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Prognostic Role of Ultrasound Diagnostic Methods in Patients with Acute Decompensated Heart Failure

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ABSTRACT

Objectives: To evaluate the prognostic value (total mortality + repeated hospitalization for heart failure (HF)) of ultrasound diagnostic methods in patients with acute decompensated HF (ADHF). ***Methods***: The subjects were patients with chronic HF, who were hospitalized for ADHF. Using ultrasound methods—lung ultrasound, ultrasound assessment of hepatic venous congestion as per the venous excess ultrasound (VExUS) protocol, and indirect elastometry—we assessed the number of B-lines, hepatic venous congestion, and liver density of the patients. Clinical outcomes were assessed using a structured telephone survey method at 1, 3, 6, and 12 months after discharge. Combined overall mortality and readmission rates associated with HF were assessed. Threshold values for different methods for detecting congestion were set as follows: the number of B-lines in ultrasound data > 5; liver density > 6.2 kPa. ***Results:*** The subjects were 207 patients (54.1% male; mean age = 70.7 ± 12.8 years). A total of 63 (30.4%) endpoints and 23 (11.1%) deaths were detected within 364 days (IQR = 197–365). Liver density > 6.2 kPa had a hazard ratio (HR) of 1.9 (95% CI: 1.0–3.3; $p = 0.029$). Hepatic venous congestion (VExUS protocol) had HR of 2.8 (95% CI: 1.3–5.7; $p = 0.004$). There was a significant increase in the risk of overall prognostic value in the presence of congestion, identified by liver fibroelastometry + lung ultrasound (HR = 10.5, 95% CI: 2.3–46.2; $p = 0.002$). The ultrasound assessment of hepatic venous congestion (VExUS + lung ultrasound protocol) yielded HR of 16.7 (95% CI: 3.9–70.7; $p < 0.001$). For all three methods combined, the overall HR was 40.1 (95% CI: 6.6–243.1; $p < 0.001$). ***Conclusions:*** A combination of ultrasound diagnostic methods that include the number of B-lines, presence of hepatic venous congestion according to the VExUS protocol, and liver density according to indirect elastometry at discharge may have an independent prognostic value for patients with ADHF.

Heart failure (HF) can be considered a multi-organ pathology as its progression leads to dysfunction of internal organs due to hypoperfusion and systemic congestion. Systemic congestion is considered the main clinical feature of decompensation in HF.[1,2] Eliminating this congestion is a main goal of therapy.[3] Acute decompensated HF

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(ADHF) is the appearance or rapid aggravation of symptoms and signs of HF, which requires emergency hospitalization of the patient and intensive therapy in combination with objective signs of heart damage, and is associated with high mortality and repeated hospitalization, yet there is a lack of predictors for an unfavorable prognosis in ADHF patients.[4,5] Of recent research interest is the prognostic significance of comprehensive evaluations using modern diagnostic methods including ultrasound to identify congestion in patients hospitalized with ADHF.[6,7] Stratification of the risk of future cardiovascular events in HF patients may help identify high-risk patients who require enhanced therapy, thereby improving their long-term outcomes.[8]

Acute and chronic decompensated HF may be accompanied by hepatic dysfunction (cardio-hepatic syndrome),[9] which is characterized by progressive liver fibrosis and declining synthetic function, associated with a worsening prognosis.[10] A characteristic feature of cardio-hepatic syndrome that can be assessed by ultrasound is an increase in venous congestion, manifested by an expansion of the hepatic and portal veins and a change in the shape of blood flow. One promising and informative method is the comprehensive sequential ultrasound assessment of venous congestion comprising the venous excess ultrasound score (VExUS) protocol (which assesses the presence and severity of congestion), the study of port-hepatic Doppler waves, and measurement of the diameter of the inferior vena cava.[11]

The purpose of this study, therefore, was to evaluate the prognostic value (including survival and re-hospitalization) of ultrasound diagnostic methods including the number of B-lines using lung ultrasound, the presence of hepatic venous congestion according to the VExUS protocol, and liver density according to indirect elastometry, performed at the time of hospital discharge on patients with ADHF.

METHODS

Decompensation of HF was diagnosed based on generally accepted criteria: the appearance or rapid aggravation of symptoms and signs of HF, requiring emergency hospitalization of the patient and intensive therapy in combination with objective signs of heart damage—systolic and/or diastolic dysfunction, left ventricular hypertrophy, left atrium enlargement according to echocardiography—and an increase in N-terminal pro-B-type natriuretic peptide (NT-proBNP).[12]

The study was conducted in the Clinical Hospital named after V.V. Vinogradov, Moscow, Russian Federation from February 2021 to Feruary 2023. This study excluded patients with acute coronary syndrome, lung diseases (exacerbation of chronic obstructive pulmonary disease, bronchial asthma), end-stage chronic kidney disease, malignant neoplasm, edematous syndrome of other etiology, primary liver pathology, acute hepatitis with increased transaminases (> 5 × the upper limits of normal), excessive alcohol consumption before hospitalization, severe cognitive deficit, or immobilization. Also excluded were patients on whom bioelectric impedance vector analysis could not be performed because of missing limbs, the presence of ulcers or pronounced trophic changes on the skin of the limbs, or the presence of metal implants and structures.

All patients signed an informed consent form to participate in the study. The study was approved by the Ethics Committee of the Peoples' Friendship University of Russia (RUDN) Medical Institute, Moscow (Protocol No. 26 of 18.02.21).

All patients underwent a standard physical examination at admission and at discharge, as well as laboratory and instrumental studies, including NT-proBNP, lung ultrasound, indirect liver fibroelastometry, and Doppler ultrasound evaluation of hepatic venous congestion according to the VExUS protocol.

NT-proBNP in blood serum was determined by ELISA enzyme immunoassay using the NT-proBNP-ELISA-BEST test systems (Russia, Vector-Best CJSC). The accuracy of the test was 96.4% and was reliable.[12]

Upon discharge, ultrasound of both sides of the chest (GE Vivid E90, convex sensor) was performed in eight areas (II and IV m/r between the parasternal and midclavicular lines, and between the anterior and middle axillary lines). The number of B-lines was calculated, defined as vertical, hyperechoic reverberation artifacts from the pleural line to the bottom of the screen, moving synchronously with the movement of the lungs.

Indirect liver fibroelastometry was performed on the day of discharge using the FibroScan® 502 touch device (Echosens, France) according to a standard technique in the projection of the right lobe of the liver at the level of 8 or 9 intercostal space along the anterior or median axillary line.[13] Studies with at least 10% and > 60% successful measurements were considered valid. The density (elasticity) of the liver in kilopascals (kPa) and the IQR in percent (%) were determined. The density quantitatively indicated the degree of fibrosis in this area of the liver parenchyma where the sensor was installed.

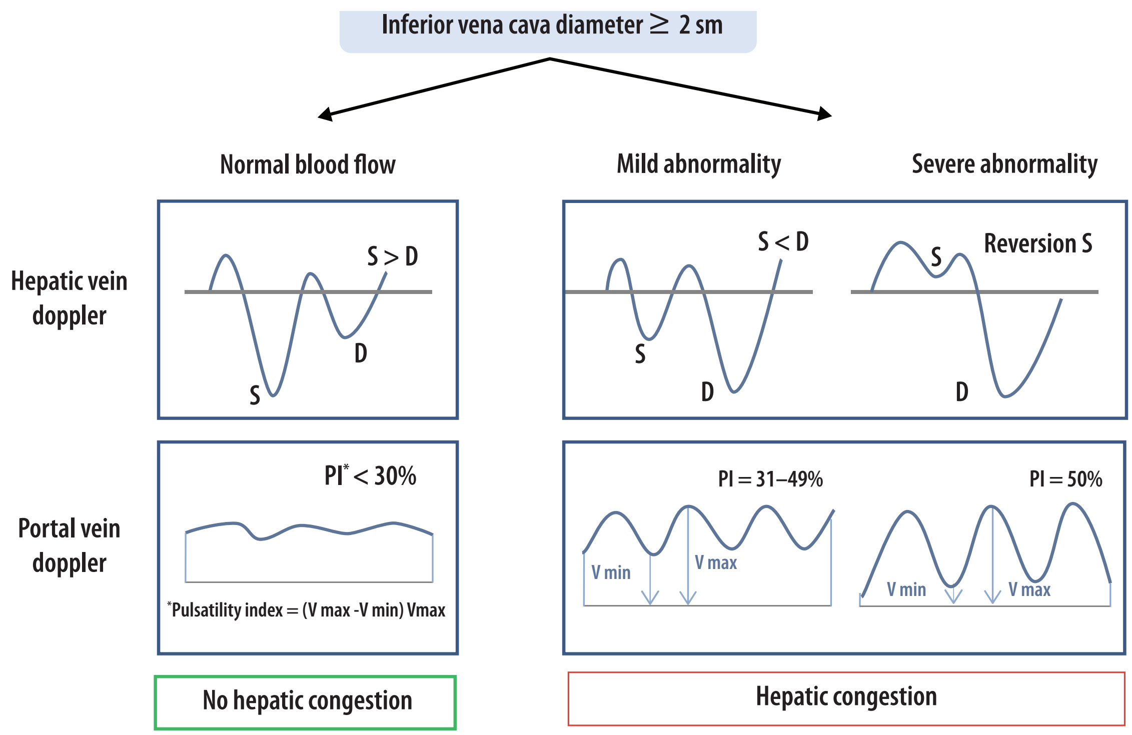
Ultrasound assessment of hepatic venous stagnation was carried out according to the VExUS protocol, on an expert-level device VIVIDTM E-90 (GE Healthcare) using abdominal and sector sensors, with an assessment of the diameter of the inferior vena cava, the shape of hepatic blood flows, and the portal in the mode of pulse-wave Dopplerography.[14] The study of Doppler curves was carried out on exhalation with simultaneous electrocardiogram registration on the monitor of the ultrasound machine. The shape of the blood flow in the port-hepatic veins was consistently evaluated according to the VExUS protocol, with the inferior vena cava diameter at ≥ 2.0 cm.

When constructing receiver operating characteristic curves for predicting outcomes (total mortality + re-hospitalization), the threshold values for assessing congestion were set as follows: (a) the number of lines on lung ultrasound > 5 and (b) liver density > 6.2 kPa.

For hepatic vein Dopplerography, the systolic phase was normally of greater amplitude than the diastolic phase, while a decrease in systolic blood flow velocity was considered a minor deviation, and the presence of a reverse systolic phase was a pronounced deviation [Figure 1].

Assessment of long-term clinical outcomes was carried out by a structured telephone survey 1, 3, 6, and 12 months after discharge. Combined parameters of total mortality and repeated hospitalizations were evaluated as the endpoint.

Analysis was performed using SPSS (IBM SPSS Statistics for Windows, version 22.0; IBM, Armonk, NY, USA). Quantitative variables were described as arithmetic mean±SD (with a normal distribution), or as the median and IQR (with an asymmetric distribution). The threshold survival value for each method was determined from the respective receiver operating characteristic curve. To assess the prognostic significance of different methods for the risk of occurrence of variables of interest, single- and multi-factor models of Cox regression analysis



The image is modified from Bhardwaj V et al.[15]

Figure 1: Assessment of hepatic venous congestion using Dopplerography.

Table 1: Clinical and demographic characteristics of patients (N = 207).

Parameters	Results
Sex	
Male, n (%)	112 (54.1)
Female, n (%)	95 (45.9)
Age, mean ± SD, year	70.7 ± 12.8
Systolic BP median; IQR, mmHg	117; 106–132
Diastolic BP median; IQR, mmHg	69; 62–77
LVEF median; IQR, %	44.0; 33.0–55.0
NT-proBNP median; IQR, pg/mL	1076; 609–2098
Arterial hypertension, n (%)	184 (88.9)
Coronary heart disease, n (%)	102 (49.3)
History of myocardial infarction, n (%)	67 (32.4)
Atrial fibrillation, n (%)	132 (63.8)
Type 2 diabetes mellitus, n (%)	69 (33.3)

IQR: interquartile range (25th and 75th percentile); BP: blood pressure; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

were used. The variables included in the model were selected based on their significance. The probability of survival was estimated by Kaplan-Meyer survival curves and the comparison was made using lograng criterion. Statistical significance was set at $p < 0.05$.

RESULTS

The participants comprised 207 chronic HF patients (54.1% men, average age = 70.7±12.8 years) who were hospitalized for decompensation of HF. The clinical and demographic characteristics of patients are presented in Table 1. Most (88.9%) participants had a history of arterial hypertension, 49.3% had coronary heart disease, and 33.3% had type 2 diabetes mellitus.

Doppler curves of liver congestion (according to the VExUS protocol) persisted in 57 (27.5%) patients as shown in Table 2 reveals. Table 3 displays the threshold values for predicting outcomes depending on the method.

Median follow-up time was 364 days (IQR = 197–365). During this period, 63 (30.4%) events were detected, including 23 deaths (11.1%) [Table 4].

Univariate Cox regression analysis demonstrated independent prognostic value with the total endpoint of all markers of congestion evaluated by different methods, such as lung ultrasound (HR = 7.0, 95% CI: 2.8 – 17.6; p <0.001), ultrasound evaluation of hepatic venous stagnation according to the VExUS protocol (HR = 2.9, 95% CI: 1.7–4.8; $p < 0.001$), liver density index according to indirect elastometry (HR = 2.2, 95% CI: 1.3–3.8; $p = 0.003$). Multivariate Cox regression analysis retained prognostic significance with respect to adverse outcomes for liver density > 6.2 kPa (HR = 1.9, 95% CI: 1.0 – 3.3; $p = 0.029$) and hepatic venous congestion according to the VExUS protocol (HR = 2.8, 95% CI: 1.3–5.7; $p = 0.004$).

The Kaplan-Meyer survival curves revealed significant differences in the cumulative probability of survival between groups of patients based on the following parameters: (a) the number of B-lines

Table 2: Characteristics of patients depending on the presence of hepatic congestion at discharge (N = 207).

Parameters	Congestion in hepatic veins (Inferior vena cava ≥ 2 cm) n = 57	No congestion in hepatic veins (Inferior vena cava < 2 cm) n = 150	Total	p-value
Age, mean ± SD, years	71.0 ± 12.7	70.6 ± 12.9	70.7 ± 12.8	0.876
Male, n (%)	37 (64.9)	75 (50.0)	112 (54.1)	0.054
Coronary heart disease, n (%)	31 (54.4)	71 (47.3)	102 (49.3)	0.387
History of myocardial infarction, n (%)	19 (33.3)	48 (32.0)	67 (32.4)	0.902
Arterial hypertension, n (%)	47 (82.5)	137 (91.3)	184 (88.9)	0.049*
Type 2 diabetes mellitus, n (%)	16 (28.1)	53 (35.3)	69 (33.3)	0.322
LVEF median; IQR, %	38.0; 30.0–48.5	48.0; 35.0–55.0	44; 33–55	< 0.001*
NT-proBNP median; IQR, pg/mL	2077; 1442–2795	923; 452–1641	1076; 609–2098	< 0.001*
Liver density median; IQR, kPa	15.5; 10.1–25.5	5.7; 4.4–7.6	6.7; 5.0–12.5	< 0.001*
Lungs ultrasound B-lines, median; IQR	20; 13–28	7; 3–12	9; 4–18	< 0.001*

**Significance; IQR: interquartile range (25th and 75th percentile); LVEF: left ventricular ejection fraction NT-proBNP: N-terminal prohormone of brain natriuretic peptide..*

Table 3: Threshold values for predicting outcomes depending on the method.

Parameters	Threshold values	Sensitivity	Specificity	AUC	*p*-value
Ultrasound of lungs, no. of B-lines	> 5	66.7	63.2	0.610	0.044
Liver density, kPa	> 6.2	68.3	54.2	0.635	0.001

AUC: area under the curve.

Table 4: Values of congestion markers in patients with acute decompensated heart failure depending on outcomes (N = 207).

Parameters	All patients	Patients without events n = 144	Patients with events n = 63	*p*-value
Lungs ultrasound (No. of B-lines) median; IQR	9; 4–18	6.5; 3–13	18; 9–26	< 0.001
Liver density median; IQR, kPa	6.7; 5.0–12.5	6; 4.7–10.2	8.3; 5.9–16.0	< 0.001
No. of patients with venous congestion, n (%)	57 (27.5)	27 (18.8)	30 (47.6)	< 0.001
NT-proBNP median; IQR, pg/mL	1076; 609–2098	987; 512–1974	1548; 936–2757	< 0.001

NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

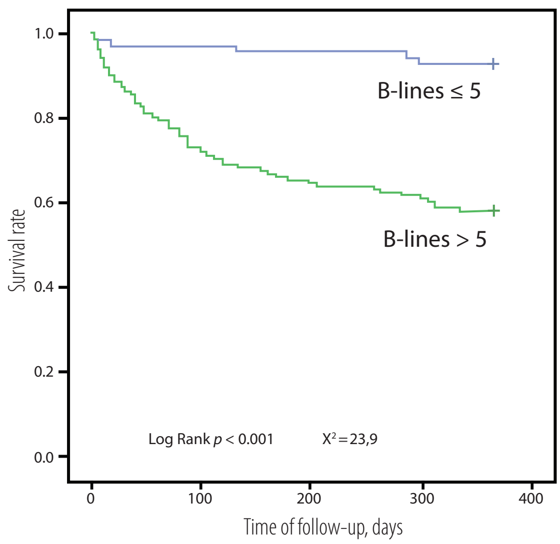


Figure 2: Kaplan-Meyer curves of cumulative probability of survival (total mortality + re-hospitalization) depending on the presence of pulmonary congestion according to ultrasound data.

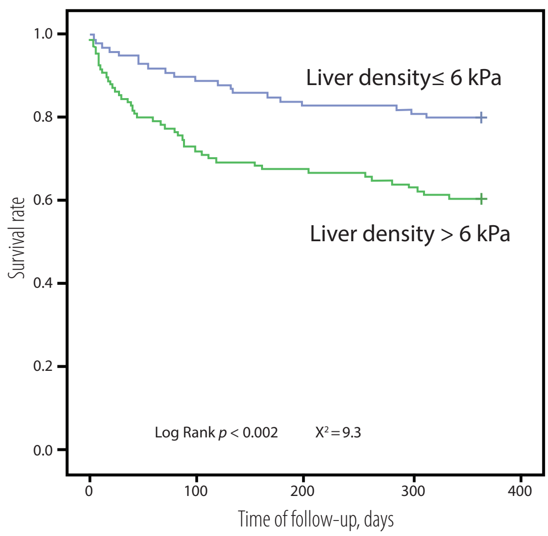


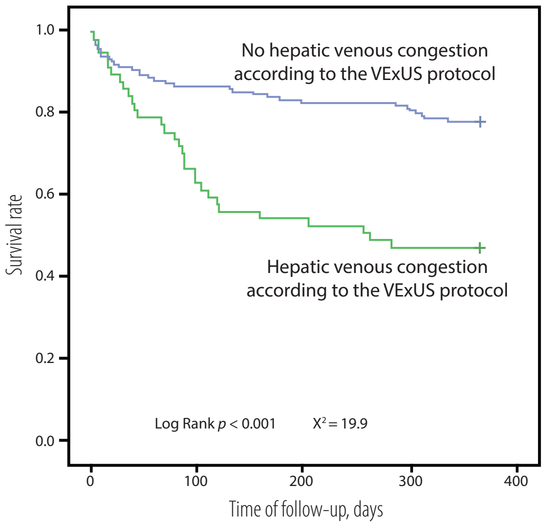
Figure 3: Kaplan-Meyer curves of cumulative probability of survival (total mortality + re-hospitalization) depending on liver density according to indirect elastometry.

[Figure 2], (b) liver density [Figure 3], and (c) hepatic venous congestion according to the VExUS protocol [Figure 4].

The Kaplan-Meyer curves of cumulative survival probability (total mortality + rehospitalization) given by the different methods used to assess congestion are shown in Figure 5. A significant increase in the risk of prognostic value was found in association with congestion detected by liver lung ultrasound + fibroelastometry (HR = 10.5, 95% CI: 2.3–46.2; p = 0.002), lung ultrasound + ultrasound of hepatic veins (HR = 16.7, 95% CI: 3.9–70.7; $p < 0.001$), and with all three methods (HR = 40.1, 95% CI: 6.6–243.1; $p < 0.001$).

DISCUSSION

The major finding of our study is that a comprehensive assessment of congestion at discharge from the hospital can predict adverse events (survival and rehospitalization) in patients with ADHF at one year. We also found that individuals in whom congestion was detected in both blood circulation and by each of the three methods (ultrasound of the



VExUS: venous excess ultrasound score.

Figure 4: Kaplan-Meyer curves of cumulative survival probability (total mortality + re-hospitalization) depending on the presence of hepatic venous congestion according to the VExUS protocol.

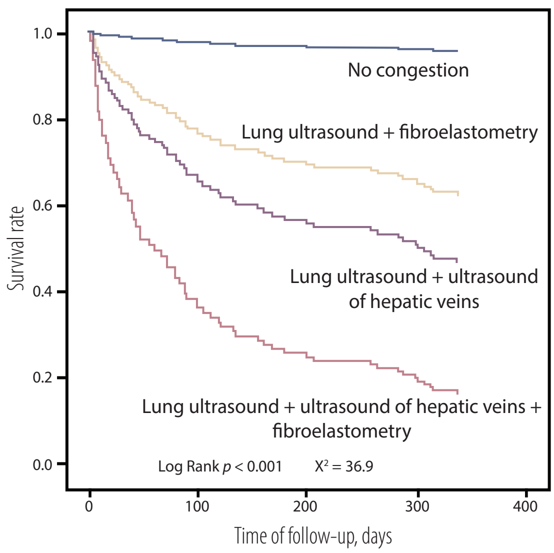


Figure 5: Kaplan-Meyer curves of cumulative survival probability (total mortality+ rehospitalization) depending on the number of methods used to assess congestion.

lungs, ultrasound of the hepatic veins according to the VExUS protocol, and liver fibroelastometry) had the worst prognosis.

In previous studies, retention of B-lines was associated with increased risk of rehospitalization for congestive HF at 3 and 6 months,[16] and patients with liver density > 6.9 kPa were characterized by a higher frequency of death and repeated hospitalizations for HF (HR = 3.57, 95% CI: 1.93–6.83; $p < 0.001$).[17] In other studies, venous congestion according to the VExUS protocol was associated with adverse outcomes including re-hospitalization for congestive HF, cardiovascular mortality, and total mortality at 12-month follow-up.[11,18–20]

In our study, comprehensive assessment of congestion using a combination of hepatic vein ultrasound + lung ultrasound had the greatest prognostic significance (HR = 16.7, 95% CI: 3.9–70.7; $p < 0.001$), and not the combination of lung ultrasound + liver fibroelastometry (HR = 10.5, 95% CI: 2.3–46.2; $p = 0.002$), which, according to the literature, has the greatest prognostic significance.[21]

CONCLUSION

In patients with acute decompensated HF, comprehensive assessment of congestion before discharge using ultrasound of the lungs counting the sums of B-lines, assessment of hepatic veins according to the VExUS protocol, and liver fibroelastometry are useful in predicting survival and re-hospitalization at one year.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

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