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The influence of Vitamin D deficiency and Anemia on the prognosis of male patients with Heart Failure with reduced and mildly reduced ejection fraction.

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The influence of vitamin D deficiency and mild anemia on the prognosis of male patients with heart failure with reduced and mildly reduced left ventricular ejection fraction

Wpływ niedoboru witaminy D i łagodnej anemii na rokowanie pacjentów płci męskiej z niewydolnością serca z obniżoną i łagodnie obniżoną frakcją wyrzutową lewej komory

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Abstract

Introduction. Anemia and vitamin D deficiency are thought to significantly impact the clinical course in patients diagnosed with heart failure (HF). Both conditions are prevalent within the general population and their incidence increases among HF patients. We investigated the prognostic value of anemia and 25-hydroxyvitamin D [25(OH)D] deficiency in patients with heart failure with reduced and mildly reduced ejection fraction.

Material and methods. The study was prospective and was conducted on 87 patients diagnosed with HF. The patients were assigned to two groups depending on the left ventricular ejection fraction (LVEF): HFrEF if LVEF ≤ 40% (n = 49) and HFmrEF if LVEF = 41–49% (n = 38). Hemoglobin levels and 25-hydroxyvitamin D concentration were measured. Survival analysis was performed after 1 and 10 years of follow-up.

Results. The prevalence of vitamin D deficiency among patients classified as HFmrEF and HFrEF was 66% and 49%, respectively, demonstrating a higher occurance than anemia, which was observed in 24% and 31% of participants. In univariate analysis 25(OH)D concentration < 20 ng/mL was found to be a significant risk of death during the 10-year follow-up period in the entire study group (OR: 95% CI: 2.64; 1.1–6.32, p = 0.029). There was no statistically significant effect of anemia on the prognosis in patients with heart failure. Univariate and multivariate analysis showed that NYHA class > II was a significant prognostic factor for 10-year mortality in the study population (OR: 95% CI: 2.52; 1.002–6.33, p = 0.0495).

Conclusions. Vitamin D deficiency and NYHA class > II showed prognostic value as a predictor of 10 years mortality in study population. A high prevalence of vitamin D deficiency and anemia, regardless of left ventricular ejection fraction, were confirmed.

Key words: heart failure, prognostic factors, vitamin D deficiency, anemia

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Introduction

Heart failure (HF) is regarded as the final stage of all forms of cardiovascular disease. It has been divided into three phenotypes based on the left ventricular ejection fraction (LVEF): HF with reduced LVEF (HFrEF), HF with mildly reduced LVEF (HFmrEF) and HF with preserved LVEF (HFpEF), assuming the possibility of specific etiological factors and differences in the prognosis of patients [1]. Heart failure remains one of the leading health problems worldwide, due to its high prevalence and 5-year mortality, reaching 67–75% in cohort studies [2, 3]. Identifying modifiable factors that may impact the prognosis of patients with HF, remains an urgent task. Previous studies highlight that vitamin D deficiency and anemia are considered risk factors for mortality among patients with heart failure and these factors frequently co-occur [4, 5].

Anemia is defined as a decrease in hemoglobin concentration resulting in an impaired ability to transport oxygen. This condition results in decreased functional capacity and heightened mortality risk in patients with heart failure [6]. Vitamin D deficiency is associated with an increased risk of cardiovascular disease, including hypertension, heart failure and coronary artery disease [7]. To our knowledge, there have been no studies assessing the effect of vitamin D deficiency and anemia on 10-year survival in HF patients with reduced and mildly reduced ejection fraction. In our opinion, this is an important topic due to the high prevalence of both conditions in the general population and their potential impact on the course of heart failure.

Material and methods

Study population

The study was prospective and involved 87 consecutive male patients over the age of 18 years, presented with left ventricular systolic dysfunction and symptoms of heart failure lasting for a minimum of three months, hospitalized in the Department of Cardiology, Medical

University of Lodz between June 2011 and September 2013. Patients were categorized according to their LVEF: HFrEF if LVEF ≤ 40% (n = 49, 56%) and HFmrEF if LVEF = 41–49% (n = 38, 44%).

Patients with history of thyroid or parathyroid disease, severe renal dysfunction (glomerular filtration rate [GFR] < 30 mL/min/1.72 m^2), chronic liver disease, autoimmune disease, vitamin D supplementation within the preceding 6 months and history of malignancy within the preceding 12 months, were excluded from the study. Vitamin D supplementation was not administered to the study group.

The study complied with the Declaration of Helsinki and was approved by the Bioethics Committee of the Medical University of Lodz. Each participant signed informed consent.

Clinical, laboratory and echocardiographic evaluations

Clinical evaluations were performed at baseline. For each patient, age, BMI, New York Heart Association (NYHA) classification, and medical history were documented.

Serum samples was collected after a 12-hour overnight fasting period and hemoglobin (Hb) and N-terminal-pro hormone B-type natriuretic peptide (NT-pro BNP) levels were measured. Anemia was diagnosed based on the definition of the World Health Organization (Hb < 13 g/dL in men) [6]. Serum concentration of 25-hydroxyvitamin D [25(OH)D] was measured using a electrochemiluminescence immunoassay method (ECLIA Roche diagnostics). Serum was separated and stored at -20°C for a maximum of 24 weeks until assayed. Patients with 25(OH)D levels < 20 ng/mL were considered deficient, according to clinical guidelines [8].

Each patient underwent transthoracic echocardiography. Left ventricular ejection fraction was calculated according to the biplane Simpson’s method.

Patient follow-up

Survival analysis was performed after 1 year and at the end of the follow-up period based on data obtained from hospital registers, central national registers, and direct interviews with patients and persons authorized by them to access medical data.

Statistical analysis

Statistical analysis was performed using Statistica 13.1 software (Tibco, Palo Alto, CA, USA) and R version 4.2.1. P-values less than 0.05 were considered statistically significant. Nominal variables are presented as both absolute values and percentages. Continuous variables are

presented as mean with standard deviation or median with interquartile range. The normality of distribution was verified by the Shapiro–Wilk test. The Chi-squared test with Yates' correction or fishers exact test for continuity was used when applicable to compare categorical variables between groups. This correction was applied to adjust for the overestimation of statistical significance in 2 × 2 contingency tables. For continuous variables, comparisons between groups were conducted using either the independent t-test or the Mann–Whitney U test, depending on the normality of the data distribution. The equality of variances was evaluated using Levene's test. Univariate logistic regression was used to assess the impact of specific factors on one-year follow-up survival and ten-year follow-up survival. Subsequently, statistically significant variables identified by univariable analysis were included in the multivariable logistic regression model.

Results

The baseline characteristics are summarized in Table 1. The study population comprised 38 man with diagnosed HFmrEF and 49 man with HFrEF, with a mean age of 62 and 60 years, respectively. No significant differences were found between age, BMI, diabetes, hypertension and hyperlipidemia among the compared groups. Neither were any significant differences observed in the baseline mean (SD) vitamin D and median (IQR) hemoglobin concentration between groups. During the 10-year follow-up period 42% and 61% of patients died in the HFmrEF and HFrEF groups, respectively.

Despite the fact that the median NYHA class in the groups of patients with LVEF>40% and LVEF ≤ 40% remains the same (NYHA - II), due to differences in the data distribution in these groups, the Mann-Whitney U test showed a significant difference in the median NYHA class (U = 646, Z = -2.62 p = 0.009), the interquartile range (IQR) in the group of patients with LVEF > 40% is I–III, while in the group of patients with LVEF ≤ 40%: II–III, which indicates a higher mean NYHA class in the group of patients with lower LVEF. Moreover, serum NT-pro-BNP levels were higher in patients with severely reduced LVEF compared to patients with LVEF > 40% (1585 pg/mL [819.2–3331] vs. 1031 pg/mL [321.5–2555], p = 0.041) (Fig. 1).

Univariate analysis showed that NYHA class > II is a significant prognostic factor for 10-year mortality in the study population, maintaining its significance in multivariate analysis (OR 95% CI: 2.52; 1.002–6.33, p = 0.0495).

Vitamin D deficiency was found to be a significant prognostic factor for 10-year mortality in the study population (OR 95% CI: 2.64; 1.1–6.32, p = 0.029) and remained

borderline statistically significant in multivariate analysis (OR 95% CI: 2.44; 0.999–5.96, p = 0.05) (Table 2, Table 3). Only in the group of patients with HFrEF, univariate analysis showed that 25(OH)D deficiency influenced the risk of death during the 10-year follow-up, close to statistical significance (OR 95% CI: 3.25; 0.97–10.92, p = 0.057) (Table 2).

The analysis did not show a statistically significant effect of anemia on the one- and ten-year prognosis in the entire study population or in the HFrEF and HFmrEF groups.

Discussion

Ongoing discussions among researchers focus on the prognostic implications for patients with heart failure in relation to the value of left ventricular ejection fraction. [2, 9]. Previous studies have indicated that patients with severe left ventricular systolic dysfunction tend to have a poorer prognosis. The disparity in circulating NT-pro-BNP levels and the significant difference in median NYHA class between HFmrEF and HFrEF observed at baseline suggest a more severe clinical course in patients with lower LVEF. There was no statistically significant difference in one-year mortality between groups; however, after ten years of follow-up, a higher number of deaths were observed in HFrEF group compared to the HFmrEF group (n = 30, 61% vs. n = 16, 42%, respectively). The use of targeted treatment depending on the etiology of heart failure including interventions on coronary arteries, antiarrhythmic or cardiac surgery treatment, could have contributed to improving the prognosis during the 12-month follow-up period in both groups.

As reported in the literature, the NYHA class remains an important element in assessing the clinical course of patients. Multivariate analysis revealed that NYHA class > II is a significant risk factor for death in 10-year follow-up. As Briongos-Figuero et al. showed, the risk of cardiovascular and all-cause death was higher in symptomatic patients in NYHA class III, undergoing ICD implantation, than in asymptomatic patients, which is consistent with our results [10].

Anemia remains a global health problem that affects almost 25% of the world's population [11]. As reported by Mentz et al. the prevalence of anemia reaches up to one third of patients with heart failure and is associated with increased mortality [12]. Among our patients with HFrEF, nearly 31% met the criteria for anemia, whereas this percentage was 24% in the HFmrEF group. Moreover, the median hemoglobin concentration in the present study was slightly higher, which indicates that anemia was not as severe as in the patients in the EVEREST trial. This may partially explain why we did not find a significant association between anemia and survival in our study population.

Similar data to EVEREST trial were obtained in the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program, which showed an association between anemia and an increased risk of death and hospitalization in HF patients. In the analysis presented by O'Meara E. et al., reduction in Hg level was significantly associated with lower eGFR and was similar in patients with LVEF > 40% and ≤ 40%. More than 50% of patients with anemia were classified as having chronic kidney disease (CKD) stage 3 or 4, whereas in our study stages 4 or 5 were established as exclusion criteria [5]. Studies show, that the incidence of anemia increases with lower eGFR and its occurrence is associated with higher mortality in patients with CKD [13]. The significant difference in renal function in patients enrolled in both studies, as well as the higher Hb concentration observed in our population, could have influenced the differences in the results of the presented studies.

The epidemiological data shows that vitamin D deficiency is common in the general population [14] and occurs in the majority of patients with heart failure [15]. Our findings are consistent with other published data. In patients with HFmrEF and HFrEF, 66% (n = 25) and 49% (n = 24), respectively, had 25(OH)D levels < 20 ng/mL.

Previous studies suggest that vitamin D deficiency significantly influences the development of heart failure through proatherosclerotic effects, increased inflammation, activation of the renin-angiotensin-aldosterone system [16], stimulation of cardiomyocyte fibrosis [17], and indirectly through the impact on renal injury [18]. The results of this study reveal increased mortality in patients with low 25(OH)D concentrations compared with those without (OR 95% CI: 2.64; 1.1–6.32, p = 0.029). Our data are consistent with the results presented by Pilz et al. In a study of 3299 participants, patients with severe vitamin D deficiency < 25 nmol/L (< 10 ng/mL) had an increased risk of death from heart failure (HR 2.84) and sudden cardiac death (HR: 5.05) compared with patients with normal 25(OH)D levels > 75 nmol/l (> 30 ng/mL) [4].

No statistical significance was observed concerning the effect of vitamin D deficiency on the risk of mortality in the HFrEF and HFmrEF groups, which may be attributed to the limited size of the study population.

Conclusions

Higher NYHA class and vitamin D deficiency were found to be comparable, significant mortality risk factors in the study population. Vitamin D deficiency and anemia are common in patients with heart failure, regardless of left ventricular ejection fraction. The impact of

both conditions on the clinical outcomes in patients with heart failure are complex and require further research.

Study limitations

This was a single-centre study and the analyzed population was relatively small. Hemoglobin and vitamin D concentration were measured only once at baseline. Furthermore, the inclusion of only male patients limits conclusions regarding gender differences.

Streszczenie

Wprowadzenie. Niedokrwistość i niedobór witaminy D są uważane za czynniki wpływające na przebieg kliniczny pacjentów z niewydolnością serca. Oba stany chorobowe są powszechne w populacji ogólnej, a ich częstość występowania wzrasta wśród pacjentów z niewydolnością serca. W prezentowanym badaniu oceniliśmy wartość prognostyczną niedokrwistości i niedoboru 25-hydroksywitaminy D [25(OH)D] u chorych z niewydolnością serca z obniżoną frakcją wyrzutową (HFrEF, heart failure with reduced ejection fraction) i łagodnie obniżoną frakcją wyrzutową (HFmrEF, heart failure with mildly reduced ejection fraction).

Materiał i metody. Badanie miało charakter prospektywny, włączono do niego 87 pacjentów płci męskiej ze zdiagnozowaną niewydolnością serca. Chorych przydzielono do dwóch grup w zależności od frakcji wyrzutowej lewej komory (LVEF): HFrEF, jeśli LVEF ≤ 40% (n = 49) i HFmrEF, jeśli LVEF = 41–49% (n = 38). U wszystkich chorych oznaczono stężenie hemoglobiny i 25-hydroksywitaminy D. Analizę przeżycia przeprowadzono po roku i 10 latach obserwacji.

Wyniki. Częstość występowania niedoboru witaminy D u pacjentów z HFmrEF i HFrEF wynosiła odpowiednio 66% i 49% i była wyższa niż częstość występowania anemii, którą stwierdzono u 24% i 31% uczestników. W analizie jednoczynnikowej wykazano, że stężenie 25(OH)D < 20 ng/mL stanowiło istotny czynnik ryzyka zgonu w 10-letnim okresie obserwacji w całej grupie badanej (OR 95% CI: 2,64; 1,1–6,32, p = 0,029). Nie stwierdzono statystycznie istotnego wpływu anemii na rokowanie u pacjentów z niewydolnością serca. W analizie jednoczynnikowej i wieloczynnikowej dowiedziono, że klasa NYHA > II była istotnym czynnikiem prognostycznym 10-letniej śmiertelności w badanej populacji (OR 95% CI: 2,52; 1,002–6,33, p = 0,0495).

Wnioski. Niedobór witaminy D oraz klasa NYHA > II i wykazały wartość prognostyczną jako czynniki ryzyka 10-letniej śmiertelności w badanej populacji. Potwierdzono wysoką

częstość występowania niedoboru witaminy D i anemii, niezależnie od frakcji wyrzutowej lewej komory u chorych z niewydolnością serca.

Słowa kluczowe: niewydolność serca, czynniki prognostyczne, niedobór witaminy D, anemia

Conflict of interest

None declared.

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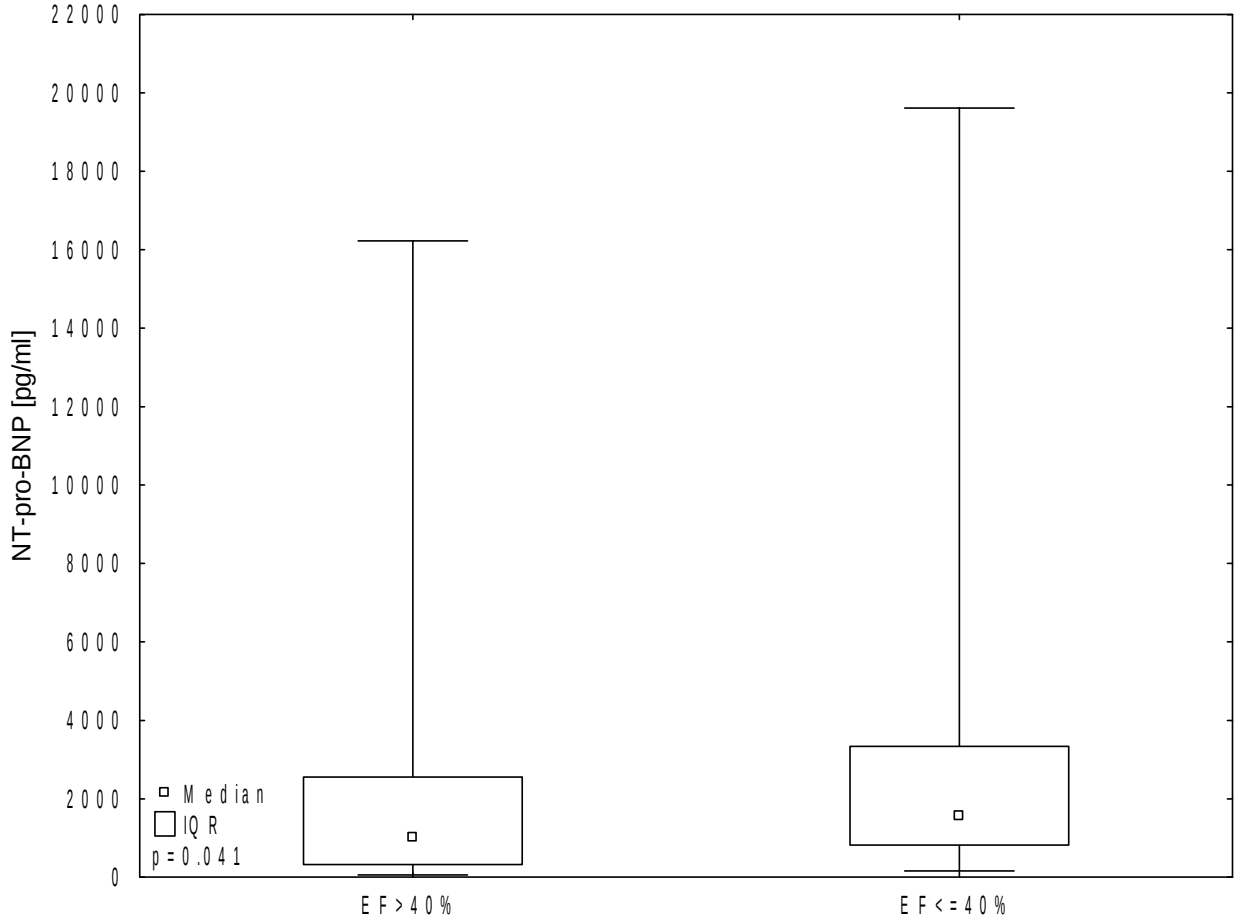

Figure 1. Box and whiskers plot of NT-pro-BNP distribution between HFmrEF and HFrEF groups.

Table 1. Clinical characteristics of the study group.

Characteristics	**HFmrEF (LVEF:41–49%)**	**HFrEF (LVEF ≤ 40%)**	p-value
Patients count [n/%]	38 (44%)	49 (56%)	-
Age [mean/SD]	61.58 (±9.79)	60.22 (±10.65)	0.544
BMI [kg/m^2]	27.51 (±4.64)	28.72 (±3.58)	0.170
25(OH)D [ng/mL]	16.93 (±9.02)	19.24 (±9.68)	0.260
Vitamin D deficiency [n/%]	25 patients (65.79%)	24 patients (48.98%)	0.177

Hemoglobin [g/dL]	14.22 (13.1–15.15)	14.21 (12.85–15.31)	0.900
Anemia [n/%]	9 patients (23.68%)	15 patients (30.61%)	0.635
NT-pro-BNP [pg/mL]	1031 (321.5–2555)	1585 (819.2–3331)	**0.041**
LVEF [%]	47.5 (45–49)	30 (25–35)	< **0.001**
NYHA class [median/IQR]	2 (1–3)	2 (2–3)	**0.009**
NYHA class > II [n/%]	10 patients (26.32%)	24 patients (48.98%)	0.054
Diabetes type 2 [n/%]	7 patients (18.42%)	18 patients (36,73%)	0.102
Arterial hypertension [n/%]	29 (76.32%)	36 (73.47%)	0.957
Hyperlipidemia [n/%]	15 (39.47%)	23 (46.94%)	0.632
Ischemic etiology [n/%]	20 patients (52.63%)	28 patients (57.14%)	0.675
Pharmacological treatment only [n/%]	21 patients (55.26%)	29 patients (59.18%)	0.714
PCI procedure [n/%]	5 patients (13.16%)	13 patients (26.53%)	0.183
CABG procedure [n/%]	2 patients (5.26%)	1 patient (2.04%)	0.578
Valve operation [n/%]	7 patients (18.42%)	3 patients (6.12%)	0.096
Death in 1year follow-up [n/%]	3 patients (7.89%)	6 patients (12.24%)	0.726
Death in 10year follow-up [n/%]	16 patients (42.11%)	30 patients (61.22%)	0.076

Data are shown as median with interquartile range (IQR) and mean with standard deviation (SD), depending on normality distribution of a certain parameter or as frequencies and percentages in certain groups. p value refers to T-test, UMW and Chi^2 test with yates correction when applicable.

BMI — body mass index; CABG — coronary artery bypass grafting; LVEF — left ventricular ejection fraction; NT-pro-BNP — N-terminal-pro hormone B-type natriuretic peptide; NYHA — New York Heart Association; PCI — percutaneous coronary intervention

Table 2. Prognostic factors in patients with HF (entire study population), HFmrEF and HFrEF - the results of univariate logistic regression analysis.

Variable	**HF patients n = 87**		**HFmrEF (LVEF:41–49%) n = 38**		**HFrEF (LVEF ≤ 40%) n = 49**	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
1 year follow-up mortality						
Vitamin D deficiency	1.63 (0.38–6.98)	0.510	-	-	0.95 (0.17–5.27)	0.957
Anemia	2.32 (0.57–9.5)	0.242	1.69 (0.13–21.12)	0.685	2.58 (0.46–14.62)	0.283
Cardiovascular re-hospitalization (1year follow-up)						
Vitamin D deficiency	1.003 (0.4–2.52)	0.995	0.53 (0.11–2.49)	0.417	0.74 (0.22–2.49)	0.625
Anemia	0.88 (0.3–2.55)	0.810	1.43 (0.27–7.44)	0.674	0.61 (0.15–2.45)	0.483
10 year follow-up mortality						
Vitamin D deficiency	2.64 (1.1–6.32)	**0.029**	3.61 (0.8–16.35)	0.096	3.25 (0.97–10.92)	0.057
Anemia	1.72 (0.66–4.51)	0.269	2.05 (0.45–9.29)	0.354	1.4 (0.39–4.997)	0.604
NYHA >II	2.73 (1.11–6.71)	**0.029**	-	-	-	-
Ischemic etiology	1.35 (0.58–3.16)	0.484	-	-	-	-

CI — confidence interval; NYHA — New York Heart Association; OR — odds ratio

Table 3. Multivariate analysis in predicting 10-year mortality in patients with heart failure.

Variable	OR (odds ratio)	Lower 95% Confidence interval	Upper 95% Confidence interval	p-value
NYHA class > II	2.52	1.002	6.330	**0.0495**

Vitamin D deficiency	2.44	0.999	5.960	**0.0500**

CI — confidence interval; NYHA — New York Heart Association; OR — odds ratio