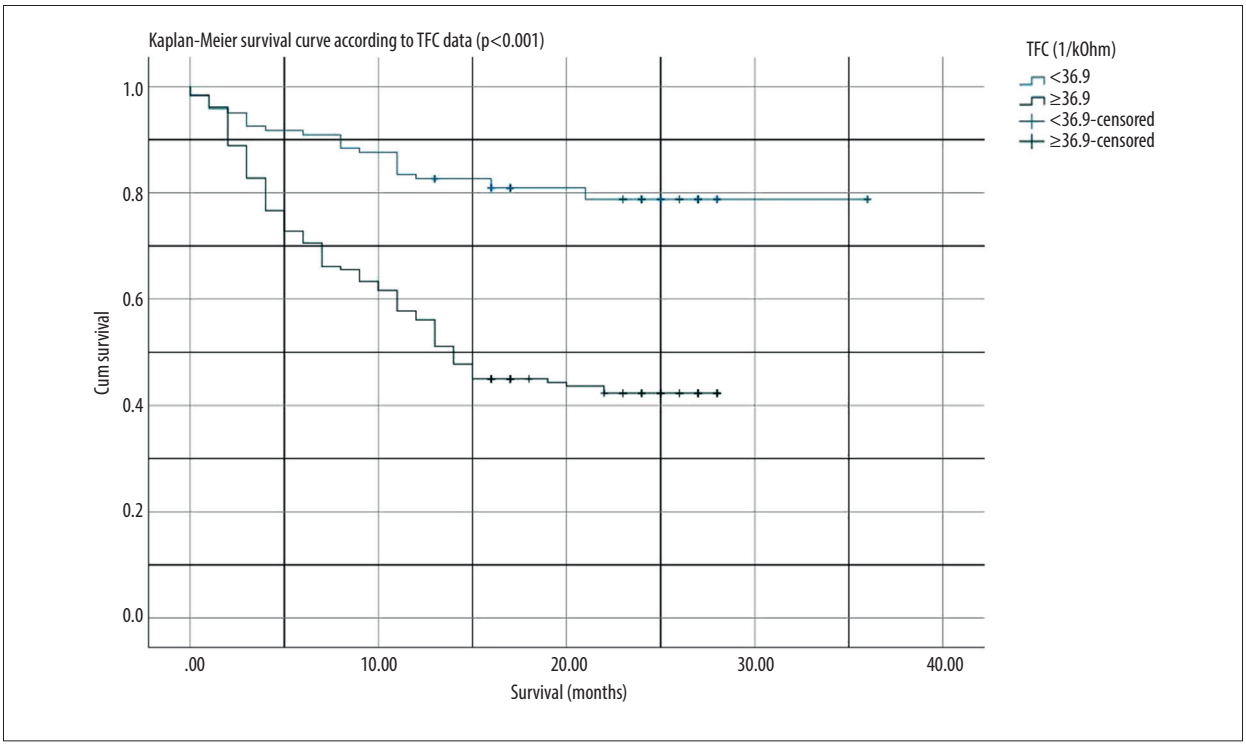

Figure 1. Kaplan-Meier survival curve according to thoracic fluid content (TFC) throughout a maximum follow-up of 36 months. Figure generated by SPSS version 27.0 (IBM Corp, Armonk, USA).

study showed that HF patients with TFC ≥36.9 1/kOhm had a 4.6-times higher risk of dying from cardiac death than patients with TFC <36.9 1/kOhm. In patients with HF with reduced ejection fraction, this risk was 4.9-fold higher than that of patients with HF with mildly reduced and preserved ejection fraction. Patients with a baseline NT-proBNP ≥425.5 pmoL/L had a 5.1-fold higher risk of death during the follow-up period. Moreover, these parameters predicted a higher risk of readmission to the hospital due to HF exacerbation. We also found that the main ICG data had a weak to moderate correlation with other noninvasive HF diagnostic tests.

Most previous studies that investigated the value of ICG in the diagnosis and prognosis of patients with HF had small sample sizes [10,12,14,15,17], whereas the data of larger randomized clinical trials are controversial. For instance, Kamath et al [13]

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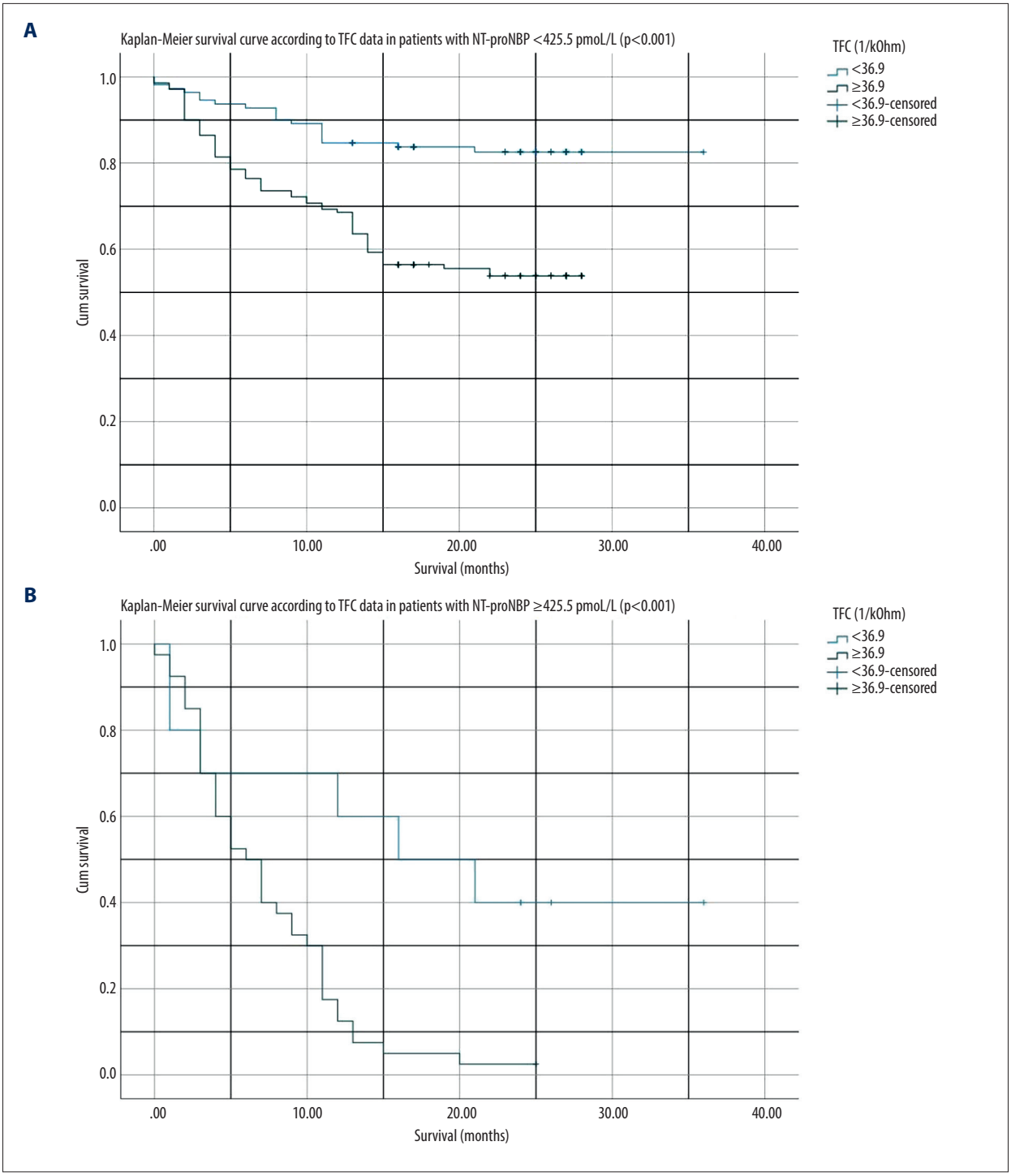

Figure 2. (**A**) Kaplan-Meier survival curve according to thoracic fluid content (TFC) in patients with amino-terminal pro-brain natriuretic peptide (NT-proBNP) <425.5 pmoL/L throughout a maximal follow-up of 36 months. (**B**) Kaplan-Meier survival curve according to TFC in patients with NT-proBNP ≥425.5 pmoL/L throughout a maximum follow-up of 36 months. Figures generated by SPSS version 27.0 (IBM Corp, Armonk, USA).

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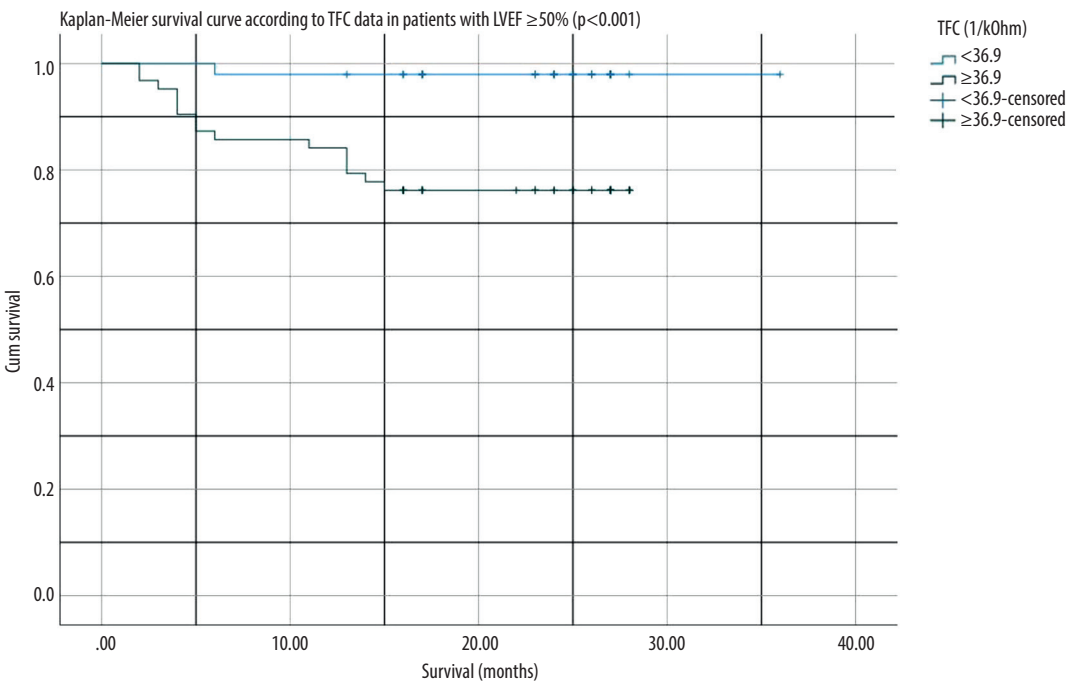

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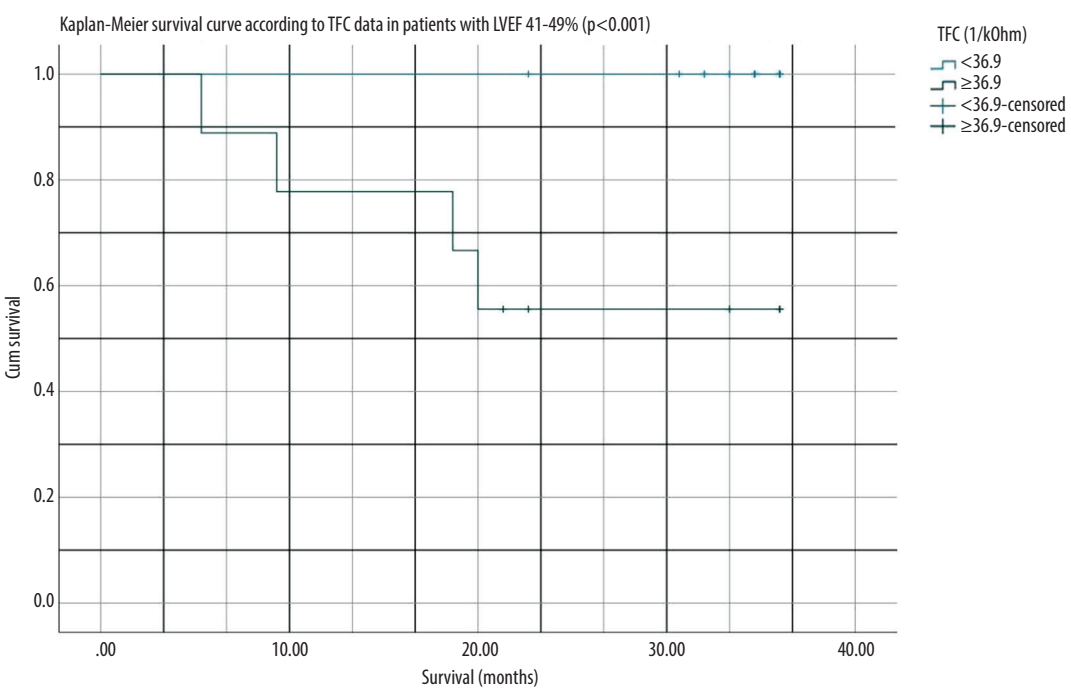

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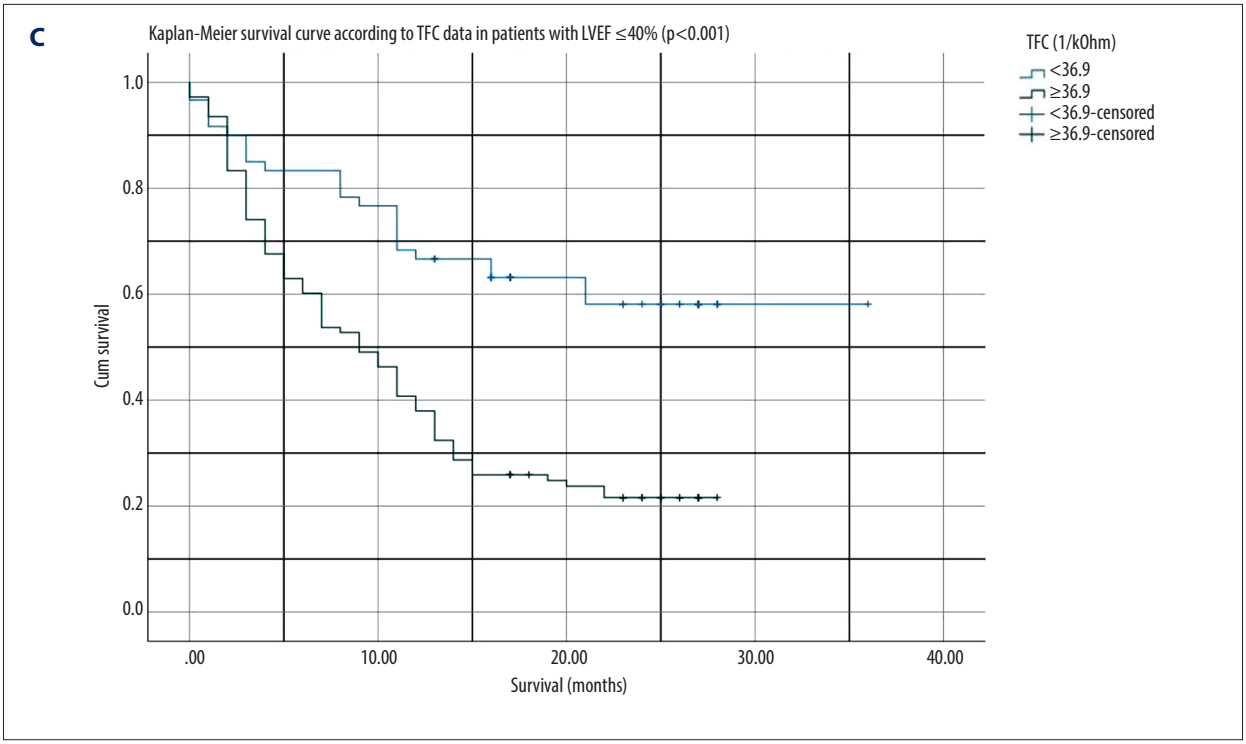

Figure 3. (**A**) Kaplan-Meier survival curve according to thoracic fluid content (TFC) in patients with left ventricular ejection fraction (LVEF) ≥50% throughout a maximum follow-up of 36 months. (**B**) Kaplan-Meier survival curve according to TFC in patients with LVEF 41-49% throughout a maximum follow-up of 27 months. (**C**) Kaplan-Meier survival curve according to TFC in patients with LVEF ≤40% throughout a maximal follow-up of 36 months. Figures generated by SPSS version 27.0 (IBM Corp, Armonk, USA).

found the following: (1) only modest correlation between ICG and invasively measured cardiac output; (2) TFC measured by ICG is not a reliable measure of pulmonary capillary wedge pressure; (3) there is poor agreement between ICG and invasively measured hemodynamic profiles (kappa ≤0.1); and (4) ICG data do not have a good prognostic value. However, Myers et al [18], in their study with more than a thousand participants, found good prognostic value in the main ICG parameters. Some previous studies did not assess the progression of HF, namely readmission to the hospital; the primary endpoint in these studies was cardiac death [11,17], and some previous studies only included stable outpatients [14,17,18]. For this reason, our study included patients with more severe HF, namely those admitted to the hospital due to exacerbation of HF, and the sample size of the study was comparatively large. We also analyzed the prognostic significance of ICG data in predicting further hospitalizations within a period of 12 months from discharge from the hospital. To the best of our knowledge, there have been no other large clinical studies with patients who were hospitalized due to HF exacerbation.

Within a median follow-up period of 17 months (maximum follow-up 36 months), there were 128 fatal outcomes due to cardiac death in total (42.5%), which may be explained by the severity of hospitalized patients: 89.1% were NYHA class III and IV. This finding agrees with previous studies, in which survival at 5 years was only 20% in decompensated HF patients [6]. In the present study, there were more readmissions to the hospital due to HF exacerbation in patients who had worse ICG parameters at baseline, which is confirmed by most of previous studies; although, Gilewski et al and Kamath et al did not find such a connection [13,19].

In agreement with our previous research [10,11], we found only a modest to moderate correlation between ICG data and other noninvasive HF diagnostic methods. Also, as mentioned above, the data of the previous studies were controversial, with some finding a strong correlation [22], while others only a modest correlation [13]. We hypothesized that the best correlation would be observed between LVEF, NT-proBNP, and the main ICG parameters, but, to our surprise, the best correlation was observed between 6MWD and ICG data, which is in agreement with research of other investigators [23,24].

To predict outcomes in patients with HF, researchers have used ICG data in conjunction with other tools, such as TTE, natriuretic peptides, cardiopulmonary exercise, and invasive tests. In our present study, we employed TTE and NT-proBNP.

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Table 6. The physical examination, laboratory, and instrumental test data comparison between deceased and survived patient groups.

Variable	Deceased patients (mean±95% CI)	Survived patients (mean±SD)	P-value
Age (years)	71.81±2.33	71.91±1.95	0.948
Heart rate (bpm)	79.97±3.75	78.34±3.43	0.525
sBP (mmHg)	129.13±5.02	135.78±3.55	**0.029**
dBP (mmHg)	79.64±3.02	80.83±2.24	0.523
RR (breaths/minute)	17.59±0.42	16.14±0.22	**<0.001**
BMI (km/m^2)	30.59±1.1	30.18±0.94	0.572
SpO_2 (%)	93.27±0.62	93.82±0.83	0.319
NYHA class	3.47±0.09	2.82±0.07	**<0.001**
6MWD (meters)	192.88±36.32	309.73±25.65	**<0.001**
LVEF (%)	25.38±2.14	43.93±1.39	**<0.001**
LVDd (millimeters)	54.38±1.63	47.82±1.33	**<0.001**
LAD (millimeters)	52.78±1.31	46.64±1.52	**<0.001**
NT-proBNP (pmoL/L)	636.14±44.48	225.29±17.76	**<0.001**
Serum creatinine level (µmoL/L)	123.09±8.61	102.06±5.92	0.1
Potassium (mmoL/L)	4.54±0.11	4.54±0.07	0.980
Sodium (mmoL/L)	137.8±0.54	138.41±0.56	0.136
Bed days	25.34±1.09	24.16±0.99	0.118
Readmissions (at 6 months)	1.59±0.15	1.09±0.11	**<0.001**
Readmissions (at 12 months)	2.39±0.25	1.69±0.17	**<0.001**
SI (mL/m^2)	34.18±1.8	37.35±1.75	**0.015**
CO (mL/m^2)	5.32±0.33	5.7±0.34	0.103
LCW (kg×m)	6.31±0.48	6.97±0.47	**0.05**
LCWI (kg×m/m^2)	3.12±0.2	3.4±0.2	0.051
STR	0.47±0.03	0.38±0.02	**<0.001**
TFC (1/kOhm)	46.56±2.08	38.54±1.4	**<0.001**
TFCI (1/kOhm/m^2)	23.69±1.25	19.5±0.89	**<0.001**

sBP – systolic blood pressure; dBP – diastolic blood pressure; RR – respiratory rate; BMI – body mass index; SpO_2 – noninvasively measured oxygen saturation; NYHA – New York Heart Association; 6MWD – 6-min walk distance; LVEF – left ventricular ejection fraction; LVDd – left ventricular end-diastolic dimension; LAD – left atrial dimension; NT-proBNP – amino-terminal pro-brain natriuretic peptide; SI – systolic index; CO – cardiac output; LCW – left cardiac work; LCWI – left cardiac work index; STR – systolic time ratio; TFC – thoracic fluid content; TFCI – thoracic fluid content index.

The sensitivity, specificity, positive predictive value, negative predictive value, and a predictive accuracy of TFC alone were not perfect, but in combination with other tests, the predictive performance slightly increased. The data in other studies, again, are conflicting. For example, Malfatto et al found that for prediction of cardiac death at the 1-year follow-up, a combination of BNP ≥450 pg/mL and TFC ≥40/kOhm had a sensitivity of 89%, specificity of 86%, positive predictive value of 88%, and negative predictive value of 92%; the combination retained its powerful predictive value of mortality at the 4-year follow-up as well. Kamath et al, however, did not find any predictive use of ICG data [13]. In agreement with most

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Table 7. Univariate and multivariate Cox proportional hazards analysis to identify heart failure patients at risk of cardiac death.

Variable (univariate analysis)	HR (95% CI)	p-value
Age	1.000 (0.987-1.014)	0.972
Gender (Male)	1.101 (0.778-1.559)	0.586
BMI	1.005 (0.978-1.032)	0.726
Heart rate	1.003 (0.996-1.011)	0.408
sBP	0.991 (0.983-0.998)	**0.014**
dBP	0.996 (0.984-1.007)	0.475
Respiratory rate	1.237 (1.161-1.318)	**<0.001**
SpO_2	0.987 (0.958-1.017)	0.399
LVEF	0.938 (0.926-0.950)	**<0.001**
LVDd	1.052 (1.034-1.071)	**<0.001**
LAD	1.035 (1.022-1.048)	**<0.001**
Serum creatinine	1.006 (1.003-1.009)	**<0.001**
Serum sodium	0.969 (0.969-1.017)	0.204
Serum potassium	0.930 (0.685-1.313)	0.678
NT-proBNP	1.003 (1.002-1.003)	**<0.001**
6MWD	0.990 (0.985-0.994)	**<0.001**
SI	0.982 (0.965-0.995)	**0.011**
CO	0.929 (0.849-1.016)	0.109
LCW	0.936 (0.847-1.000)	0.051
LCWI	0.851 (0.723-1.001)	0.052
TFC	1.037 (1.024-1.050)	**<0.001**
TFCI	1.058 (1.034-1.082)	**<0.001**
STR	1.158 (1.016-1.209)	0.056
Variable (multivariate analysis)*	**HR (95% CI)**	**p-value**
Total fluid content ≥36.9 1/kOhm	4.604 (2.701-7.849)	**<0.001**
NT-proBNP ≥425.5 pmoL/L	5.104 (3.326-7.832)	**<0.001**
LVEF ≤40%	4.942 (2.8256-8.647)	**<0.001**

BMI – body mass index; sBP – systolic blood pressure; dBP – diastolic blood pressure; SpO_2 – noninvasively measured oxygen saturation; LVEF – left ventricular ejection fraction; LVDd – left ventricular end-diastolic dimension; LAD – left atrial dimension; NT-proBNP – amino-terminal pro-brain natriuretic peptide; 6MWD – 6-min walk distance; SI – systolic index; CO – cardiac output; LCW – left cardiac work; LCWI – left cardiac work index; STR – systolic time ratio; TFC – thoracic fluid content; TFCI – thoracic fluid content index. * Adjusted for age, sex, NYHA class, and body mass index.

of the small-scale studies, we found a great prognostic value in the combination of TFC with LVEF or TFC with NT-proBNP. With univariate analysis, systolic blood pressure, respiratory rate, LVEF, left ventricular end-diastolic dimension, left atrial dimension, serum creatinine, serum NT-proBNP, 6MWD, systolic index, TFC, and TFCI showed increased HRs for cardiac death, but this association was not clinically significant (the HRs were approximately equal to 1). In the present study, we used ICG and other noninvasive, widely available, and inexpensive diagnostic tests and found that these simple diagnostic tests

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Table 8. Predictive value of the main heart failure parameters.

Parameter (p<0.001)	TFC ≥36.9 1/kOhm	TFC ≥36.9 1/kOhm +LVEF ≤40%	TFC ≥36.9 1/kOhm +NT-proBNP ≥425.5 pmoL/L
Sensitivity (%), (n)	80.5 (103/128)	77.8 (84/108)	86.7 (39/45)
Specificity (%), (n)	55.5 (92/173)	53.0 (60/113)	54.8 (92/168)
Positive predictive value (%), (n)	57.2 (103/180)	77.8 (84/108)	97.5 (39/40)
Negative predictive value (%), (n)	79.3 (96/121)	98.4 (60/61)	82.9 (92/111)
Predictive accuracy (%), (n)	66.0 (199/301)	85.2 (144/169)	86.8 (131/151)

TFC – thoracic fluid content; LVEF – left ventricular ejection fraction; NT-proBNP – amino-terminal pro-brain natriuretic peptide.

had great prognostic power in the prediction of HF worsening and fatal outcomes.

There were 4 main limitations in our study. First, we enrolled all patients with HF regardless of their LVEF. Second, it was a single-center observational study, so data can be biased. Third, we included only hospitalized patients with moderate to severe HF, and patients with stable HF were not enrolled. Therefore, our results should not be generalized to the outpatient population, especially to those who have mild HF. Finally, as multiple studies suggest, ICG produces controversial data in both diagnostic and prognostic fields; therefore, clinicians cannot rely solely on ICG data.

Conclusions

The combination of noninvasively measured TFC, LVEF, and NT-proBNP is of great prognostic value for predicting readmissions and cardiac death in patients with CHF. However, the predictive value of these parameters in patients with CHF needs further evaluation.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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