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***Original Article***

# Prognostic Value of Admission-to-Discharge Change in Integral Congestion Assessment for Predicting Adverse Outcomes in Patients with Decompensated Heart Failure

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**Abstract**

This study was performed to evaluate the prognostic value of relative changes from admission to discharge (Δ%) of integrated congestion assessment to predict adverse outcomes in patients with irreversible heart failure (HF) during a one-year follow-up. The study included 122 patients (60% males, median age of 69 years) with decompensated HF. Most of the patients (92%) had a history of arterial hypertension, 53.3% had coronary heart disease, and 40.2% had type 2 diabetes mellitus. All patients underwent assessments, including NT-proBNP, lung ultrasound (LUS) B-line score, liver stiffness by transient elastography, and resistance and reactance by bioimpedance vector analysis (BIVA). The assessments were performed at admission and discharge, and a relative change from admission (delta percentage, Δ%) was calculated. Long-term clinical outcomes were assessed by a structured interview conducted 1, 3, 6, and 12 months after discharge. The cut-offs for the occurrence of the endpoint events were Δ% NT-proBNP of ≥ -25, Δ% liver stiffness of ≥ -44, Δ% B-line score on lung ultrasound of ≥ -73, Δ% BIVA resistance of ≤ 18, and Δ% BIVA reactance of ≤ 40. It was revealed that 55% of endpoint events, including 22 (18%) deaths and 33 (27%) readmissions, occurred within a median of 74 days (interquartile range: 33-147). Patients with an endpoint event had significantly worse values of all studied parameters in contrast to patients without it. There was a significant direct association between Δ% NT-proBNP and Δ% B-lines (r=0.18; *P*=0.04), and a highly reliable inverse association was observed between Δ% liver stiffness and Δ% BIVA reactance (r=-0.4; *P*<0.001). No significant associations were found between the other parameters. Univariate Cox regression analysis demonstrated the independent prognostic value of all congestion markers under study (NT-proBNP, LUS B-lines, liver stiffness, and BIVA reactance) for predicting the combined endpoint. Multivariate Cox regression analysis confirmed the independent prognostic value in predicting the risk of endpoint event for the following parameters: NT-proBNP (hazard rate [HR] 2.5, *P*=0.001), liver stiffness (HR 2.3, *P*=0.012), LUS B-line score (HR 2.2, *P*=0.008). However, it did not find any significant prognostic value for BIVA resistance and reactance. The relative admission-to-discharge change in the integral assessment of congestion had a prognostic value for predicting the risk of adverse outcomes (all-cause mortality and readmission rate) in patients with decompensated HF during a one-year follow-up.

**Keywords:** Heart failure, Assessment of congestion, Survival, Prognosis, Delta, Lung ultrasound, BIVA, Transient elastography, NT-proBNP

## 1. Introduction

Patients with heart failure (HF), suffer from a variety of symptoms due to HF, such as shortness of breath, dizziness, angina, edema, and ascites (1). Compared to cancer patients, these patients live longer with the disability due to the disease and have to adapt to an unforeseen death. Many of these patients, especially late in the illness, experience stress and poor control of their symptoms and often feel they are a burden on the community and their loved ones. If the unpredictability of the prognosis of HF is compared with some common cancers, it can be said that HF is one of the most malignant and dangerous diseases (2). For this reason, the need for palliative care in these patients is essential, and one of the important points in specialized palliative care is respect for human dignity.

Human or inherent dignity indicates that all human beings enjoy equal human rights, is closely related to the basic rights of individuals, and is considered a basic precondition of all individual rights (3). Therefore, to provide appropriate care, caregivers must establish an honest relationship with the patient and respect their individual and professional rights and values (4). According to surveys, caregivers do not provide enough information to patients and are more concerned about the day-to-day work at the ward than talking to patients (5). However, patients prefer to receive factual information about the disease and its prognosis from caregivers. According to the results of studies, after discharge, heart disease patients are exposed to problems related to daily activities, lack of awareness of symptoms, side effects, side effects of medications, and diet (6). In this regard, the findings of a study by Mangolian, Shahnazari (7) showed that 85%, 92.5%, 95%, 82.5%, and 85% of patients with HF needed training regarding recognizing the nature of the disease, diet, medication, rest and sexual activity, and follow up on treatment, respectively (7). In this respect, it is necessary to adopt measures to reduce patients' problems in various dimensions and improve their care, help them maintain communication and education, and follow up after discharge. Among these measures can be informing patients of the disease, the causes, and the aggravation of the disease; emphasizing the correct and timely use of prescribed drugs after discharge; highlighting the aspects of self-care; and informing them of risk factors and timely referral to a physician for follow-up treatment (8). Respectful communication of caregivers with patients and the use of various communication methods are effective factors in maintaining the self-esteem and dignity of individuals.

Based on the results of research, patients with HF expect to receive the necessary information from care workers; otherwise, there is a feeling of being forgotten and neglected in them. These patients believe that they feel as if they are not supported by the care staff. They will be imposed on others and will be alone, and this loneliness will increase their suffering and affect their sense of well-being and health (9). For this reason, when patients with HF receive support on an ongoing basis with the necessary information and dignified behavior from caregivers, they will feel comfortable, hopeful, and confident.

Discharge is a period of hospital-to-home transition in which the responsibility of caregivers is transferred to the patient, and may lead to new problems for the patient and his/her family (10). Monitoring patients after discharge significantly reduces mistakes in medical prescriptions during discharge because most of these mistakes are preventable (11). Inadequate follow-up of patients after discharge leads to an increased risk of readmission within 1 month of discharge. The current unplanned hospitalization is considered a factor indicating the poor performance of the healthcare system. Patients with lower financial income are more likely to be re-admitted because they are unable to benefit from follow-up services, which in turn increases costs. The results of studies in the United States (2004) showed that the rate of readmission was 19.6% within 30 days of discharge costing $ 17.4 billion (12, 13). That is why, since 2012, the US government has begun to penalize hospitals with clinical re-admission statistics. Treatment and prevention of HF is a growing public health problem and is now becoming an epidemic, with the prevalence of HF patients estimated at more than 23 million cases worldwide. As the incidence and prevalence of this disease are increasing, it requires greater attention (14).

The leading pathophysiological mechanism of HF decompensation and the cause of hospitalization is systemic congestion, which is associated with an adverse prognosis (15). Systemic congestion leads to dysfunction of target organs, and this is of great clinical and prognostic significance. The incidence of congestion in patients at discharge is rather high. Residual congestion is one of the causes leading to the readmission of patients with acute decompensated HF, reaching 18% within the first 30 days after discharge (16). Most accurately, congestion severity can be assessed using cardiac catheterization to measure right atrium pressure and pulmonary capillary wedge pressure; however, the use of this method is limited due to its invasiveness.

According to relevant literature, prognostically valuable methods to evaluate congestion include the measurement of brain natriuretic peptide levels (NT-proBNP), B-line score on lung ultrasound (LUS), and liver stiffness by transient elastography, and the assessment of hydration using bioelectrical impedance vector analysis (BIVA).

A high incidence of residual congestion was shown in a number of studies that had used individual instrumental methods; such as LUS, liver transient elastography, and hydration status measurement using BIVA (17). However, very few studies have investigated integral assessment of residual or subclinical congestion using instrumental laboratory methods and their prognostic value (18).

Therefore, this study aimed to evaluate the prognostic value of the relative change from admission to discharge (Δ %) in the integral assessment of congestion for predicting adverse outcomes in patients with decompensated HF during a one-year follow-up.

## 2. Materials and Methods

The study included 122 chronic HF patients hospitalized for decompensated HF. The mean age of the participants was obtained at 69 years (ranging from 61.7 to 78.3 years). Heart failure decompensation was diagnosed based on standard criteria, including the onset and rapid aggravation of HF signs and symptoms requiring emergency hospitalization and intensive care of the patient, combined with objective signs of heart involvement, including systolic and/or diastolic dysfunction, left ventricular hypertrophy, left atrial enlargement based on echocardiographic data, and increased NT-proBNP levels (19).

The study excluded patients with acute coronary syndrome, lung diseases (e.g., bronchial asthma and exacerbation of chronic obstructive pulmonary disease), end-stage renal failure, malignancies, edematous syndrome of another etiology, primary liver disease, acute hepatitis with transaminase levels more than five times.

The clinical and demographic characteristics of the patients are presented in table 1. Males prevailed accounting for 60% of the patients. Most patients (92%) had a history of arterial hypertension. It was found that 60% of the patients had coronary heart disease, while 37% had a history of myocardial infarction. Moreover, 14% of the subjects showed a history of acute cerebrovascular accidents, and 61.5% had atrial fibrillation. Regarding concomitant diseases, 40.2% of the patients had type 2 diabetes mellitus. It was also revealed that 45% of the patients had a reduced ejection fraction (EF) of less than 40%, 37% of the patients had preserved EF, and 18% had mildly reduced EF.

**Table 1.** Clinical and demographic data of patients

| Parameter | n=122 |
|---|---|
| Gender: M/F, n (%) | 73/49 (60/40%) |
| Age (Me (IQR) | 69 (61.7;78.3) |
| Current smokers, n (%) | 41 (33.6%) |
| LVEF, n (%) | 42 (30;53) |
| -<40% | 55 (45%) |
| -40-49% | 22 (18%) |
| ->50% | 45 (37%) |
| Arterial hypertension, n (%) | 112 (92%) |
| Coronary heart disease, n (%) | 65 (53.3%) |
| History of miocardial infarction, n (%) | 45 (37%) |
| History of ACVA, n (%) | 17 (14%) |
| Atrial fibrillation, n (%) | 75 (61.5%) |
| Type 2 diabetes mellitus, n (%) | 49 (40.2%) |

Me: Median; IQR: Interquartile range; ACVA: Acute cerebrovascular accident; LVEF: Left ventricular ejection fraction

At admission and discharge, all patients underwent standard physical examinations and laboratory investigations, including NT-proBNP levels, B-lines on LUS, liver stiffness based on transient elastography, and BIVA.

Serum levels of NT-proBNP were determined by enzyme immunoassay enzyme-linked immunosorbent assay (ELISA) using the NT-proBNP-ELISA-BEST test system, reagent kit A-9102 (CJSC Vector-Best, Russia).

Lung ultrasonography was performed (Sonosite, convex probe) in 8 zones (II and IV intercostal spaces between the parasternal and midclavicular lines and between the anterior and midaxillary lines). B-lines were counted; they are defined as vertical hyperechoic reverberation artifacts that arise from the pleural line extending to the bottom of the screen without fading and move synchronously with lung sliding.

Liver transient elastography was performed on a FibroScan® 502 touch device (ECHOSENS, France) according to a standard procedure, in the projection of the right lobe of the liver at the level of the $8^{th}$ or $9^{th}$ intercostal space along the anterior or median axillary line. The evaluation was considered valid if it included at least 10 valid measurements, with a success rate of > 60% and an interquartile range under 25%. Liver stiffness (elasticity) was measured in kilopascals (kPa). The stiffness quantitatively reflected the severity of fibrosis in the region of liver parenchyma where the transducer was located.

All patients underwent BIVA on a bioimpedance analyzer (ABC-01 'Medass', Russia). This method is based on measuring the electrical conductivity of various tissues of the whole body or individual body segments using special devices and bioimpedance analyzers. The electrical impedance of biological tissues has two components, namely resistance (R) and reactance (X). The material substrate of resistance R in a biological object is cellular and extracellular fluids, which possess the ionic conduction mechanism. The substrate of reactance X is the cell membranes (dielectric partitions between the conductive regions). The measurements of BIVA were performed with a standard tetrapolar electrode placement on the wrist and ankle joints, at a single 50-kHz frequency. The measured resistance and reactance values were normalized for standing height. Tissues containing more water (liquid) had higher electrical conductivity and lower resistance (impedance). Hence, lower impedance indicated higher hydration.

Long-term clinical outcomes were assessed by a structured telephone interview 1, 3, 6, and 12 months after discharge. The combined overall mortality plus readmission rate was used as the endpoint. For each study variable, the difference between its values at discharge and admission was calculated as follows: $\Delta$ = value at discharge – value at admission, which was also presented as a percentage, $\Delta$%.

Statistical data processing was performed using Statistica software (version 8.0; Statsoft), MedCalc software (version 11.5.0.0), and SPSS software (version 22.0). Quantitative variables were expressed as arithmetic mean and standard deviation (for normally distributed data) or as median and interquartile range (IQR) (for skewed data). For quantitative variables, the significance of differences between groups was assessed using the Mann-Whitney U test. Categorical variables were summarized as counts and percentages. The Pearson chi-squared test was used for the inter-group comparisons. The significance of within-group differences at different time points was assessed using the Wilcoxon W-test. Multiple comparisons were performed using one-way ANOVA or the Kruskal-Wallis test for skewed distribution. Survival probability was estimated by constructing Kaplan-Meier survival curves, with a comparison based on the log-rank test. The prognostic value of different methods estimating the risk of the occurrence of events of interest was assessed using univariate and multivariate Cox regression analysis models. The choice of variables included in the models was based on their clinical relevance. The cut-off values for the prediction of survival were determined by receiver operating characteristic (ROC) curve analysis. A p-value of less than 0.05 was considered statistically significant.

## 3. Results

The follow-up period lasted 400 days. Fifty-five endpoint events, including 22 (18%) deaths and 33 (27%) readmissions, occurred within a median of 74 days (IQR: 33-147). As shown by the analysis of deltas of all parameters included in the integral assessment of congestion, patients with events had significantly worse values of all study parameters, as opposed to patients without events (Table 2).

A direct association was identified between NT-proBNP Δ% and B-line Δ% (r=0.18; *P*=0.04), and a highly significant inverse association between liver stiffness Δ% and BIVA reactance Δ% (r=-0.4; *P*<0.001). No significant correlation was found for the other variables.

As a result of ROC curve analysis for predicting outcomes (death or readmission), the following cut-offs were obtained for different methods used to assess congestion (Table 3).

Univariate Cox analysis demonstrated an independent prognostic value of each congestion marker NT-proBNP, B-line score, and liver stiffness by transient elastography, and BIVA resistance and reactance for the prediction of the risk of combined endpoint. Multivariate Cox analysis confirmed the independent prognostic values for the prediction of the risk of combined endpoint for the following markers: NT-proBNP (hazard ratio [HR] 2.5 (1.4-4.4), *P*=0.001), liver stiffness (HR 2.3 (1.2-4.6) *P*=0.012), LUS (HR 2.2 (1.2-4.1), *P*=0.008); however, it did not confirm any significant prognostic value of BIVA resistance or reactance (Table 4).

**Table 2.** Integral congestion assessment based on Δ% for the prediction of adverse outcomes in patients with acute decompensated heart failure during a 12-month follow-up

| | All patients, n=122 | Without event n=67 (55%) | With event n=55 (45%) | *P*-value |
|---|---|---|---|---|
| NT-proBNP, Δ% | -37 (-52; -8) | -43 (-56; -24) | -14 (-48; 10) | <0.001 |
| Liver stiffness, Δ% | -30 (-55.2; -9.7) | -39 (-68; 16) | -20 (-38; 0) | 0.002 |
| B-lines, Δ% | -69 (-88; -43) | -81 (-89; -52) | -54 (-79; -24) | 0.001 |
| Resistance, Δ% | 12 (4; 24) | 19 (7; 33) | 7 (1; 18) | 0.001 |
| Reactance, Δ% | 24.5 (6.7; 44.5) | 32 (12; 56) | 17 (3; 35) | 0.002 |

**Table 3.** Cut-off values for outcome prediction by parameters

| | Cut-off, Δ% | Sensitivity | Specificity | AUC | *P*-value |
|---|---|---|---|---|---|
| NT-proBNP | ≥-25 | 61.8 | 74.6 | 0.69 | <0.001 |
| Liver stiffness | ≥-44 | 80 | 49.3 | 0.66 | 0.001 |
| Lung US (B-lines) | ≥-73 | 70.9 | 62.7 | 0.67 | <0.001 |
| BIVA (resistance) | ≤18 | 76.4 | 52.2 | 0.66 | <0.001 |
| BIVA (reactance) | ≤40 | 87.3 | 41.8 | 0.66 | <0.001 |

AUC: Area under the curve; US: Ultrasound; BIVA: Bioelectrical impedance vector analysis

**Table 4.** Univariate and multivariate Cox regression analysis for different congestion markers of the risk of combined endpoint (all-cause mortality + readmission)

| Congestion marker | Univariate regression analysis | | Multivariate regression analysis | |
|---|---|---|---|---|
| | RR (95% CI) | *P*-value | RR (95% CI) | *P*-value |
| NT-proBNP | 3.1 (1.8-5.4) | *P*<0.001 | 2.5 (1.4-4.4) | 0.001 |
| Liver stiffness | 2.8 (1.4-5.4) | *P*=0.002 | 2.3 (1.2-4.6) | 0.012 |
| B-line score | 2.9 (1.6-5.3) | *P*<0.001 | 2.2 (1.2-4.1) | 0.008 |
| BIVA resistance | 2.7 (1.4-5.1) | *P*=0.001 | 1.8 (0.8-3.9) | 0.136 |
| BIVA reactance | 3.7 (1.7-8.3) | *P*=0.001 | 2.1 (0.8-5.8) | 0.117 |

RR: Relative risk; CI: Confidence interval; BIVA: Bioelectrical impedance vector analysis

Analysis of Kaplan-Meier survival curves revealed significant differences between the patient groups with Δ% NT-proBNP of ≥ -25 (Figure 1), Δ% liver stiffness of ≥ -44 (Figure 2), Δ% LUS B-linescore of ≥ -73 (Figure 3), Δ% BIVA resistance of ≤ 18 (Figure 4), and Δ% BIVA reactance of ≤ 40 (Figure 5).

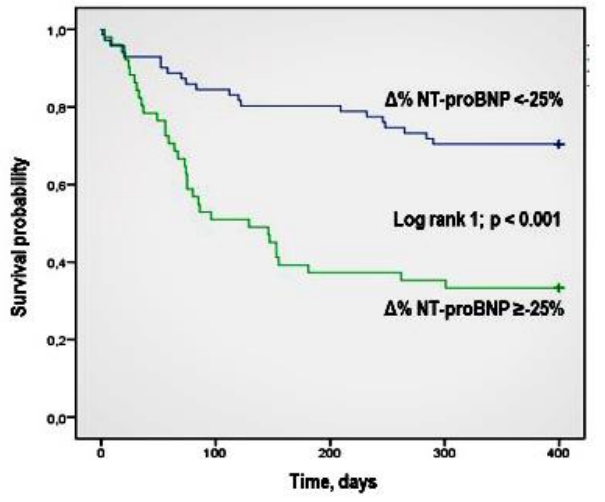


**Figure 1.** Kaplan-Meier cumulative survival curves (all-cause mortality + readmission) according to congestion presence and severity based on NT-proBNP, Δ%

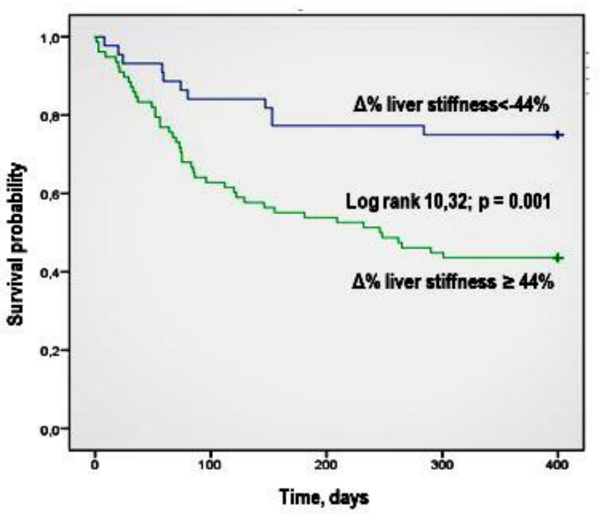


**Figure 2.** Kaplan-Meier cumulative survival curves (all-cause mortality + readmission) according to congestion presence and severity based on liver stiffness, Δ%

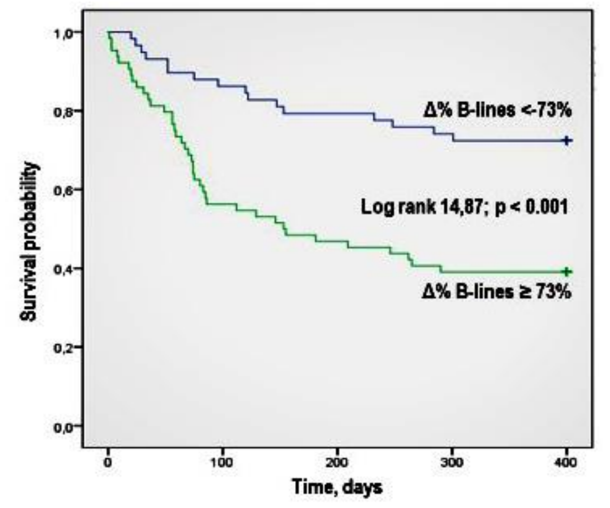


**Figure 3.** Kaplan-Meier cumulative survival curves (all-cause mortality + readmission) according to congestion presence and severity based on B-line score, Δ%

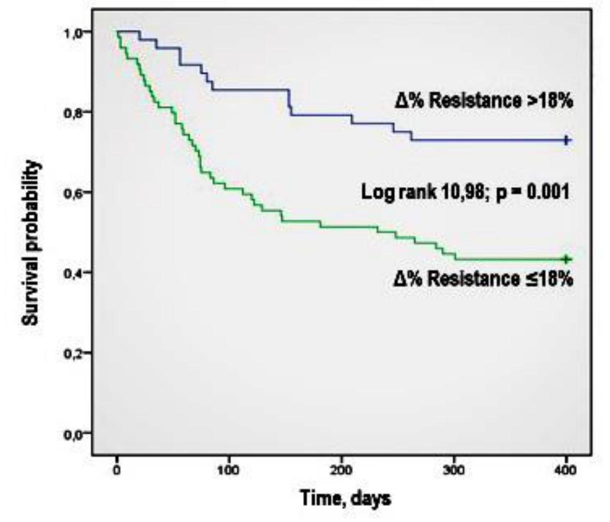


**Figure 4.** Kaplan-Meier cumulative survival curves (all-cause mortality + readmission) according to congestion presence and severity based on BIVA resistance, Δ%

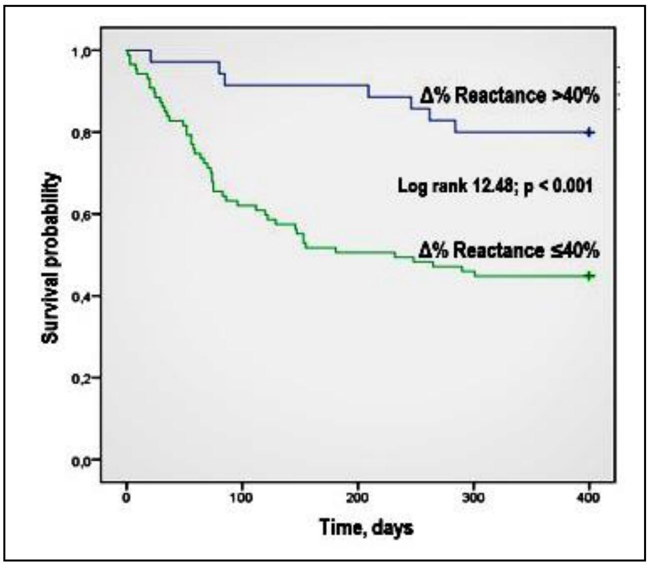


**Figure 5.** Kaplan-Meier cumulative survival curves (all-cause mortality + readmission) according to congestion presence and severity based on BIVA reactance, Δ%

## 4. Discussion

Systemic congestion in HF is the focus of numerous studies; however, there are no common criteria for its diagnosis, on the one hand, and methods that can confirm its complete elimination or the achievement of the so-called euvolemia (20), on the other hand. This situation enhances the relevance of studies that compare the clinical and prognostic value of different diagnostic approaches to congestion assessment.

The results of this study have demonstrated the prognostic value of an integral congestion assessment, which included several laboratory instrumental methods measuring different signs of congestion for predicting the combined endpoint (i.e. all-cause mortality plus readmission rate). Patients with more marked congestive phenomena at discharge were shown to be at a higher risk of developing adverse events, such as death or readmission for chronic HF.

The literature widely discusses the prognostic value of some ultrasonic methods for congestion assessment, one of which assesses pulmonary congestion based on a B-line score. The findings of a randomized study on 518 patients with acute onset dyspnea showed that the inclusion of LUS into routine screening for diagnosing acute decompensated HF was more valuable than the traditional approach, including physical examination, chest X-ray, and NT-proBNP test (21). The accuracy of HF diagnosis based on LUS was significantly higher than that based on physical examination alone (area under the curve [AUC]: 0.95 vs 0.88, $P$<0.01) or in combination with chest X-ray and NT-proBNP test (AUC: 0.95 vs 0.87, $P$<0.01). Moreover, chest X-ray and NT-proBNP test added no advantage compared to clinical assessment only (AUC: 0.87 vs 0.85 respectively, $P$>0.05). According to the results of published studies, the B-line score can be used to identify risk groups for long-term adverse outcomes among both outpatients and hospitalized patients with HF. In an outpatient study, a B-line score of ≥ 3 with LUS according to 5- or 8-zone protocol was associated with a four-fold risk of death or readmission for HF within 6 months (22). In patients with acute HF, at discharge B-line score of >15 on scanning of 28 zones was associated with a more than five-fold increase in the risk of death or readmission with HF (22, 23). There are also other findings showing that the persistence of B-lines at discharge in patients hospitalized with acute decompensated heart failure (ADHF) was associated with a risk of readmission for ADHF within 3 and 6 months (24, 25). This suggests that LUS can be used for detecting residual hemodynamic congestion where there are no significant clinical signs of fluid accumulation.

The adverse effect of residual liver congestion on the prognosis for HF patients was demonstrated in several studies (24, 25). The results of a study conducted on 171 subjects hospitalized for HF indicated that increased liver stiffness at discharge was a predictor of adverse prognosis; accordingly, patients with liver stiffness of > 6.9 kPa had higher rates of death and readmission for HF (RR=3.57; 95% confidence interval [CI]: 1.93-6.83; $P$<0.001) (26). The researchers, therefore, concluded that liver stiffness at discharge might probably reflect the presence of residual subclinical liver congestion and could 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 liver function tests (26).

The findings of a number of studies have shown the importance of hydration assessment by bioelectrical impedance analysis when making the prognosis for patients with HF, especially concerning total mortality within 90 days and 1 year of follow-up (24, 27). Reactance was shown to be a more valuable predictor of mortality within a 90-day follow-up (AUC 0.712, 95% CI: 0.655-0.76; $P<0.007$) than resistance (AUC 0.65, 95% CI: 0.29-0.706; $P<0.025$). When used in combination, the BIVA and NT-proBNP parameters demonstrated a higher prognostic value (AUC 0.74, 95% CI: 0.69-0.76; $P<0.001$) (28).

In this study, in ADHF patients, the discharge values of Δ% NT-proBNP of < -25% (RR: 3.5 (1.9-6.5); $P<0.001$), Δ% B-line score of > -73% (RR: 2.05 (1.1-3.7); $P=0.018$), Δ% liver stiffness of > 44% (RR: 2.6 (1.3-5.3); $P=0.006$), Δ% resistance of > 18% (RR: 10.1 (1.4-73.6); $P=0.022$), and Δ% reactance of > 40% (RR: 3.06 (1.2-7.2); $P=0.011$) were independently associated with a higher risk of endpoint event (death of any cause or readmission). The obtained results suggested that the integral assessment of congestion based on admission-to-discharge deltas had an independent prognostic value for predicting the risk of adverse outcomes in ADHF patients.

In conclusion, clinical assessment combined with an admission-to-discharge change in natriuretic peptide concentration may be insufficient as surrogate markers of residual congestion in chronic HF patients. The addition of a combination of objective congestion measures to clinical assessment can help identify various degrees of congestion, and therefore, provide more appropriate therapy and follow-up for such patients. Over-time changes in LUS B-line score, liver stiffness, and BIVA resistance and reactance all have a demonstrated prognostic value.

## Authors' Contribution

Concept and design of the study: Z. K.
Analysis of the received data and writing the text: V. V. T.
Analysis of the received data and writing the text: F. C. M.
Collection and processing of materials: B. S., S. G., A. A. L. and M. L. D.

## Ethics

The study design was approved by the ethics committee of the People's Friendship University of Russia, Moscow, Russia.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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