



## Integral assessment of congestion in patients with acute decompensated heart failure

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**Aim.** To assess the prognostic value of the integral assessment using various modern methods for diagnosing congestion in patients hospitalized with acute decompensated heart failure (ADHF).

**Material and methods.** This single-center prospective study included 165 patients with ADHF. All patients underwent a standard clinical and paraclinical examination, including assessing NT-proBNP levels, lung ultrasound B-lines, liver transient elastography, bioelectrical impedance vector analysis (BIVA) at admission and discharge. To assess clinical congestion, the Heart Failure Association consensus document scale was used. Long-term clinical outcomes were assessed by telephone survey 1, 3, 6, 12 months after discharge. As an end point, the all-cause mortality and readmissions were estimated.

**Results.** In patients hospitalized with ADHF, at discharge, differences were found in the incidence of residual congestion according to certain paraclinical methods — from 22 to 38%, subclinical — from 14,5 to 27%. When using the integral assessment of stagnation, the incidence of residual and subclinical congestion was 53,6% and 35%, respectively. Patients with residual congestion had more severe symptoms of congestion, compared with those with subclinical congestion. Patients in whom congestion was detected by 4 methods, in contrast to those by 1, 2, and 3 methods, had worse clinical and paraclinical parameters. There was a significant increase in the risk of all-cause mortality and readmission in the presence of congestion, identified by 3 (hazard ratio, 9,4 (2,2-40,6);  $p < 0,001$ ) and 4 methods (hazard ratio, 15,2 (3,3-68,1);  $p < 0,001$ ).

**Conclusion.** For patients hospitalized with ADHF, integral assessment of residual and subclinical congestion at should

be performed at discharge. The introduction of an integral assessment of congestion into routine practice will allow to identify a group of patients with more unfavorable prognostic characteristics in relation to the risk of death and readmissions, as well as to intensify drug therapy and follow-up at the outpatient stage.

**Keywords:** acute decompensated heart failure, subclinical congestion, integral assessment of congestion, N-terminal pro-brain natriuretic peptide.

**Relationships and Activities:** none.

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The problem of heart failure (HF) remains quite acute. An important role is played by improving the quality of healthcare, as well as an increase in the population of elderly and senile patients. There is an obvious high need for the introduction of novel approaches, one of which is the creation of expert-level clinics to help patients with HF, clinical and diagnostic centers and primary healthcare institutions to improve the care provision to patients with heart failure (HF), the introduction of modern diagnostic methods into practice and treatment, organization of preventive measures and registries of patients.

Alternation of periods of compensation and decompensation is typical for HF [1]. It is believed that one of the markers of HF therapy success during hospitalization is the absence of congestion by the time of hospital discharge [2]. However, data from observational studies demonstrate that a significant proportion of patients retain congestion at the time of discharge, which leads to an increased risk of rehospitalization for HF and all-cause death [3-6].

The accuracy of conventional clinical symptoms and signs of congestion is relatively low compared to intracardiac hemodynamic assessment [7]. Evaluation of the N-terminal pro-brain natriuretic peptide (NT-proBNP) is the main method for diagnosing HF, which has the highest class of evidence according to modern guidelines, and one of the main markers reflecting the severity of congestion and prognosis [8]. To assess the degree of residual congestion, as well as risk stratification in patients with HF, an assessment of the sum of B-lines on lung ultrasound, liver elastography, and hydration by bioelectrical impedance analysis (BIA) can be used.

The absence of universal criteria for detecting congestion and methods confirming its complete elimination or the achievement of so-called "euvolemia" [7] emphasize the relevance of studies to compare the clinical and prognostic value of various diagnostic approaches in its assessment.

The aim of the study was to assess the prognostic value of the integral assessment using various modern methods for diagnosing congestion in patients hospitalized with acute decompensated heart failure (ADHF).

### Material and methods

The study included 165 patients hospitalized with ADHF in the HF Center on the basis of the multidisciplinary V.V. Vinogradov City Clinical Hospital (Moscow).

ADHF was diagnosed on the basis of generally accepted criteria [9].

The study did not include patients with acute coronary syndrome, severe somatic diseases and cancer, edema of a different etiology, acute hepatitis with

elevated transaminases  $>5$  upper normal limits, immobilization, and if BIA was impossible to perform. All patients signed an informed consent prior to the study procedures. The study was performed in accordance with Good Clinical Practice and Declaration of Helsinki standards. The study protocol was approved by the local ethics committee.

All patients underwent a standard physical examination, paraclinical investigations, including NT-proBNP, lung ultrasound, liver elastography, and BIA at admission and at discharge.

To assess clinical congestion, the HFA congestion clinical assessment score was used [10].

Serum NT-proBNP was determined by ELISA using the NT-proBNP-ELISA-BEST test systems (Russia, ZAO Vector-Best).

Lung ultrasound (VIVID iq, GE) with the calculation of B-lines sum was performed in 8 areas (II and IV between the parasternal and midclavicular lines and between the anterior and midaxillary lines on both sides).

Liver elastography was performed using the FibroScan® 502 touch system (Echosens, France) in the projection of the right liver lobe at the level of the 8<sup>th</sup> or 9<sup>th</sup> intercostal space along the anterior or midaxillary line. Liver density (elasticity) was determined in kilopascals (kPa) and the interquartile range as a percentage (%).

To assess the hydration status, BIA (ABC-01 "Medass") was performed. The values of active (Xc/h) and reactive (R/h) resistance were given by growth. Lower values of active and reactive resistance corresponded to a greater degree of hydration.

Long-term clinical outcomes were assessed using a telephone survey 1, 3, 6, and 12 months after discharge. The endpoint was the sum of total mortality and readmissions.

Residual congestion at discharge was evidenced by clinical and paraclinical data confirming the congestion, while subclinical congestion — by the absence of clinical but presence of paraclinical evidence of congestion. The absence of clinical and paraclinical data confirming the congestion was regarded as euvolemia. In case of clinical signs without paraclinical evidence of congestion, an alternative diagnosis was considered.

For statistical data processing, MedCalc Software's VAT Version 19.0 and SPSS (version 22.0) were used. Quantitative variables were described as the arithmetic mean (M) and standard deviation of the mean (SD) (for normal distribution) or as median (Me) and interquartile range (IQR) (for nonnormal distribution). The definition of survival threshold values for each of the methods was carried out with ROC curves.  $P < 0,05$  was considered significant. Uni- and multivariate Cox regression

**Table 1**  
**Clinical and demographic characteristics of patients with ADHF (n=165)**

Parameters	Value
Gender (M/F), n (%)	101 (61)/64 (39)
Age, years (M±SD)	70,0±16,8
BMI, kg/m <sup>2</sup> , (M±SD)	32,0±7,0
SBP, mm Hg (M+SD)	138,1±26,0
DBP, mm Hg (M+SD)	77,1±15,2
LVEF, % (M±SD)	41,2±13,0
LVEF, n (%)	
<40%	75 (45,5)
40-49%	31 (18,8)
≥50%	59 (35,8)
NT-proBNP, pg/ml (Me (IQR))	2393 (1215; 4609)
Hypertension, n (%)	152 (92)
Coronary artery disease, n (%)	90 (54)
Prior stroke, n (%)	20 (12)
Atrial fibrillation, n (%)	103 (62)
Type 2 diabetes, n (%)	67 (40)

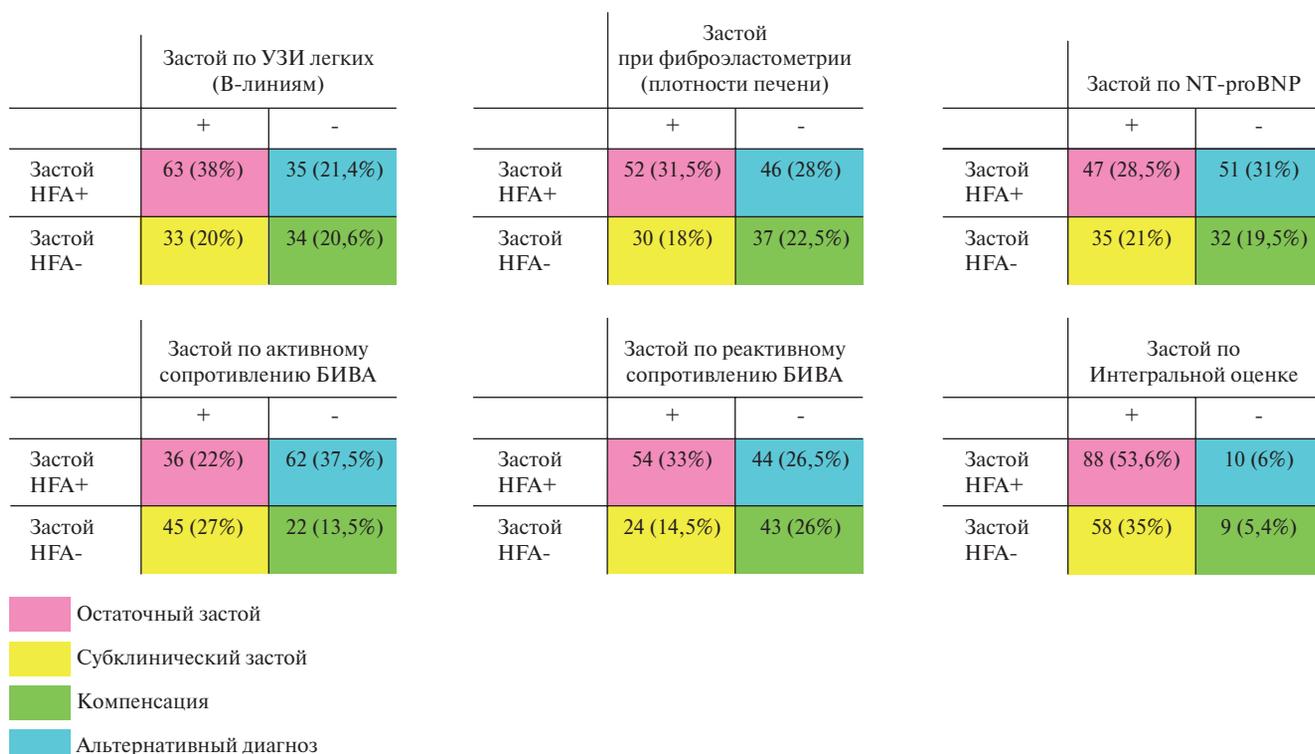
**Note:** data are presented as median, 25<sup>th</sup> and 75<sup>th</sup> percentile (Me (IQR)) or arithmetic mean (M) and standard deviation of the mean (SD).

**Abbreviations:** DBP — diastolic blood pressure, BMI — body mass index, SBP — systolic blood pressure, LVEF — left ventricular ejection fraction, NT-proBNP — N-terminal probrain natriuretic peptide.

analysis models were used to assess the predictive value of different methods on the risk of occurrence of variables. The choice of variables included in the models was carried out taking into account their significance. The probability of survival was assessed with Kaplan-Meier survival curves, while comparison was made using the log-rank test.

## Results

Clinical and demographic characteristics of patients hospitalized with ADHF are presented in Table 1. On the background of standard therapy, the prevalence of residual congestion according to certain methods (lung ultrasound, liver elastography, BIA, NT-proBNP assessment) ranges from 22 to 38%, while subclinical — from 14,5 to 27%. The number of patients who achieved compensation ranged from 13,5 to 26%. When using the integral assessment, the prevalence of residual congestion was 53%, subclinical — 35%, compensation group — 5,4% (Figure 1). The characteristics of patients with an alternative diagnosis are presented in Table 2. This group ranged from 21,4% to 37,5% according to individual methods and significantly decreased to 6% when using an integral assessment. It was found that the alternative diagnosis group included patients who had signs of congestion in another circulation system. For example, in patients from



**Figure 1.** Gradation of patients according to the presence/absence of congestion at discharge using individual methods and an integral assessment.

**Table 2**

**Characteristics of patients with an alternative diagnosis depending on the research method**

	Lung ultrasound, n=35 (21,4%)	Liver elastography, n=46 (28%)	R/h, n=44 (26,5%)	Xc/h, n=62 (37,5%)	NT-proBNP, n=51 (31%)
Clinical examination data					
Orthopnea	5 (14,3%)	28 (60,9%)	22 (50%)	18 (47,4%)	27 (52,9%)
Bulging neck veins	12 (33,3%)	6 (13,1%)	13 (29,6%)	11 (28%)	14 (27,5%)
Hepatomegaly	15 (42,5%)	4 (8,7%)	19 (43,2%)	18 (47,4%)	19 (37,2%)
Edema	20 (57,1%)	26 (56,5%)	7 (15,9%)	12 (31,6%)	23 (45,7%)

**Note:** data are presented as median, 25<sup>th</sup> and 75<sup>th</sup> percentile (Me (IQR)).

**Abbreviations:** Xc/h — active resistance, NT-proBNP — N-terminal pro-brain natriuretic peptide, R/h — reactive resistance.

**Table 3**

**Comparative characteristics of patients with subclinical and residual congestion at discharge**

Congestion assessment methods	Subclinical congestion, n=58	Residual congestion, n=88	p
NT-proBNP, pg/ml	2163 (1146; 3438)	2409 (1164; 5063)	0,310
Liver density, kPa	7,8 (5,1; 12)	10 (6; 16,7)	0,049
Sum of B-lines	6 (3; 17)	20 (5; 30)	<0,001
Xc/h, Ohm/m	502 (448; 549,7)	436 (373; 501)	<0,001
R/h, Ohm/m	44 (40; 54)	38 (33; 47)	<0,001

**Abbreviations:** Xc/h — active resistance, NT-proBNP — N-terminal pro-brain natriuretic peptide, R/h — reactive resistance.

**Table 4**

**Congestion detection rate in patients with ADHF at discharge depending on the number of methods used for assessment**

	No congestion, n=19	1 method, n=44	2 methods, n=38	3 methods, n=38	4 methods, n=26	p
Clinical assessment of congestion (HFA scale)	1 (0; 2)	0 (0; 2)	2 (0; 3)	2 (0; 3)	3 (0; 5)	0,003
NT-proBNP, pg/ml	610 (220; 1028)	1375 (428; 2212)	1595 (900; 3270)	3024 (1579; 5465)	3652 (2660; 6080)	<0,001
Liver density, kPa	4,7 (3,7; 6)	5,6 (4,6; 7)	8 (5; 12)	13 (7,6; 19)	16 (10; 30)	<0,001
Sum of B-lines	3 (2; 4)	4 (3; 6)	17 (4; 30)	19 (8; 29)	20 (17; 29)	<0,001
Xc/h, Ohm/m	526 (486; 556)	499 (454; 539)	481 (413; 537)	472 (376; 510)	406 (364; 458)	<0,001
R/h, Ohm/m	51 (49; 60)	48 (42; 56)	44 (37; 52)	38 (33; 44)	34 (28; 37)	<0,001

**Note:** data are presented as median, 25<sup>th</sup> and 75<sup>th</sup> percentile (Me (IQR)).

**Abbreviations:** Xc/h — active resistance, NT-proBNP — N-terminal pro-brain natriuretic peptide, R/h — reactive resistance.

the category of an alternative diagnosis according to pulmonary ultrasound (n=35), the presence of edema (n=20), hepatomegaly (n=15) and bulging jugular veins (n= 12) took the first place in clinical manifestations; i.e. congestion manifestations in the systemic circulation.

When comparing patients with subclinical and residual congestion, the latter were characterized by

more pronounced (worse) congestion phenomena, identified using all paraclinical methods (Table 3).

Patients in whom congestion was detected by 4 methods (lung ultrasound, liver elastography, BIA, NT-proBNP assessment), in contrast to patients in whom congestion was detected by methods 1, 2 and 3, had worse clinical and paraclinical characteristics (Table 4).

Table 5

## Thresholds for predicting outcomes by method

	Thresholds	Sensitivity	Specificity	AUC	p
NT-proBNP, pg/ml	>2336	64,4	70,8	0,702	<0,001
Liver density, kPa	>9,7	64,4	73,6	0,704	<0,001
Sum of B-lines	>5	74,5	0,94	0,59	0,041
Xc/h, Ohm/m	≤470,7	55,9	62,3	0,605	0,025
R/h, Ohm/m	≤36,6	44,1	83	0,64	0,002

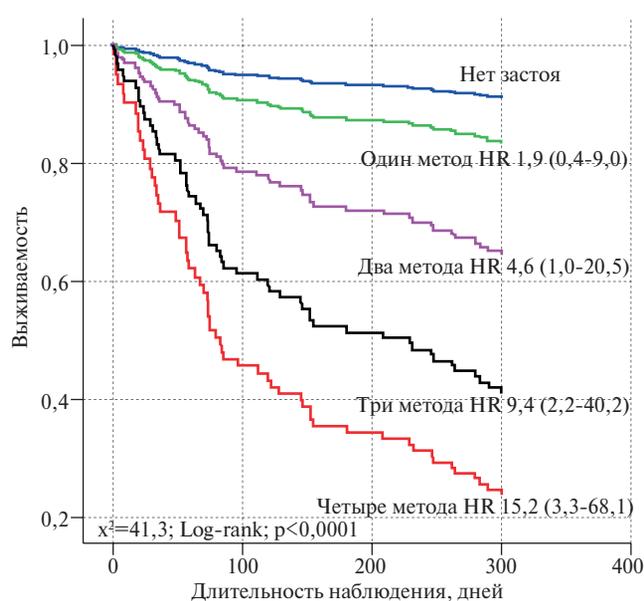
**Abbreviations:** Xc/h — active resistance, NT-proBNP — N-terminal pro-brain natriuretic peptide, R/h — reactive resistance.

Table 6

## Univariate and multivariate Cox regression analysis for congestion markers assessed by different methods for composite endpoint risk (mortality + readmission)

Congestion markers	Univariate regression analysis		Multivariate regression analysis	
	HR (95% CI)	p	HR (95% CI)	p
NT-proBNP, pg/ml	3,05 (1,7-5,2)	<0,001	2,1 (1,2-3,8)	0,006
Liver density, kPa	2,4 (1,3-4,3)	0,003	1,8 (1,0-3,3)	0,044
Sum of B-lines	3,5 (2,0-6,9)	<0,001	2,2 (1,2-4,1)	0,005
Xc/h, Ohm/m	2,7 (1,6-4,5)	<0,001	1,6 (0,8-3,1)	0,117
R/h, Ohm/m	1,8 (1,0-3,0)	0,024	1,1 (0,5-2,1)	0,732

**Abbreviations:** CI — confidence interval, HR — hazard ratio, Xc/h — active resistance, NT-proBNP — N-terminal pro-brain natriuretic peptide, R/h — reactive resistance.



**Figure 2.** Kaplan-Meier curves for the cumulative probability of survival (all-cause mortality + readmission) depending on the number of methods used to assess congestion.

When constructing ROC curves for predicting outcomes (total mortality + readmission), threshold values of various methods for assessing stagnation were identified (Table 5). Data from univariate and multivariate Cox regression analysis for the risk of

combined endpoint (mortality + readmission) are presented in Table 6. When constructing Kaplan-Meier curves for cumulative survival, four congestion indicators were used — liver elastography, lung ultrasound, NT-proBNP and R/h (Figure 2).

Thus, a significant increase in the risk of total mortality and rehospitalization was revealed in the presence of congestion, identified by three and four methods. The best prognostic value was found in the combination of lung ultrasound, liver elastography and NT-proBNP (hazard ratio (HR), 6,3 (1,9-21,0),  $p=0,003$ ) (Table 7, Figure 3).

## Discussion

Our work shows that integrated assessment in patients hospitalized with ADHF increases the detection of residual congestion up to 53,6%, and subclinical congestion up to 35%, while when using single methods, the detection rate does not exceed 40%, subclinical — 30%. At the same time, the group of patients with the so-called alternative diagnosis turned out to be the most interesting. This group included patients who had signs of congestion in a different circulation system, different from what a specific technique reveals.

According to numerous studies, lung ultrasound can be used to quantify extravascular fluid in the lungs in patients with heart failure at rest or during physical activity [11-15]. Evaluation of the sum of

Table 7

**Estimation of HR in reaching the composite endpoint (mortality + readmission) depending on the combination of different methods**

Methods	OR	p
Lung ultrasound + liver elastography	5,4 (1,5-19,2)	0,009
Ultrasound of lungs + R/h	2,6 (0,4-14,6)	0,253
Lung ultrasound + NT-proBNP	3,7 (1,0-13,4)	0,039
Lung ultrasound + liver elastography + NT-proBNP	6,3 (1,9-21,0)	0,003
Lung ultrasound + liver elastography + R/h	6,1 (1,3-27,3)	0,018
Lung ultrasound + NT-proBNP + R/h	5,8 (1,0-31,7)	0,042
Lung ultrasound + liver elastography + NT-proBNP + R/h	16,6 (5,3-51,3)	<0,001

**Abbreviations:** HR — hazard ratio, Xc/h — active resistance, NT-proBNP — N-terminal pro-brain natriuretic peptide, R/h — reactive resistance.

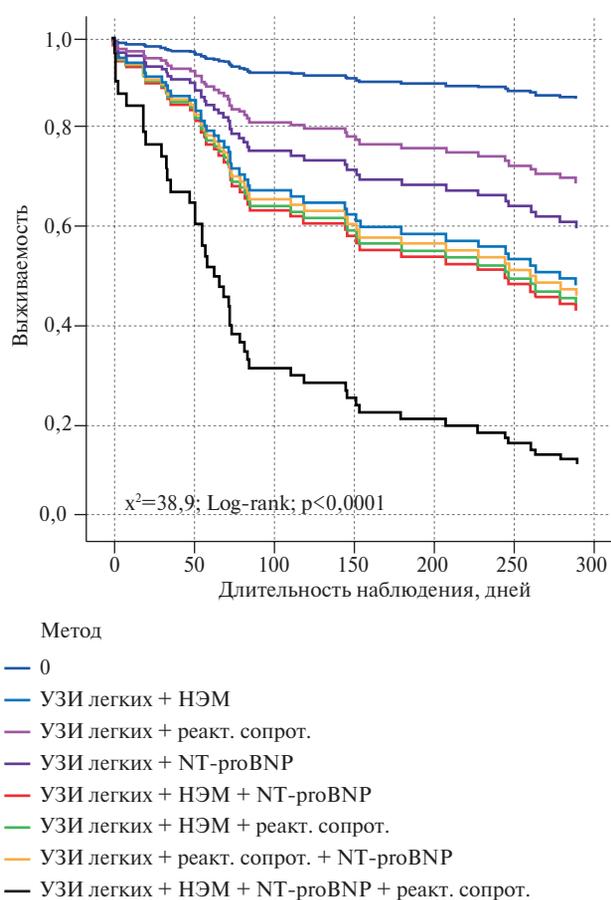
B-lines makes it possible to identify a risk group for adverse long-term outcomes in both the population of outpatients and hospitalized patients with HF [4, 16-18].

The adverse effect of residual liver congestion on the prognosis of HF patients has been shown in a number of studies [6, 19]. In patients with ADHF, liver density above  $\geq 11,1$  kPa at admission and  $\geq 8,2$  kPa at discharge was associated with clinical and echocardiographic signs of right heart dysfunction and with a greater likelihood of rehospitalization with HF [20]. In the study with 171 HF patients, liver density  $>6,9$  kPa at discharge had a higher rate of mortality and readmissions for HF (HR, 3,57; 95% confidence interval (CI): 1,93-6,83;  $p < 0,001$ ) [21].

A number of studies have shown a significant role of BIA assessment of hydration status in assessing the prognosis in HF patients, especially in relation to 90-day and 1-year all-cause mortality [22, 23]. It was shown that R/h is a more significant predictor of mortality after 90-day follow-up (AUC, 0,712, 95% CI: 0,655-0,76;  $p < 0,007$ ) than Xc/h (AUC, 0,65, 95% CI: 0,29-0,706;  $p < 0,025$ ). The combined use of BIA and NT-proBNP has a greater predictive value (AUC, 0,74, 95% CI: 0,69-0,76;  $p < 0,001$ ) [24].

Our study demonstrates a significant increase in the risk of all-cause mortality and readmission in patients with congestion detected by three (HR, 9,4 (2,2-40,2);  $p < 0,001$ ) and four methods (HR 15,2 (3,3-68,1);  $p < 0,001$ ).

**Study limitations.** The results obtained in our study open up new perspectives not only for the assessment of congestion in HF patients, but in the strategy for managing congestion in treatment. However, further study of the diagnostic and prognostic value of integral congestion assessment in a larger group of patients with HF is needed. In addition, the universality of findings, given the small sample of patients, is extremely limited and needs to be confirmed in other populations and countries.



**Figure 3.** Kaplan-Meier curves of the cumulative probability of survival (all-cause mortality + readmission) depending on the combination of methods used to assess congestion.

### Conclusion

The introduction of an integral assessment of congestion into routine practice will allow to identify a group of patients with more unfavorable prognostic characteristics in relation to the risk of death and readmissions, as well as to intensify drug therapy and

follow-up at the outpatient stage. Early diagnosis, identification of high-risk groups for HF allows not only to start treatment as early as possible, but also to reduce the risk of hospitalizations for

decompensated HF, which may reduce the burden on healthcare in the long term.

**Relationships and Activities:** none.

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