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# Heart failure as a multi-system clinical syndrome – an experience in cohort of acutely decompensated patients

## Niewydolność serca jako wielonarządowy zespół kliniczny – charakterystyka kliniczna chorych hospitalizowanych z powodu zaostrzenia niewydolności serca

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## Abstract

**Background:** Heart failure is a condition with diverse aetiology and pathogenesis. This is associated with higher rates of comorbidities, such as i.e. hypertension, atrial fibrillation chronic kidney disease, anaemia and iron deficiency. The purpose of this study was to characterise patients hospitalised due to acutely decompensated heart failure, with a particular emphasis on any comorbidities and laboratory test abnormalities. **Material and methods:** A total of 102 patients aged over 18 years, hospitalised due to acute decompensated heart failure. Thorough medical history (including any concomitant diseases) was obtained from all patients. They also underwent a clinical examination and biochemical tests. **Results:** The subjects included were mostly men (76.5%) with ischemic aetiology (63.7%). The most common comorbidity was hypertension (66.6%), while hypotension affected only 2% of patients. The most common heart failure subtype was heart failure with reduced ejection fraction (60.8%). The detected blood test abnormalities included elevated cystatin C levels in 94.7%, hyperuricaemia in 75.5%, anaemia in 55.9%, and iron deficiency in 78.3% of patients. **Conclusion:** Most of acute decompensated heart failure patients suffer from comorbidities with a documented impact on prognosis. Cardiovascular decompensation poses a risk of multi-organ dysfunction and estimating its actual consequences requires a detailed assessment of complex laboratory tests, including levels of creatinine, cystatin C, uric acid, red blood cell parameters and iron metabolism parameters.

**Keywords:** acute heart failure, laboratory tests, kidney failure, creatinine, anaemia

## Streszczenie

**Wstęp:** Niewydolność serca jest jednostką chorobową o zróżnicowanej etiologii i patogenezie. Dodatkowo w grupie chorych z niewydolnością serca obserwuje się liczne choroby współistniejące, takie jak: nadciśnienie tętnicze, migotanie przedsionków, przewlekła choroba nerek, niedokrwistość i niedobór żelaza. Celem pracy jest charakterystyka pacjentów hospitalizowanych z powodu zaostrzenia niewydolności serca, ze szczególnym uwzględnieniem chorób współistniejących oraz nieprawidłowości w badaniach laboratoryjnych. **Metody:** Do badania włączono 102 chorych powyżej 18. roku życia, hospitalizowanych z powodu zaostrzenia objawów niewydolności serca. W badanej grupie zebrano szczegółowy wywiad dotyczący chorób współistniejących, dokonano oceny klinicznej oraz oznaczono parametry biochemiczne. **Wyniki:** Wśród chorych hospitalizowanych z powodu zaostrzenia niewydolności serca dominowali mężczyźni (76,5%) i przeważała niedokrwienna etiologia niewydolności serca (63,7%). Najczęstszą chorobą współistniejącą było nadciśnienie tętnicze (66,6%), a hipotensja występowała u 2% chorych. Największą grupę stanowili chorzy z niewydolnością serca z obniżoną frakcją wyrzutową (60,8%). Spośród nieprawidłowości w badaniach laboratoryjnych podwyższone stężenie cystatyny C stwierdzono u 94,7% chorych, a hiperurykemię u 75,5%. Niedokrwistość występowała u 55,9%, a niedobór żelaza u 78,3% chorych. **Wnioski:** Chorzy z niewydolnością serca są szczególnie trudną grupą, w związku z występowaniem licznych chorób współistniejących, często mających wpływ na rokowanie. Dekompensacja układu sercowo-naczyniowego stwarza ryzyko dysfunkcji wielu narządów, co wymaga szczegółowej oceny biochemicznej, w tym oznaczeń stężeń kreatyniny, cystatyny C, kwasu moczowego, parametrów czerwonokrwinkowych i parametrów metabolizmu żelaza.

**Słowa kluczowe:** ostra niewydolność serca, badania laboratoryjne, niewydolność nerek, kreatynina, niedokrwistość

## INTRODUCTION

Heart failure (HF) is currently one of the few conditions whose prognosis has not improved despite rapid advances in medicine[1]. An estimated 2% of the general population suffers from HF[2], with the proportion exceeding 10% in people over 70 years of age[3]. Due to its prolonged negative effects on the patients' quality of life and ability to work, HF carries a high social burden[4]. Also, the economic costs of HF must not be overlooked from the perspective the healthcare system[5].

One of the factors responsible for the growing rates of HF is aging of the general population. This is associated with higher rates of comorbidities, such as ischaemic heart disease, peripheral atherosclerosis, lung conditions, diabetes mellitus, and chronic kidney disease (CKD)[6]. Additionally, anaemia and iron deficiency have been receiving more and more attention recently[7–10]. The presence of these comorbidities may confound the diagnosis of HF and worsen both short-term and long-term prognoses[2,11–13]. Some of them are strongly related to the applied therapy – such as renal dysfunction, which in acutely decompensated HF (ADHF) may result either from inadequate function of the heart as a pump, or a too rapid and severe dehydration[14]. Thus, comprehensive evaluation of patients hospitalised due to ADHF is essential to determine the optimal treatment.

Therefore, the purpose of this study was to thoroughly assess a group of patients hospitalised due to ADHF, with a particular emphasis on the clinical presentation, comorbidities, and blood chemistry abnormalities.

## MATERIAL AND METHODS

This prospective, observational study enrolled patients of both sexes, aged ≥18 years who were admitted to the Department of Cardiology and Internal Diseases due to ADHF (defined according to the European Society of Cardiology guidelines[2]) in the period between November 2014 and March 2017 and required intravenous diuretic treatment. Exclusion criteria were: 1) unstable angina; 2) history of acute coronary syndrome (ACS) within the last 12 weeks and/or coronary artery bypass grafting (CABG) surgery within the last 12 weeks; 3) cardiac resynchronisation therapy (CRT) introduced within the last year (or planned CRT implantation within the next 24 months); 4) non-cardiogenic shock; 5) valvular disease or other acquired heart defects requiring surgical intervention; 6) hypertrophic cardiomyopathy; 7) severe pulmonary hypertension or other severe lung conditions (severe form of chronic obstructive pulmonary disease (COPD) or bronchial asthma); 8) poorly controlled hypertension; 9) anaemia (haemoglobin <10.0 g/dL); 10) acute and/or decompensated non-cardiovascular disease; 11) pulmonary embolism; 12) end-stage CKD and/or ongoing haemodialysis therapy; 13) severe or chronic inflammatory disease, severe infection (including febrile conditions, radiologically-confirmed pneumonia, suspected septic shock); 14) neoplastic disease; 15) severe psychiatric disorder; 16) the lack of informed consent.

The study protocol was approved by the Military Institute of Medicine Institutional Review Board (approval No. 14/WIM/2012), and all study participants provided their written informed consent. This study was registered at ClinicalTrials.gov (NCT 02355769).

Clinical examinations were conducted with a particular emphasis on the history of symptoms, concomitant diseases, and current medication. The following were measured on physical examination: heart rate (HR), office systolic blood pressure (SBP), office diastolic blood pressure (DBP), and body parameters (height, body weight, body mass index (BMI), waist circumference).

Laboratory tests were conducted on fasting peripheral venous blood samples collected in the morning (7:30–8:30 a.m.). The following whole-blood parameters were measured: haemoglobin levels, haematocrit, and red blood cell distribution width (RDW). The following were measured in blood serum: urea, creatinine, cystatin C, fasting glucose (FG), uric acid (UA), total cholesterol (T-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity troponin T (hsTnT), iron, ferritin (data available for 60 subjects), unsaturated iron-binding capacity (UIBC), and total iron-binding capacity (TIBC). The cut-off values for non-standard parameters, adopted depending on the laboratory techniques used, were as follows: cystatin C >0.95 mg/L, creatinine >1.2 mg/dL, hsTnT >14 ng/L, iron <70 μg/dL, UA >7 mg/dL for men and >5.7 mg/dL for women. The value of estimated glomerular filtration rate (eGFR) was calculated with the MDRD (Modification of Diet in Renal Disease study) equation, which is a recognised method of calculating eGFR in patients with HF[15]. Abnormal NT-proBNP levels and iron deficiency criteria adopted for this study were based on the current guidelines[2], i.e.: NT-proBNP levels of >300 pg/mL, iron deficiency when ferritin level was of <100 μg/L and/or ferritin level of 100–299 μg/L with transferrin saturation (serum iron divided by TIBC and multiplied by 100%) of <20%.

Echocardiographic examinations were conducted with Vivid S6 (GE-Healthcare, USA) and Vivid 7 (GE-Healthcare, Chicago, Illinois, USA) ultrasound systems. The following parameters were evaluated: cardiac chamber dimensions, left ventricular wall thickness and contractility, ejection fraction, as well as valvular structure and function. Echocardiography reports included any moderate-to-severe mitral, tricuspid, and/or aortic regurgitation; severe aortic stenosis; as well as the numerical values of the following parameters: left ventricular end-diastolic diameter (LVEDD), right ventricular end-diastolic diameter (RVEDD), interventricular septum (IVS), and left atrial diameter (LAD), measured in the parasternal long-axis view.



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## Statistical analysis

The statistical analysis was conducted with the use of MS Office Excel 2013 and Statistica 12.0 (StatSoft Inc.). Data distribution was presented on histograms and evaluated visually. The results for qualitative variables were expressed as numbers and percentages; while continuous (quantitative) variables were expressed as means ± standard deviation (*SD*).

# RESULTS

## Patient characteristics

The study group comprised mostly men (*n* = 78, 76.5%); the mean age was 71.4 ± 12.5 years. Most patients (*n* = 66, 64.7%) had New York Heart Association (NYHA) class III symptoms, while 36 patients (35.3%) reported symptoms at rest (NYHA class IV). Eleven patients (10.8%) presented with decompensated HF in the form of pulmonary oedema. One-third (*n* = 34, 33.3%) of patients presented with new-onset HF. In nearly two-thirds (*n* = 65, 63.7%) of patients, the aetiology of HF decompensation was ischemic. The most commonly reported symptoms included dyspnoea on exertion, orthopnoea, and oedema (Tab. 1). Auscultation revealed evidence of pulmonary congestion in nearly all patients (98.1%); three-fourths of patients presented with peripheral oedema. There were no cases of clinically significant bradycardia, and only 2% of patients had hypotension with SBP of <90 mm Hg.

The detailed history of the patients' comorbidities is presented in Tab. 2. History-taking most commonly revealed ischemic heart disease, hypertension, atrial fibrillation, valvular disease, and diabetes mellitus. Tab. 3 lists medications used prior to admission (data obtained from 100 patients).

## Echocardiographic examination

The echocardiographic examination was conducted in 97 patients. The mean left ventricular ejection fraction (LVEF) was 37.3 ± 14.1%, LVEDD was 59.2 ± 10.2 mm, RVEDD was 35.3 ± 5.7 mm, and LAD was 47.3 ± 0.60 mm. The following proportions of patients had moderate-to-severe valvular disease: mitral regurgitation (MR) 48.4% (*n* = 47), tricuspid regurgitation (TR) 36.1% (*n* = 35), aortic regurgitation (AR) 2.1% (*n* = 2), and aortic stenosis (AS) 10.3% (*n* = 10). The patients were stratified into three HF subgroups based on their LVEF values (Fig. 1).

## Laboratory tests

**Cardiac markers.** The mean NT-proBNP levels were significantly elevated; the mean hsTnT levels of <14 ng/L significantly exceeded the 99$^{th}$ percentile value in a healthy reference population (Tab. 4). What is noteworthy is a pronounced right-skewed distribution of these variables,

| | ***n*** **(%)/mean ± *SD*** |
|---|---|
| **Interview** | |
| Dyspnoea at rest, *n* (%) | 41 (40.2) |
| Dyspnoea on effort, *n* (%) | 100 (98.1) |
| Orthopnoea, *n* (%) | 78 (76.4) |
| Paroxysmal nocturnal dyspnoea, *n* (%) | 44 (43.1) |
| Chest pain, *n* (%) | 25 (24.5) |
| Palpitations, *n* (%) | 33 (32.4) |
| Oedema, *n* (%) | 80 (78.4) |
| Pathological weight gain, *n* (%) | 40 (39.2) |
| Loss of appetite, *n* (%) | 21 (20.6) |
| **Physical examination** | |
| HR, 1/min, mean (*SD*) | 87.4 ± 24.2 |
| SBP, mm Hg, mean (*SD*) | 135.4 ± 26.8 |
| DBP, mm Hg, mean (*SD*) | 81.8 ± 13.5 |
| Hypertension (SBP >140 mm Hg, DBP >90 mm Hg), *n* (%) | 26 (25.5) |
| Hypotension (SBP <90 mm Hg), *n* (%) | 2 (1.9) |
| Tachycardia >120 bpm, *n* (%) | 7 (6.7) |
| Bradycardia <40 bpm, *n* (%) | 0 (0.0) |
| Tachypnoe, *n* (%) | 21 (20.6) |
| Rales, *n* (%) | 100 (98.1) |
| Oedema, *n* (%) | 77 (75.5) |
| Ascites, *n* (%) | 16 (15.7) |
| Peripheral hypoperfusion, *n* (%) | 10 (9.8) |
| Hepatomegaly, *n* (%) | 18 (17.7) |
| **bpm** – beats per minute; **DBP** – diastolic blood pressure; **HR** – heart rate; **SBP** – systolic blood pressure; ***SD*** – standard deviation. | |

*Tab. 1. Patient characteristics*

| **Concomitant disease** | ***n*** **(%)** |
|---|---|
| Prior MI, *n* (%) | 42 (41.1) |
| Procedure: CABG, *n* (%) | 18 (17.6) |
| Procedure: PTCA, *n* (%) | 36 (35.3) |
| Hypertension, *n* (%) | 68 (66.6) |
| Atrial fibrillation, *n* (%) | 54 (52.9) |
| Moderate-to-severe valvular disease, *n* (%) | 60 (58.8) |
| Procedure: prior surgical treatment of valvular disease, *n* (%) | 12 (11.7) |
| Procedure: ICD, *n* (%) | 10 (9.8) |
| Procedure: CRT, *n* (%) | 6 (5.9) |
| Procedure: PPM, *n* (%) | 16 (15.7) |
| Prior stroke, *n* (%) | 9 (8.8) |
| Peripheral artery disease, *n* (%) | 6 (5.9) |
| Diabetes mellitus, *n* (%) | 50 (49.0) |
| COPD, *n* (%) | 15 (14.7) |
| CKD (stadium ≥3), *n* (%) | 30 (29.4) |
| Smoking, *n* (%) | |
| Actually | 14 (13.7) |
| In the past | 58 (56.9) |
| Data are presented as *n* (%). **CABG** – coronary artery bypass graft; **CKD** – chronic kidney disease, GFR <60 ml/min/1,73 m$^2$; **COPD** – chronic obstructive pulmonary disease; **CRT** – cardiac resynchronisation therapy; **ICD** – implantable cardioverter defibrillator; **MI** – myocardial infarction; **PPM** – permanent pacemaker; **PTCA** – percutaneous transluminal coronary angioplasty. | |

*Tab. 2. Patient characteristics – medical history*



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| | *n* (%) | |
|---|---|---|
| | **Whole group (*n* = 100)** | **Prior HF (*n* = 67)** |
| ACE-I, *n* (%) | 62 (62.0) | 46 (68.7) |
| ARB, *n* (%) | 10 (10.0) | 7 (10.4) |
| Beta-blocker, *n* (%) | 78 (78.0) | 60 (89.6) |
| Aldosterone antagonists, *n* (%) | 33 (33.0) | 28 (41.8) |
| Diuretics, *n* (%) | 74 (74.0) | 60 (89.6) |
| Iwabradine, *n* (%) | 2 (2.0) | 1 (1.5) |
| Digoxin, *n* (%) | 7 (7.0) | 5 (7.5) |
| Amiodarone, *n* (%) | 13 (13.0) | 12 (17.9) |
| Nitrates, *n* (%) | 12 (12.0) | 9 (13.4) |
| Calcium channel blocker, *n* (%) | 21 (21.0) | 11 (16.4) |
| Statin, *n* (%) | 58 (58.0) | 49 (73.1) |
| Antiplatelet, *n* (%) | 37 (37.0) | 30 (44.8) |
| Anticoagulants, *n* (%) | 47 (47.0) | 38 (56.7) |
| Data are presented as *n* (%)<br>**ACE-I** – angiotensin-converting enzyme inhibitor; **ARB** – angiotensin receptor blocker.<br>Data available for *n* = 100. | | |

*Tab. 3. Patient characteristics – medication use before hospitalisation*

with the median and interquartile range for NT-proBNP 3,952 pg/mL and 1,775–8,181 pg/mL, respectively, and for hsTnT 35.3 ng/L and 23.0–58.7 ng/L, respectively.

**Renal function and metabolic parameters.** In over a half of patients, eGFR values were <60 mL/min/1.73 m$^2$ (Tab. 4, Fig. 2). At the same time, nearly all patients (94.7%), including the 42 patients (89.4%) with eGFR of >60 mL/min/1.73 m$^2$, had elevated cystatin C levels (Fig. 3). The metabolic parameter of note was uric acid, whose levels were significantly elevated (hyperuricaemia) in 75.5% of patients.

**Iron metabolism and haematology parameters.** Over a half of the evaluated patients (55.9%) were diagnosed with anaemia (Tab. 4). Over three-fourths (78.3%, data for 60 subjects) of them demonstrated iron deficiency.

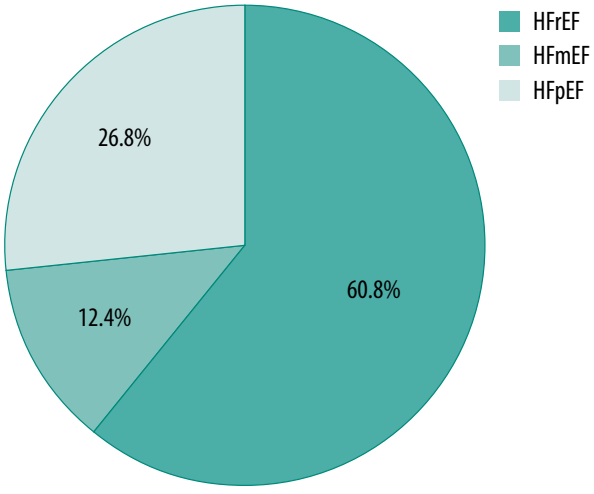


*Fig. 1. HF categories in the studied group (HFrEF – HF with reduced ejection fraction, <40%; HFmEF – HF with mid-range ejection fraction, 40–49%; HFpEF – HF with preserved ejection fraction, ≥50%)*

## DISCUSSION

A detailed assessment of patients with ADHF demonstrated the complexity of clinical issues to consider during the diagnosis and treatment of this condition. Clinical examinations revealed high rates of prognosis-worsening comorbidities in the study population. A detailed assessment of blood chemistry parameters proved that a number of disorders might remain undetected until hospital admission. Expanding the panel of diagnostic tests (to include cystatin C level, red blood cell parameters, and iron metabolism parameters) allowed us to identify clinically significant disorders associated with decompensated HF.

**Medical history and clinical presentation.** The study group was predominantly male, the mean age was over 70 years, and the most common cause of HF was post-infarct left-ventricular remodelling. The baseline characteristics of our study group were consistent with the data from the following HF-related registries: ATTEND[16], ADHERE[17], OPTIMIZE-HF[18], and EHFS II[19] (Tab. 5). In one-third of patients, clinical decompensation was the first manifestation of undiagnosed HF, which is consistent with the data from large registries[19,20]. Pulmonary oedema was detected in 11% of the patients, which made it a relatively rare clinical presentation in comparison with the rates reported in earlier studies (16–37%)[19,20]. Hypotension was present in only 1 out of 50 patients, which is consistent with the current knowledge[2]. This last finding supports the use of nitroglycerin (a vasodilatory agent), which can be safely administered in most ADHF patients[2]. Still, this is not so in common practice; according to various registries nitroglycerin is administered in less than a half of ADHF patients[19,21–24].

**Echocardiographic findings.** Although the study group comprised predominantly patients with HF with reduced ejection fraction (HFrEF), there was also a considerable proportion of patients with HFpEF (HF with preserved ejection fraction). Our findings confirmed earlier observations. According to relevant registries, 40–50% of patients hospitalised due to ADHF had normal, or nearly normal, left ventricular systolic function[25–28]. Thirty percent of patients in the NHFA study[27] and 26% of patients in the RELAX-AHF study had LVEF of >50%[29].

**Treatment.** Despite the fact that two-thirds of the evaluated patients had already been diagnosed with HF prior to their hospitalisation, the treatment they had been receiving was not optimal. Over 20% of patients received neither angiotensin-converting enzyme (ACE) inhibitors nor angiotensin II receptor blockers (ARBs), and 10% of patients received no beta-blocker. At the same time, nearly all patients (90%) required treatment with diuretics. The data reported by others are no more reassuring. In the JCARE-CARD study[24,25] only 51.2% of patients received ACE inhibitors or ARBs, with a similar



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| | ***n* (%)/mean ± *SD*** |
|---|---|
| **Cardiac biomarkers** | |
| NT-proBNP[101a], pg/mL, mean (*SD*) | 6197 ± 7057 |
| hsTnT[100], ng/L, mean (*SD*) | 103.1 ± 257.5 |
| **Renal parameters** | |
| Creatinine[102], mg/dL, mean (*SD*) | 1.31 ± 0.51 |
| Urea[102], mg/dL, mean (*SD*) | 54.0 ± 26.2 |
| eGFR MDRD[102], mL/min/1.73 m$^2$, mean (*SD*) | 62.2 ± 23.9 |
| Cystatin C[95], mg/dL, mean (*SD*) | 1.62 ± 0.58 |
| Cystatin C >0.95 mg/L[95], *n* (%) | 90 (94.7) |
| **Metabolic parameters** | |
| Glucose[102], mg/dL, mean (*SD*) | 137.7 ± 76.0 |
| TC[98], mg/dL, mean (*SD*) | 136.7 ± 47.1 |
| HDL-C[98], mg/dL, mean (*SD*) | 43.1 ± 16.8 |
| LDL-C[98], mg/dL, mean (*SD*) | 87.5 ± 38.9 |
| TG[98], mg/dL, mean (*SD*) | 100.8 ± 53.9 |
| UA[98], mg/dL, mean (*SD*) | 8.52 ± 2.37 |
| Hyperuricaemia, >7 mg/dL [M] and >5.7 mg/dL [F][98], *n* (%) | 74 (75.5) |
| **Iron parameters** | |
| Iron[97], µg/dL, mean (*SD*) | 56.4 ± 28.3 |
| Ferritin[60], µg/L, mean (*SD*) | 144.4 ± 197.5 |
| UIBC[97], µg/dL, mean (*SD*) | 273.8 ± 79.2 |
| TIBC[97], µg/dL, mean (*SD*) | 327.2 ± 76.5 |
| Transferrin saturation[97], %, mean (*SD*) | 18.3 ± 10.9 |
| Iron deficiency (ferritin <100 µg/L and/or ferritin 100–299 µg/L with transferrin saturation <20%)[60], *n* (%) | 45 (78.3) |
| **Parameters of blood morphology** | |
| WBC[102], k/m$^3$, mean (*SD*) | 8.59 ± 3.61 |
| RBC[102], mln/m$^3$, mean (*SD*) | 4.35 ± 0.79 |
| Hb[102], g/dL, mean (*SD*) | 12.6 ± 2.6 |
| RDW[99], g/dL, mean (*SD*) | 15.5 ± 2.6 |
| Hematocrit[102], %, mean (*SD*) | 38.5 ± 6.2 |
| Anaemia (Hb <13 g/dL [M], Hb <12 g/dL [F])[102], *n* (%) | 57 (55.9) |

[a] The upper index indicates the number of patients in whom the given parameter was determined.
Data are presented as mean.
**eGFR** – estimated glomerular filtration rate; **Hb** – haemoglobin; **HDL-C** – high-density lipoprotein cholesterol; **hsTnT** – high-sensitivity troponin T; **LDL-C** – low-density lipoprotein cholesterol; **MDRD** – Modification of Diet in Renal Disease Study; **NT-proBNP** – N-terminal pro-brain natriuretic peptide; **RBC** – red blood cells; **RDW** – red cell width; **TC** – total cholesterol; **TG** – triglicerydes; **TIBC** – total iron-binding capacity; **UA** – uric acid; **UIBC** – unsaturated iron-binding capacity; **WBC** – white blood cells.

*Tab. 4. Patient characteristics – laboratory data on admission*

proportion (63.1%) reported in the EHFS II study[19]. An even lower proportion of patients in these studies received beta-blocker therapy (22% and 43.2%, respectively).

**Comorbidities.** Overall, the comorbidity profile in our study group was similar to that reported in large registries and clinical trials (Tab. 4), with only somewhat higher rates of diabetes mellitus (44%) in our study (EHFS II – 32.8%[19], JCARE-CARD – 29.8%[24]). We observed high proportion of patients with atrial fibrillation, which is consistent with the data from Polish registries (56.8%)[30].

**Laboratory tests.** Extending the scope of laboratory diagnostics revealed that a number of concomitant disorders of

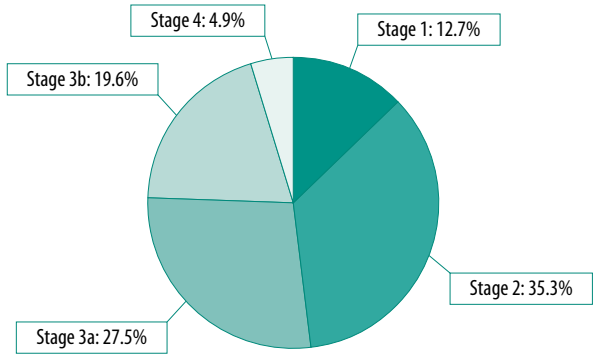


*Fig. 2. Categories of CKD according to eGFR (stage 1 – eGFR >90 mL/min/1.73 m$^2$, stage 2 – eGFR 60–89 mL/min/1.73 m$^2$, stage 3a – 45–59 mL/min/1.73 m$^2$, stage 3b – eGFR 30–44 mL/min/1.73 m$^2$, stage 4 – eGFR <30 mL/min/1.73 m$^2$)*

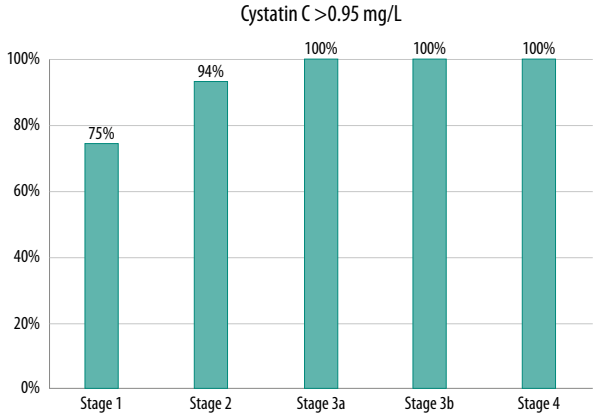


*Fig. 3. Percentage of patients with elevated cystatin C values in the subsequent stages of CKD (stage 1 – eGFR >90 mL/min/1.73 m$^2$, stage 2 – eGFR 60–89 mL/min/1.73 m$^2$, stage 3a – 45–59 mL/min/1.73 m$^2$, stage 3b – eGFR 30–44 mL/min/1.73 m$^2$, stage 4 – eGFR <30 mL/min/1.73 m$^2$)*

high prognostic importance remain undiagnosed until hospitalisation. Anamnesis revealed CKD in 29.4% of patients, whereas baseline tests showed eGFR of <60 mL/min/1.73 m$^2$ in 60% of patients. The authors of large registries: JCARE-CARD[24], ADHERE[17] and EHFS II[19] reported CKD rates of 11.3%, 30.0%, and 16.8%, respectively. In contrast to eGFR values, cystatin C levels indicated that only 5% of patients may have had unimpaired kidney function. Increased cystatin C was noted even in patients with normal creatinine levels and eGFR values of >90 mL/min/1.73 m$^2$. Thus, the addition of cystatin C level testing in evaluating renal function in patients with HF seems justified. A study by Breidthardt et al.[31] demonstrated that elevated cystatin C levels in patients with ADHF was a risk factor for all-cause mortality and that it was independent of brain natriuretic peptide (BNP) levels. Importantly, cystatin C levels are independent of the age or muscle mass, in contrast to creatinine[32,33].

The assessment of red blood cell parameters conducted as part of our study showed both anaemia and abnormal RDW



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| | Study group | EHFS II[19] | ADHERE[17] | OPIMIZE-HF[18] | ATTEND[16] | JCARE-CARD[24] |
|---|---|---|---|---|---|---|
| **Feature** | | | | | | |
| HR, 1/min | 87.4 | NA | NA | 86.6 | 99 | 87.8 |
| SBP, mm Hg | 135.4 | 132.1 | 143.8 | 142.7 | 147 | 134.3 |
| DBP, mm Hg | 81.8 | NA | 79 | 76.4 | NA | 75.4 |
| Dyspnea at rest, % | 40.2 | NA | 34 | 44 | NA | 66.7 |
| Dyspnea on effort, % | 98.1 | NA | 89 | 61 | NA | 85.8 |
| Orthopnea, % | 77.2 | NA | NA | 27.4 | 68.5 | NA |
| Oedema, % | 75.5 | NA | 65 | 65 | 67.7 | 53.3 |
| Rale, % | 98.1 | NA | 68 | NA | 77.6 | 51.7 |
| **Medical history, %** | | | | | | |
| Hypertension | 66.6 | 62.5 | 73 | 71 | 70.6 | 52.1 |
| Diabetes mellitus | 49 | 32.8 | 44 | 42 | 34 | 29.8 |
| Renal dysfunction | 29.7 | 16.8 | 30 | 20 | NA | 11.3 |
| Anaemia | 55.9 | 14.7 | 53 | 18 | NA | 20.3 |
| COPD | 14.7 | 19.3 | 31 | 28 | 9 | 5.8 |
| Atrial fibrillation | 52.9 | 38.7 | 31 | 31 | 40 | 34.9 |
| **Medication use before hospitalisation, %** | | | | | | |
| ACE-I | 62 | 55 | 41 | 40 | | 26.5 |
| ARB | 10 | 9.3 | 12 | 12 | | 28.9 |
| Beta-blocker | 78 | 43.2 | 48 | 53 | | 22.3 |
| MRA | 33 | 28.1 | NA | 7 | | 24.1 |
| Diuretics | 74 | 71.2 | 70 | 65.7 | | 61 |

NA – not available.
**ACE-I** – angiotensin-converting enzyme inhibitor; **ARB** – angiotensin receptor blocker; **COPD** – chronic obstructive pulmonary disease; **DBP** – diastolic blood pressure; **HR** – heart rate; **MRA** – mineralocorticoid receptor antagonist; **SBP** – systolic blood pressure.

*Tab. 5. Comparison of the basic characteristics of the studied group with data from large registers*

values to be common in ADHF patients. Anaemia was detected in 56% of patients, whereas in the Polish population of the HF Pilot Survey registry it was present in only close to one-fourth of patients[30]. The mean RDW value in our study group was 15.3%, which falls within the upper interquartile range reported by others investigating this parameter in HF patients[34]. Wasilewski et al.[34] observed significantly lower LVEF and larger left ventricular dimensions in a subgroup with the highest RDW (>14.6%) compared with these parameters in the subgroup with the lowest RDW values. Moreover, the highest RDW subgroup demonstrated 8-fold higher mortality than that observed in the subgroup with the lowest RDW.

Out of our study population 78.3% of patients exhibited iron deficiency. Iron deficiency has a negative effect on cardiomyocyte metabolism and function, and triggers sympathetic system activation, which may be one of the causes of HF decompensation[35]. The treatment of this metabolic disorder is particularly important in the light of reports on the beneficial effects of intravenous iron supplementation in patients with chronic HF[8,36,37].

Of note is also the observed high proportion of patients with elevated UA levels. Hyperuricaemia in 75% of patients was a surprising finding, especially when compared with the its considerably lower prevalence reported in the available literature (in 43% of patients with HFrEF and in 57% of patients with HFpEF)[38]. One of the factors responsible for hyperuricaemia may be long-term diuretic therapy[39]. However, even this fails to explain the extent of this phenomenon. The important clinical issue in such cases is selecting the course of treatment as well as determining whether all such patients should receive xanthine oxidase inhibitors (as has been suggested by some experts[40]).

We consider these observed chemical imbalances to be a particularly important finding, as their presence proves the complex pathophysiology of ADHF. Although any causal relationships in this case are difficult to ascertain, establishing a treatment protocol that would incorporate controlling these abnormalities may have a great impact on prognosis in these patients. Certainly this topic requires further studies.

## STUDY LIMITATIONS

The possibility to extrapolate our findings onto all patients with ADHF is limited by some of our exclusion criteria. For instance, we excluded patients with acute coronary syndrome, who had not been excluded from some registries (EHFS II). Due to the scope of study methods, not all patients with ADHF who were admitted to our Department consented to participate, which limited our sample size. Another limitation, in a sense, is the fact that the echocardiographic examination was conducted after a varied length of time post-admission. Because of this, the findings may



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not accurately reflect the LVEF or the severity of valvular disease at the moment when the decompensation was the most pronounced. The few instances of missing data, indicated in the Results section, should not have any significant effect on data interpretation.

## CONCLUSION

The diagnosis and treatment of patients with ADHF require a comprehensive approach. Most of such patients suffer from concomitant conditions with a documented impact on prognosis. Cardiovascular decompensation poses a risk of multi-organ dysfunction and estimating its actual consequences requires a detailed clinical assessment and additional diagnostic evaluations. Expanding the scope of laboratory tests to include cystatin C, red blood cell parameters, and iron metabolism parameters, helps identify pathophysiologically significant abnormalities, which should not be overlooked during the treatment of patients with HF.

### Conflict of interest

*None declared.*

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