Predictive value of the integral assessment of congestion in patients with chronic heart failure

Valor predictivo de la valoración integral de la congestión en pacientes con insuficiencia cardiaca crónica

Kobalava Z., Russian People's Friendship University (RUDN University), 5-100 global@ores.su,
Tolkacheva V., Russian People's Friendship University (RUDN University), 5-100, global@prescopus.com,
Cabello-Montoya F., Russian People's Friendship University (RUDN University), 5-100, info@prescopus.com,
Sarlykov B., Russian People's Friendship University (RUDN University), 5-100, info@ores.su,
Galochkin S., Russian People's Friendship University (RUDN University), 5-100, global@ores.su,
Received/Recibido: 12/24/2021 Accepted/Aceptado: 03/19/2022 Published/Publicado: 04/25/2022 DOI: http://doi.org/10.5281/zenodo.6661275

Abstract

Purpose: to assess the predictive value of NT-proBNP, B-lines according to ultrasound of the lungs, liver density according to indirect elastometry, reactance according to bioimpedance vector analysis (BIVA), performed at discharge from the hospital in patients with chronic heart failure (H.F.), on survival rates (overall mortality and readmission).

Material and methods: the study included 105 patients (72% men, mean age 66.5 ± 11.5 years) with CHF. Arterial hypertension in the anamnesis had 94%, coronary heart disease - 60%, type 2 diabetes mellitus - 40% of patients. All patients underwent the following research: NT-proBNP, Ultrasound of the lungs (B-lines, 8 zones), liver density according to indirect elastometry, reactance according to bioimpedance vector analysis (BIVA) at discharge. Long-term clinical outcomes were assessed using a structured telephone survey method 1,3,6,12 months after discharge. The combined overall mortality and readmission rates were assessed as an endpoint. Threshold values were calculated for different methods for detecting congestion - the number of B lines according to ultrasound data> 5, NT-proBNP> 3465 pg/mL, liver density (> 9.2 kPa), reactance according to BIVA data ≤23.8.

Results: Identified 46 (44%) endpoints, 19 (18%) deaths within 190 days (IQR: 161-246). Significant direct associations of the NT-proBNP index with the number of B-lines according to lung ultrasound (r = 0.3; p <0.001), liver density (r = 0.2; p = 0.014) according to indirect elastometry and inverse with reactance were shown according to BIVA (r = -0.2; p = 0.01), as well as liver density and reactive resistance (BIVA) (r = -0.4; p <0.001). NT-proBNP level, the number of B-lines according to lung ultrasound, and liver density were significantly higher, and the reactance value was significantly lower in patients with endpoints. Cox univariate regression analysis demonstrated independent predictive value for the cumulative endpoint of all congestion markers assessed by different methods such as NT-proBNP, pulmonary ultrasound, indirect elastometry, and BIVA. Cox Multivariate Regression Analysis Confirmed Independent Predictive Significance for the Potential Endpoint Risk for the following - Reactance (HR 2,4 (1,1-5) p=0,016), the number of B-lines by ultrasound of the lungs (HR 2.1 (1.1-4.0), p = 0.015), NT-proBNP (HR 2.0 (1.0-4.1), p = 0.043). There was a significant increase in the risk of overall mortality in the presence of congestion, identified by three (RR 4.4 (1.2-16.6), p = 0.02) and four methods (RR 12.0 (3.4-41.7), p <0.001).

Conclusion: NT-proBNP levels, the number of B lines by ultrasound of the lungs, liver density and reactive resistance according to the BIVA, performed at discharge from the hospital in patients with chronic heart failure, have an independent prognostic value, while the prognostic role of assessing the reactance according to the BIVA had maximum input.

Keywords: heart failure, congestion assessment, survival, prognosis, pulmonary ultrasound, BIVA, indirect elastometry, NT-proBNP

Resumen

Propósito: evaluar el valor predictivo de NT-proBNP, líneas B según ultrasonido de los pulmones, densidad hepática según elastometría indirecta, reactancia según análisis de vector de bioimpedancia (BIVA), realizado al alta del hospital en pacientes con Insuficiencia cardiaca crónica (ICC), sobre las tasas de supervivencia (mortalidad global y reingresos).

Material y métodos: el estudio incluyó a 105 pacientes (72% hombres, edad media 66,5 ± 11,5 años) con ICC. Del total presentaban hipertensión arterial en anamnesis - 94%, enfermedad coronaria - 60%, y diabetes mellitus tipo 2 - 40%. A todos los pacientes se les evaluó al alta: NT-proBNP, Ultrasonido de los pulmones (líneas B, 8 zonas), densidad hepática según elastometría indirecta, reactancia según análisis de vector de bioimpedancia (BIVA). Los resultados clínicos a largo plazo se evaluaron mediante un método de encuesta telefónica estructurada 1, 3, 6 y 12 meses después del alta. Las tasas combinadas de mortalidad general y de reingreso se evaluaron como criterio de valoración. Se calcularon valores umbral para diferentes métodos de detección de congestión: número de líneas B según datos de ultrasonido > 5, NT-proBNP > 3465 pg/mL, densidad hepática (> 9,2 kPa), reactancia según datos de BIVA ≤ 23,8.

Resultados: identificados 46 (44%) puntos finales, 19 (18%) muertes dentro de los 190 días (IQR: 161-246). Se encontraron asociaciones directas significativas del índice NT-proBNP con el número de líneas B según ecografía pulmonar (r = 0,3; p < 0,001), densidad hepática (r = 0,2; p = 0,014) según elastometría indirecta e inversa con reactancia mostrado según BIVA (r = -0,2; p = 0,01), así como la densidad hepática y la resistencia reactiva (BIVA) (r = -0,4; p <0,001). El nivel de NT-proBNP, el número de líneas B según la ecografía pulmonar y la densidad del hígado fueron significativamente mayores, y el valor de reactancia fue significativamente menor en los pacientes con criterios de valoración. El análisis de regresión univariable de Cox demostró un valor predictivo independiente para el criterio de valoración acumulativo de todos los marcadores de congestión evaluados mediante diferentes métodos, como NT-proBNP, ecografía pulmonar, elastometría indirecta y BIVA. El análisis de regresión multivariable de Cox confirmó la significación predictiva independiente para el riesgo potencial de punto final para lo siguiente: reactancia (HR 2,4 (1,1-5) p=0.016), el número de líneas B por ultrasonido de los pulmones (HR 2,1 (1,1-4,0), p = 0.015), NT-proBNP (HR 2,0 (1,0-4,1), p = 0.043). Hubo un aumento significativo del riesgo de mortalidad general en presencia de congestión, identificado por tres (RR 4,4 (1,2-16,6), p = 0.02) y cuatro métodos (RR 12,0 (3,4-41,7), p <0.001).

Conclusión: Los niveles de NT-proBNP, el número de líneas B por ecografía pulmonar, la densidad hepática y la resistencia reactiva según el BIVA, realizados al alta hospitalaria en pacientes con insuficiencia cardíaca crónica, tienen valor pronóstico independiente, mientras que el papel de pronóstico de la evaluación de la reactancia de acuerdo con el BIVA tuvo entrada máxima.

Palabras clave: insuficiencia cardíaca, valoración de la congestión, supervivencia, pronóstico, ecografía pulmonar, BIVA, elastometría indirecta, NT-proBNP

Introduction

The primary pathophysiological mechanism of H.F. decompensation and determination of the need for hospitalization is systemic congestion[1], which is associated with a poor prognosis[2]. It is systemic congestion that leads to dysfunction of target organs, which is of great clinical and prognostic significance. Quite often, congestion phenomena can go unnoticed, since in some cases they do not manifest themselves clinically[3] but can only be detected by laboratory and/or instrumental methods. The incidence of congestion in patients at discharge is high. Residual congestion is one of the reasons for repeated patients' hospitalizations with acute decompensated heart failure, the frequency of which reaches 18% in the first 30 days after discharge. The most accurate method for assessing the severity of congestion is cardiac catheterization with measurement of pressure in the right atrium and the pressure of pulmonary capillary wedge, the widespread use of which is limited due to the invasiveness of the method.

Among the instrumental methods for assessing congestion, which, according to the literature, have prognostic value, are the concentration of B-type natriuretic peptide (BNP) and N-terminal-pro-BNP (NTproBNP), the assessment of the number of B-lines according to lungs ultrasound, evaluation of liver density by indirect elastometry, as well as assessment of hydration by the method bioimpedance measurement (BIVA).

Assessment of BNP and NTproBNP is considered the "gold standard" method for diagnosing heart failure, and one of the main markers reflecting the severity of congestion and prognosis[4]. Since blood NTproBNP concentration itself does not reflect the pathophysiological variants of congestion, pulmonary ultrasound, indirect elastometry, and hydration assessment can be used to assess the degree of residual congestion, as well as risk stratification in patients with heart failure.

Pulmonary congestion is a common cause of hospitalization in H.F. patients. Persistent clinical symptoms and signs of pulmonary congestion in patients at discharge and among outpatients are strong predictors of poor outcomes. In severe pulmonary congestion, clinical and radiographic symptoms and signs are often obvious, but they may not be detected with mild congestion. In recent years, more and more attention has been attracted by the method of ultrasound examination (ultrasound) of the lungs with the calculation of the number of B-lines. It has been shown that the presence of ultrasound signs of pulmonary congestion in patients with heart failure is associated with unfavorable long-term outcomes[5].

Prolonged congestion of blood in the hepatic parenchyma is associated with the progressive development of fibrosis up to liver cirrhosis[6], which is associated with worsening symptoms, increased risk of adverse outcomes, and limited therapeutic options. Indirect elastometry (I.E.) is a fast, low-cost, fairly accurate, and non-invasive method compared to biopsy, widely used not only to assess the severity of fibrosis in chronic liver diseases but also to assess congestion of the liver parenchyma[7-11]. It has been shown that liver density has clinical significance for assessing the severity and prognosis of heart failure[7,11-15].

One of the simplest and fastest methods for assessing the state of hydration[16] is bioimpedansometry (BIVA), which has prognostic value in patients with heart failure[17–19].

Several studies have shown a high frequency of residual congestion when using certain instrumental methods[5,15,20], but the study of the integral assessment of the identification of residual and subclinical congestion by laboratory-instrumental methods and their influence on the prognosis has been investigated in single works[2,18,21]. Thus, the purpose of this study was to assess the prognostic value of NT-proBNP blood levels ~~parameters~~, lung ultrasound, liver density according to indirect elastometry data, reactance according to bioimpedance vector analysis (BIVA), performed at discharge from the hospital in patients with acute decompensated heart failure (H.F.), on survival rates (total mortality and readmission).

Materials and methods

The study included 105 patients (72% men, mean age 66.5 ± 11.5 years) with chronic heart failure, who were admitted to the hospital for decompensated heart failure. H.F. decompensation was diagnosed based on generally accepted criteria: the appearance or rapid aggravation of symptoms and signs of H.F., which requires urgent hospitalization of the patient and intensive therapy in combination with objective signs of heart damage (systolic and/or diastolic dysfunction, left ventricular hypertrophy (LVH), enlargement of the L.A. according to Echo-KG data) and an increase in the level of NT-proBNP[22]. The study did not include patients with acute coronary syndrome (ACS), lung diseases (exacerbation of COPD, B.A.), end-stage chronic kidney disease, malignant neoplasm, edematous syndrome of a different etiology, primary liver pathology, acute hepatitis with increased transaminases (T.A.)> 5 upper limits of the normal, alcoholic excess before hospitalization, severe cognitive deficit, immobilization and patients with inability to perform BIVA (amputation of limbs, ulcers or severe trophic changes on the skin of the limbs, the presence of metal implants and structures). The clinical and demographic characteristics of the patients are presented in Table 1. From the 105 patients included in the study, the majority had a history of arterial hypertension (A.H.) (94%), coronary heart disease occurred in 60% of cases, and type 2 diabetes mellitus - 40%.

Table 1. Clinical and demographic characteristics of patients.

Parameters	Value
Sex (m / f), n (%)	76 (72)/ 29 (28)
Age, years (M ± SD)	66.5±11.5
BMI, g / m2, (M ± SD)	29.8±5.9
SBP, mmHg (M ± SD)	129±24.8
DBP, mmHg (M ± SD)	77.11±13.9
LVEF,% (M ± SD)	38.2±13
LVEF, n (%) <40% 40-49% ≥50%	 64 (61) 14 (13.3) 27 (25.7)
NT-proBNP, pg / mL (Me (IQR))	3152 (1050; 5469)
Arterial hypertension, n (%)	99 (94.3)
Ischemic heart disease, n (%)	63 (60)
Dilated cardiomyopathy, n (%)	39 (37)
Atrial fibrillation, n (%)	68 (64.8)
Type 2 diabetes mellitus, n (%)	42 (40)

Data are presented as median, 25th and 75th percentile (Me (IQR)) or arithmetic mean (M) and standard deviation of the mean (S.D.).

All patients underwent a standard physical examination at admission and discharge. As clinical symptoms and signs of pulmonary congestion, the presence and severity of dyspnea at rest and during physical exertion, orthopnea, moist fine bubbling rales, swelling of the cervical veins, hepatomegaly, and edema of the lower extremities were considered. NTproBNP in blood serum was determined by ELISA using the NT-proBNP-ELISA-BEST test system, reagent kit A-9102 (Russia, CJSC Vector-Best). At discharge, ultrasound of both sides of the chest (Sonosite, convex probe) was performed in 8 areas (II and IV m / r between the parasternal and midclavicular lines and between the anterior and midaxillary lines). The number of B-lines was counted, defined as vertical, hyperechoic artifacts of reverberation from the pleural line to the bottom of the screen, moving synchronously with the movement of the lungs. Indirect liver elastometry was performed on the day of discharge using the FibroScan® 502 touch apparatus (Echosens, France) according to the standard technique in the projection of the right lobe of the liver at the level of the 8th or 9th intercostal space along the anterior or median axillary line. Studies were considered valid if there were at least 10 and> 60% of successful measurements. The index of density (elasticity) of the liver was determined in kilopascals (kPa) and the interquartile range in percent (%). The density quantitatively indicated the severity of fibrosis in this area of the liver parenchyma where the transducer was installed. Before discharge from the hospital, all patients underwent bioimpedance vector analysis (BIVA) to assess the hydration status using the Russian serial bioimpedance analyzer AVS-01 «Medass». The method is based on measuring the electrical conductivity of various tissues of the whole body or individual body segments using special devices - bioimpedance analyzers. The electrical impedance of biological tissues has two components: active (R) and reactive (Xc) resistances. The material substrate of active resistance R in a biological object is cellular and extracellular fluids, which have an ionic conduction mechanism. The substrate of the reactance Xc is the cell membrane (dielectric partitions between the conductive regions). Measurements by the BIVA method were performed according to the standard tetrapolar scheme with the arrangement of electrodes on the wrist and ankle joints at a probing current frequency of 50 kHz in a single mode. The values of active and reactive resistance were given in terms of growth. The more water (liquid) in the tissues, the higher their electrical conductivity and lower resistance (impedance). Consequently, lower impedance values corresponded to a higher degree of hydration.

Long-term clinical outcomes were assessed using a structured telephone survey method 1, 3, 6, 12 months after discharge. The endpoint was the total overall mortality and readmission rates.

Statistica (version 8.0; Statsoft) and SPSS (version 22.0) software were used for statistical data processing. Quantitative variables were described as arithmetic mean (M) and standard deviation of the mean (S.D.) (with normal distribution) or as median (Me) and interquartile range (IQR) (with skewed distribution). The significance of differences between the two groups in terms of quantitative variables was assessed using the Mann-Whitney U-test. Qualitative variables were represented by absolute (n) and relative (%) values. To compare groups in terms of the frequency of qualitative variables, the Pearson chi-square test ($\chi2$) was used. The significance of differences in one group at different points was assessed using the Wilcoxon W-test. For multiple comparisons, one-way ANOVA was used, with an abnormal distribution - the Kruskal-Wallis test. The probability of survival was assessed by the Kaplan – Meier survival curves method; a comparison was made using the log-rank test. To assess the prognostic significance of different methods (as a continuous and discrete value) on the risk of the onset of interest variables, one- and multivariate Cox regression analysis models were used. The choice of variables included in the model was carried out considering their clinical significance. To determine the threshold values of survival, the method of constructing ROC curves was used. P <0.05 was considered significant.

Results

Our results show a significant direct association between the NT-proBNP index with the number of lines according to ultrasound of the lungs, liver density according to indirect elastometry, and an inverse association with reactance according to BIVA, as well as liver density and active and reactive resistance (BIVA). No reliable relationship was found between the rest of the parameters (Table 2).

Table 2. Correlation between congestion markers, assessed by different methods

Lung ultrasound	NT-proBNP	Liver density
Liver density	r=0.3; p<0.001	
BIVA (reactance)	r=0.2; p=0.014	
BIVA (active resistance)	r=-0.2; p=0.01	r=-0.4; p<0.001
Lung ultrasound		r=-0.4; p<0.001

The observation period was 400 days. There were 46 (44%) endpoints, 19 (18%) deaths within 190 days (IQR: 161-246). Levels of NT-proBNP, the number of B-lines according to ultrasound of the lungs, and liver density were significantly higher, and the values of active and reactive resistance were significantly lower in patients with events (Table 3).

Table 3. Congestion markers in patients with CHF depending on outcomes

	All patients n=105	No event=59	Event n=46	p
Lung ultrasound (In line)	6 (3;12)	4 (3; 9)	7,5 (3;15)	0,026
Liver density	8,7 (5,7;14)	6,6 (4,4; 11,6)	11 (6,9; 20)	0,000
NT-proBNP	3152 (1050; 5469)	2160 (980; 4670)	3787 (1694; 6179)	0,009
BIVA (reactance)	25 (21,8; 31)	27 (24; 32,8)	22,9 (19,7; 28,7)	0,002
BIVA (active resistance)	284,8 (244,6; 323,9)	296 (262; 325)	271 (228,8; 307,7)	0,032

When constructing ROC curves to predict outcomes (total mortality + readmission), the following threshold values of different methods for assessing congestion were identified - the number of B lines according to ultrasound data> 5, NT-proBNP> 3465 pg/mL, liver density (> 9.2 kPa), the indicator of reactance according to the BIVA data is ≤23.8, the indicator of the active resistance according to the BIVA data is ≤279.5 (Table 4).

Table 4. Thresholds for predicting outcomes by a method

	Thresholds	Sensitivity	Specificity	AUC	p
Lung ultrasound (In line)	>5	66.7	63.16	0.61	0.044
Liver density	>9.2	68.75	68.42	0.70	<0.001
BIVA (reactance)	≤23.8	56.25	80.70	0.67	0.001
BIVA (active resistance)	≤279.5	60.42	66.67	0.61	0.035
NT-proBNP	>3465	56.25	66.67	0.62	0.023

Cox's univariate regression analysis demonstrated independent predictive value for the cumulative endpoint of all congestion markers assessed by different methods, such as NT-proBNP, pulmonary ultrasound, liver density index according to indirect elastometry, active and reactive resistance according to BIVA. Multivariate Cox regression analysis confirmed the independent predictive value in relation to the risk of the total endpoint for the indicators of reactance according to BIVA (HR 2.4 (1.1-5) p = 0.016), ultrasound of the lungs (HR 2.1 (1.1– 4.0), p = 0.015) NT-proBNP (HR 2.0 (1.0–4.1), p = 0.043), with respect to active resistance, the result was unreliable, therefore, for further calculations, the reactance was used (Table 5).

Table 5. Univariate and multivariate Cox regression analyses for congestion markers assessed by different methods for the risk of a combined endpoint (mortality + readmission)

Congestion markers	One-way regression analysis		Multivariate regression analysis	
	HR (95%)	p	HR (95%)	p
NT-proBNP	2.2 (1.2–4.1)	0.006	2.0 (1.0– 4.1)	0.043
Lung ultrasound	2.5 (1.3–4.7)	0.003	2.1 (1.1 – 4.0)	0.015
Liver density	3.1 (1.6–5.9)	<0.000	2.2 (1.0– 4.5)	0.03
BIVA (reactance)	3.4 (1.9–6.2)	<0.000	2.4 (1.1–5)	0.016
BIVA (active resistance)	2.1 (1.1-3.8)	0.013	1.1 (0.5-2.5)	0.7

By analyzing the Kaplan-Meier survival curves, significant differences were obtained between the groups of patients with NT-proBNP> 3465 pg/mL (Fig. 1), depending on the presence and severity of pulmonary congestion according to ultrasound data (B line> 5) (Fig. 2), liver density> 9.2 kPa (Fig. 3), indicators of reactance according to BIVA data> 23.8 (Fig. 4).

Kaplan-Meier curves of the cumulative probability of survival (total mortality + readmission) depending on the number of methods used to estimate congestion (one, two, three, four) are presented in Figure 5. There was a significant increase in the risk of overall mortality in the presence of congestion, identified by three (RR 4.4 (1.2-16.6), p = 0.02) and four methods (RR 12.0 (3.4-41.7), p <0.001).

Fig 1. Kaplan-Meier curves of the cumulative probability of survival (total mortality + readmission) depending on the presence and severity of congestion in terms of NT-proBNP

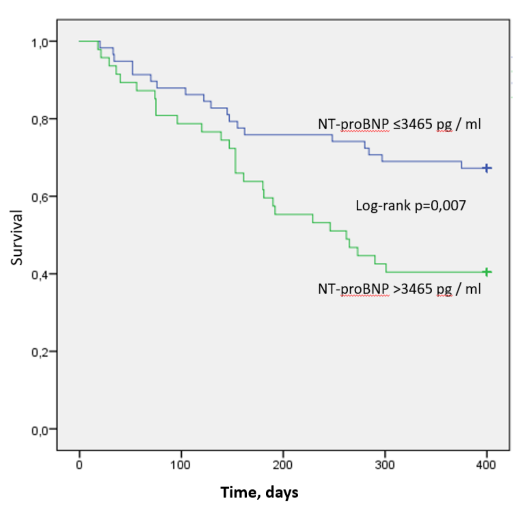


Fig 2. Kaplan-Meier curves of the cumulative probability of survival (total mortality + readmission) depending on the presence and severity of pulmonary congestion according to ultrasound data

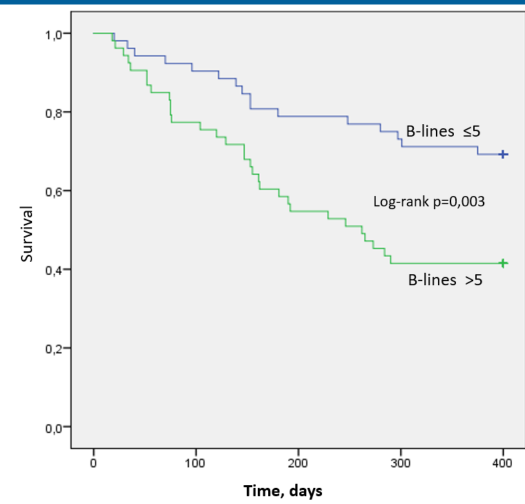


Fig 3. Kaplan-Meier curves of cumulative probability of survival (total mortality + hospital readmission) versus liver density according to indirect elastometry data.

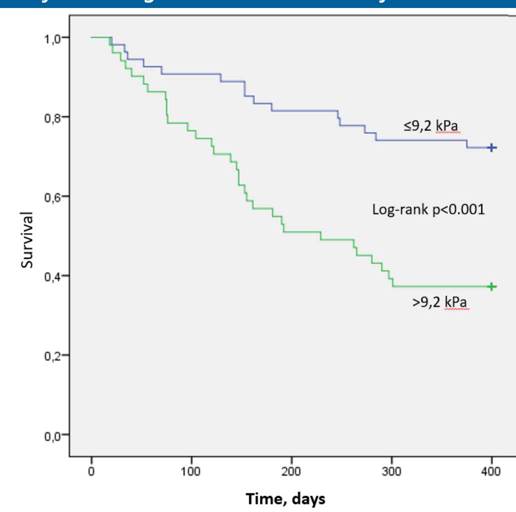


Fig 4. Kaplan-Meier curves of the cumulative probability of survival (total mortality + readmission) depending on the data of the BIVA.

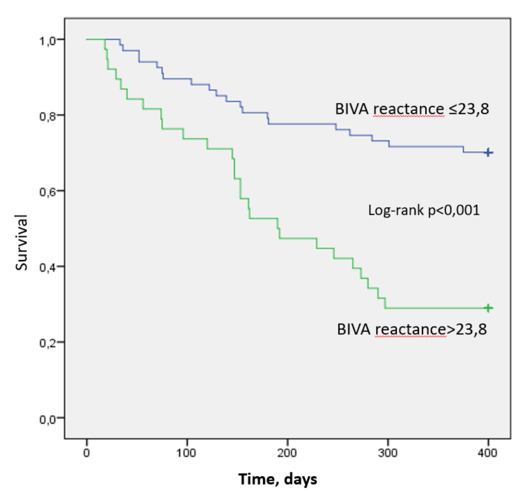
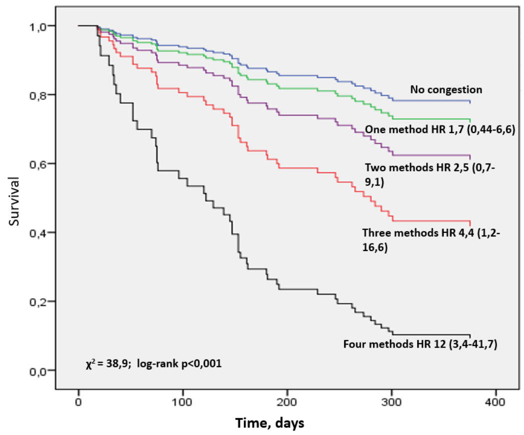


Fig. 5. Kaplan-Meier curves of the cumulative probability of survival (total mortality + readmission) versus the number of methods used to assess congestion.



Discussion

Systemic congestion in heart failure is the leading and most studied problem and is characterized by more complex pathophysiology than simply the accumulation of excess water in the body[21-23]. The lack of universal criteria for its detection, on the one hand, and methods confirming its complete elimination or the achievement of the so-called «euvolemia»[24], emphasize the relevance of studies comparing the clinical and prognostic value of various diagnostic approaches in its assessment. This study has demonstrated the predictive value of laboratory-instrumental methods reflecting different components of congestive phenomena in heart failure in relation to the total rate of total mortality and readmission rates. Assessment of «hemodynamic» congestion was carried out by examining blood levels of NT-proBNP, «pulmonary» congestion by ultrasound of the lungs, «hepatic» congestion by assessing liver density using indirect elastometry, peripheral hydration by bioimpedansometry (BIVA).

Undoubtedly, in practice, physical examination remains the main tool for assessing congestion. However, the accuracy of traditional clinical symptoms and signs of congestion, reflecting an increase in intracardiac filling pressure and/or, consequently, excessive accumulation of extravascular fluid, is relatively low compared to the intracardiac assessment of hemodynamics[24].

The use of a quantitative ultrasonic method based on the calculation of B-lines may be promising. In a randomized study[25] in 518 patients with acute onset dyspnea, it was demonstrated that an approach based on the integration of pulmonary ultrasonography into routine screening examination at the stage of diagnosis of acute H.F. decompensation is more significant than an approach based on traditional physical examination, chest x-ray, and NT-proBNP levels assessment. The accuracy of H.F. diagnosis using pulmonary ultrasound was significantly higher compared to physical examination alone (area under the curve [AUC] 0.95 versus 0.88 at, p <0.01) or its combination with X-ray examination and NTproBNP determination (AUC 0,95 versus 0.87, p <0.01). In contrast, assessment of chest radiographs and NTproBNP levels did not have an additional benefit over clinical assessment alone (AUC 0.87 and 0.85, respectively, p> 0.05). The accuracy of H.F. diagnosis using pulmonary ultrasound was significantly higher compared to physical examination alone (area under the curve [AUC] 0.95 versus 0.88 at, p <0.01) or its combination with X-ray examination and NTproBNP determination (AUC 0,95 versus 0.87, p <0.01). The evidence indicate that the assessment of the number of B lines allows us to identify a risk group for adverse long-term outcomes in both outpatients and hospitalized H.F. patients. In a study in outpatients, a B-line sum of ≥3 on ultrasound using a 5- or 8-zone scan was associated with a 4-fold risk of death or readmission with H.F. within 6 months[26]. In patients with acute H.F., the sum of B-lines > 15 at discharge on scanning of 28 zones was associated with a more than 5-fold increase in the risk of death or readmission with HF[26-28].

This study demonstrated a significant direct association between the lung ultrasound score and NT-proBNP levels ($r = 0.3$; $p < 0.001$). Univariate Cox regression analysis demonstrated an independent predictive value of pulmonary ultrasound in relation to the cumulative endpoint of the risk of all-cause mortality and readmission to the hospital, which was also confirmed by multivariate analysis. By analyzing the Kaplan-Meier survival curves, significant differences were obtained between groups of patients depending on the presence and severity of pulmonary congestion according to ultrasound data (B line ≤5 and> 5).

The adverse effect of residual liver congestion on the prognosis of patients with heart failure has been shown in several studies[29,30]. In a study of 171 patients hospitalized with heart failure, an unfavorable predictive value of increased liver density at discharge was demonstrated, while patients with liver density > 6.9 kPa had a higher rate of death and readmission for heart failure (R.R. = 3.57; 95% CI: 1.93-6.83; p <0.001)[31]. Thus, the authors concluded that the liver density values measured at discharge probably reflect the presence of subclinical residual liver congestion and can be used as a surrogate marker of residual congestion and adverse events even in patients with optimized therapy, without visible signs and symptoms of volume overload or increased laboratory parameters of liver function[31-33]. A reliable direct association of the liver density index with NT-proBNP levels ($r = 0.2$; $p = 0.014$), as well as a reliable inverse liver density and active and reactive resistance indicators according to the BIVA data ($r = -0.4$; $p < 0.001$). Univariate Cox regression analysis demonstrated an independent predictive value of the liver density study for the cumulative endpoint of risk for all-cause mortality and hospital readmissions, which was not supported by multivariate analysis. By analyzing the Kaplan-Meier survival curves, significant differences were obtained between groups of patients depending on the density of the liver (> 9.2 kPa).

A number of studies have shown a significant role in assessing the state of hydration by bioimpedance measurement in assessing the prognosis in patients with heart failure, especially in relation to overall mortality after 90 days and 1 year of observation[17, 18]. It has been shown that the reactance index is a more significant predictor of mortality after 90 days of observation (AUC 0.712, 95% CI: 0.655–0.76; p <0.007) than the active resistance indicator (AUC 0.65, 95% CI: 0.29–0.706; p <0.025). The combined use of BIVA and NT-proBNP levels have a higher predictive value (AUC 0.74, 95% CI: 0.69–0.76; p <0.001)[16]. In this study, significant inverse associations of reactive resistance according to BIVA data with NT-proBNP (r = -0.2; p = 0.014), as well as liver density (r = -0.4; p <0.001) were observed. Univariate Cox regression analysis demonstrated the independent predictive value of active and reactive resistance according to BIVA in relation to the cumulative endpoint (overall mortality and readmission), however, in multivariate analysis, the data were reliable only for the reactivity index, which is consistent with literature data.

When assessing the prognostic value of NT-proBNP, ultrasound of the lungs, liver density, and reactive resistance according to BIVA data performed at discharge from the hospital, on the survival rates in patients with acute decompensated heart failure, all methods had an independent value, but the method for assessing reactive resistance had the maximum contribution according to BIVA (HR 2.4 (1.1-5) p = 0.016), in second place is the indicator of liver density (2.2 (1.0-4.5), p = 0.03), in third lungs ultrasound (HR 2.1 (1.1-4.0), p = 0.015) and ~~NT-proBNP~~ NT-proBNP (HR 2.0 (1.0-4.1), p = 0.043). A significant increase in the risk of overall mortality was shown in the presence of congestion, identified (RR 4.4 (1.2-16.6), p = 0.02) and four methods (RR 12.0 (3.4-41.7), p <0.001).

Thus, clinical evaluation and assessment based on changes in the concentration of brain natriuretic peptides at discharge as surrogate markers of residual congestion in patients with chronic heart failure may be insufficient. A combination of objective measures of congestion assessment in addition to clinical evaluation can help to identify different degrees of congestion and lead to more rational therapy and follow-up of this group of patients. At the same time, ultrasound of the lungs, the assessment of liver density, and the study of reactive resistance according to the BIVA data have a proven prognostic value and maximum contribution to the prognosis.

Acknowledgments: not applicable. A self-funded study. No conflict of interest.

References

1. Dupont M, Mullens W, Tang WH. Impact of systemic venous congestion in heart failure. Current heart failure reports. 2011 Dec;8(4):233-41.

2. Girerd N, Seronde MF, Coiro S, Chouihed T, Bilbault P, Braun F, Kenizou D, Maillier B, Nazeyrollas P, Roul G, Fillieux L. Integrative assessment of congestion in heart failure throughout the patient journey. JACC: Heart Failure. 2018 Apr;6(4):273-85.

3. Pellicori P, Kaur K, Clark AL. Fluid management in patients with chronic heart failure. Card Fail Rev. 2015;1:90–5.

4. Maisel AS, Duran JM, Wettersten N. Natriuretic peptides in heart failure: atrial and B-type natriuretic peptides. Heart failure clinics. 2018 Jan 1;14(1):13-25.

5. Massari F, Scicchitano P, Iacoviello M, Passantino A, Guida P, Sanasi M, Piscopo A, Romito R, Valle R, Caldarola P, Ciccone MM. Multiparametric approach to congestion for predicting long-term survival in heart failure. Journal of Cardiology. 2020 Jan 1;75(1):47-52.

6. Gelow JM, Desai AS, Hochberg CP, Glickman JN, Givertz MM, Fang JC. Clinical predictors of hepatic fibrosis in chronic advanced heart failure. Circulation: Heart Failure. 2010 Jan 1;3(1):59-64.

7. Millonig G, Friedrich S, Adolf S, Fonouni H, Golriz M, Mehrabi A, Stiefel P, Pöschl G, Büchler MW, Seitz HK, Mueller S. Liver stiffness is directly influenced by central venous pressure. Journal of hepatology. 2010 Feb 1;52(2):206-10.

8. Nishi H, Toda K, Miyagawa S, Yoshikawa Y, Fukushima S, Kawamura M, Saito T, Yoshioka D, Daimon T, Sawa Y. Novel method of evaluating liver stiffness using transient elastography to evaluate perioperative status in severe heart failure. Circulation Journal. 2014:CJ-14.

9. Jalal Z, Iriart X, De Lédinghen V, Barnetche T, Hiriart JB, Vergniol J, Foucher J, Thambo JB. Liver stiffness measurements for evaluation of central venous pressure in congenital heart diseases. Heart. 2015 Sep 15;101(18):1499-504.

10. Kashiyama N, Toda K, Nakamura T, Miyagawa S, Nishi H, Yoshikawa Y, Fukushima S, Saito S, Yoshioka D, Sawa Y. Evaluation of right ventricular function using liver stiffness in patients with left ventricular assist device. European Journal of Cardio-Thoracic Surgery. 2017 Apr 1;51(4):715-21.

11. Taniguchi T, Ohtani T, Kioka H, Tsukamoto Y, Onishi T, Nakamoto K, Katsimichas T, Sengoku K, Chimura M, Hashimoto H, Yamaguchi O. Liver stiffness reflecting right-sided filling pressure can predict adverse outcomes in patients with heart failure. Cardiovascular Imaging. 2019 Jun 1;12(6):955-64.

12. Colli A, Pozzoni P, Berzuini A, Gerosa A, Canovi C, Molteni EE, Barbarini M, Bonino F, Prati D. Decompensated chronic heart failure: increased liver stiffness measured by means of transient elastography. Radiology. 2010 Dec;257(3):872-8.

13. Saito Y, Kato M, Nagashima K, Monno K, Aizawa Y, Okumura Y, Matsumoto N, Moriyama M, Hirayama A. Prognostic relevance of liver stiffness assessed by transient elastography in patients with acute decompensated heart failure. Circulation Journal. 2018:CJ-17.

14. Omote K, Nagai T, Asakawa N, Kamiya K, Tokuda Y, Aikawa T, Fukushima A, Noguchi K, Kato Y, Komoriyama H, Nishida M. Impact of admission liver stiffness on long-term clinical outcomes in patients with acute decompensated heart failure. Heart and Vessels. 2019 Jun;34(6):984-91.

15. Campos-Murguía A, Ruiz-Margáin A, González-Regueiro JA, Macías-Rodríguez RU. Clinical assessment and management of liver fibrosis in non-alcoholic fatty liver disease. World journal of gastroenterology. 2020 Oct 21;26(39):5919.

16. Massari F, Iacoviello M, Scicchitano P, Mastropasqua F, Guida P, Riccioni G, et al. Accuracy of bioimpedance vector analysis and brain natriuretic peptide in detection of peripheral edema in acute and chronic heart failure. Heart Lung 2016;45:319–26

17. Santarelli S, Russo V, Lalle I, De Berardinis B, Vetrone F, Magrini L, Di Stasio E, Piccoli A, Codognotto M, Mion MM, Castello LM. Prognostic value of decreased peripheral congestion detected by Bioelectrical Impedance Vector Analysis (BIVA) in patients hospitalized for acute heart failure: BIVA prognostic value in acute heart failure. European Heart Journal: Acute Cardiovascular Care. 2017 Jun 1;6(4):339-47.

18. Santarelli S, Russo V, Lalle I, De Berardinis B, Navarin S, Magrini L, Piccoli A, Codognotto M, Castello LM, Avanzi GC, Villacorta H. Usefulness of combining admission brain natriuretic peptide (BNP) plus hospital discharge bioelectrical impedance vector analysis (BIVA) in predicting 90 days cardiovascular mortality in patients with acute heart failure. Internal and emergency medicine. 2017 Jun;12(4):445-51.

19. Nunez J, Mascarell B, Stubbe H, Ventura S, Bonanad C, Bodi V, Nunez E, Minana G, Facila L, Bayes-Genis A, Chorro FJ. Bioelectrical impedance vector analysis and clinical outcomes in patients with acute heart failure. Journal of Cardiovascular Medicine. 2016 Apr 1;17(4):283-90.

20. Mamatov BM, Villevalde SV, Klimenko AS, Kobalava ZhD. The value of bioimpedance vector analysis in the diagnosis of subclinical blood stasis in patients with decompensated heart failure. Wedge Pharmacol Ter. 2016;25 (5):45-49.

21. Massari F, Scicchitano P, Iacoviello M, Passantino A, Guida P, Sanasi M, Piscopo A, Romito R, Valle R, Caldarola P, Ciccone MM. Multiparametric approach to congestion for predicting long-term survival in heart failure. Journal of Cardiology. 2020 Jan 1;75(1):47-52.DOI: https://doi.org/10.1016/j.jjcc.2019.05.017

22. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M. ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129-200.

23. Fudim M, Hernandez AF, Felker GM. Role of volume redistribution in the congestion of heart failure. Journal of the American Heart Association. 2017 Aug 17;6(8):e006817.

24. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WW, Orso F, Rossignol P, Metra M. The use of diuretics in heart failure with congestion—a position statement from the Heart Failure Association of the European Society of Cardiology. European journal of heart failure. 2019 Feb;21(2):137-55.

25. Pivetta E, Goffi A, Nazerian P, Castagno D, Tozzetti C, Tizzani P, Tizzani M, Porrino G, Ferreri E, Busso V, Morello F. Lung ultrasound integrated with clinical assessment for the diagnosis of acute decompensated heart failure in the emergency department: a randomized controlled trial. European journal of heart failure. 2019 Jun;21(6):754-66.

26. Platz E, Merz AA, Jhund PS, Vazir A, Campbell R, McMurray JJ. Dynamic changes and prognostic value of pulmonary congestion by lung ultrasound in acute and chronic heart failure: a systematic review. European journal of heart failure. 2017 Sep;19(9):1154-63.

27. Coiro S, Porot G, Rossignol P, Ambrosio G, Carluccio E, Tritto I, Huttin O, Lemoine S, Sadoul N, Donal E, Zannad F. Prognostic value of pulmonary congestion assessed by lung ultrasound imaging during heart failure hospitalisation: A two-centre cohort study. Scientific reports. 2016 Dec 20;6(1):1-8.

28. Gargani L, Pang PS, Frassi F, Miglioranza MH, Dini FL, Landi P, Picano E. Persistent pulmonary congestion before discharge predicts rehospitalization in heart failure: a lung ultrasound study. Cardiovascular ultrasound. 2015 Dec;13(1):1-9.

29. Rubio-Gracia J, Demissei BG, Ter Maaten JM, Cleland JG, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison BA, Givertz MM. Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure. International journal of cardiology. 2018 May 1;258:185-91.

30. Saito Y, Kato M, Nagashima K, Monno K, Aizawa Y, Okumura Y, Matsumoto N, Moriyama M, Hirayama A. Prognostic relevance of liver stiffness assessed by transient elastography in patients with acute decompensated heart failure. Circulation Journal. 2018:CJ-17.

31. Taniguchi T, Ohtani T, Kioka H, Tsukamoto Y, Onishi T, Nakamoto K, Katsimichas T, Sengoku K, Chimura M, Hashimoto H, Yamaguchi O. Liver stiffness reflecting right-sided filling pressure can predict adverse outcomes in patients with heart failure. Cardiovascular Imaging. 2019 Jun 1;12(6):955-64.

32. Ramírez-Coronel AA, Cárdenas-Castillo PF, Martínez-Suárez PC, Yambay-Bautista XR, Mesa-Cano IC, Minchala-Urgilés RE, Andrade-Molina MC, Sarmiento-Pesántez MM, González-León FM, Pogyo-Morocho GL, Cárdenas-Cordero AJ. Impacto psicológico del confinamiento por COVID-19 hacia un nuevo constructo clinimétrico ansioso-depresivo en mujeres adultas de Azogues. Archivos Venezolanos de Farmacologia y Terapéutica. 2020;39(8):923-34.

33. Chabla-Inga MF, Mesa-Cano IC, Ramírez-Coronel AA, Jaya-Vásquez LC. Diabetes como factor de riesgo de mortalidad intrahospitalaria en pacientes con COVID-19: revisión sistemática. Archivos Venezolanos de Farmacologia y Terapéutica. 2021;40(3):240-7. https://doi.org/10.5281/zenodo.5038351.