https://doi.org/10.5272/jimab.2024304.5910

Journal of IMAB
ISSN: 1312-773X
https://www.journal-imab-bg.org

Journal of IMAB. 2024 Oct-Dec;30(4)

Original article

PREDICTORS OF MORTALITY AMONG DEPRESSIVE PATIENTS WITH HFPEF, HFMEF, HFREF

Ralitsa Pancheva, Ventsislava Pencheva, Emil Manov, Vasil Kolev, Blagovest Stoimenov.
Department of Propaedeutics of Internal Diseases, UMHAT "Alexandrovska"; Medical Faculty, Medical University – Sofia, Bulgaria.

ABSTRACT

Background: Heart failure patients accompany heightened risks of depression. The coexistence of these diseases not only increases mortality rates but also leads to more frequent hospitalizations.

Aim: This study aims to analyze prognostic factors in hospitalized HF patients with depression.

Materials and methods: A single-center cohort study enrolled HF patients admitted between January 2019 and January 2022. Tests for depression (Hamilton Depression Rating Scale; HAM-D) were performed on all participants.

Results: The study cohort comprised 114 patients with an average age of 70.6 ± 9.6 years. Most patients were classified as New York Heart Association (NYHA) Class II/III prior to the index admission, and around 60% exhibited a left ventricular ejection fraction (LVEF) above 50%. Depression severity varied across HF subgroups. CAD and secondary pulmonary hypertension are crucial in determining the prognosis of patients with HF with preserved (HFpEF) and reduced ejection fraction (HFrEF). Anemia is a common factor increasing mortality in HFpEF and with HF with mid-range ejection fraction (HFmEF). Diabetes, especially insulin-dependent, affects survival in patients with HFpEF, while it does not impact prognosis in other subgroups. Advanced age and chronic kidney disease are determining factors for survival in patients with HFpEF. Atrial fibrillation, alcohol abuse and previous stroke are factors associated with higher mortality in patients with HFmEF.

Conclusions: This study provides valuable insights for clinicians, aiding in the identification of high-risk patients and the implementation of proactive measures for their management, thereby improving the care of HF patients with depression.

Keywords: Depression; mortality; predictors, heart failure, ejection fraction,

BACKGROUND

Heart failure (HF) marks the advanced phase of cardiovascular diseases (CVDs). Despite notable progress in diagnosing, treating, and handling HF, patients continue to confront heightened risks of mortality and readmission. Recent research underscores mortality and readmission rates of 17.4% and 43.9% among acute HF patients and 7.2% and 31.9% among those with chronic heart failure (CHF). [1]

In a study conducted in Bulgaria, the authors pointed out that patients' willingness to pay for pharmacotherapy of ishaemic heart disease (IHD) is relatively low, so it is supposed to be the same with HF. [2] Patients with HF face a heightened risk of depression [3] and this condition affects approximately 20% of patients with chronic heart failure (CHF). [4] This co-occurrence of depression with CHF is linked to elevated mortality rates, increased hospitalizations, and greater healthcare resource utilization. Moreover, events such as CHF-related hospitalizations tend to exacerbate depressive symptoms further. [5]

The current guidelines from the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) for heart failure (HF) recommend screening for depression in HF patients and subsequent treatment when necessary. [6, 7]

Presently, depression symptoms are predominantly assessed through questionnaire scales like the Patient Health Questionnaire (PHQ)-9, Beck Depression Inventory (BDI), Self-Rating Depression Scale, and Hamilton Depression Scale (HAMD). [8, 9] However, due to variations among these scales and individual subjectivity, they still somewhat compromise the accuracy of depression screening and diagnosis in patients with HF. [10]

Developing a predictive model holds significant value for early disease screening, guiding clinical treatment, and offering prognosis insights. Hence, constructing such a model using clinically objective variables might prove more effective and timely in identifying depressive symptoms compared to conventional subjective scales.

AIM

This study seeks to analyze the factors influencing the prognosis of hospitalized HF patients. Additionally, it aims to establish a dependable predictive model for depressive symptoms in hospitalized HF patients and furnish objective indicators for the early detection and treatment of these patients' depressive symptoms.

MATERIALS AND METHODS:

The study is a single-center cohort study that enrolled patients with heart failure (HF) admitted to the Department of Propaedeutics of Internal Diseases, Cardiology clinic at University Hospital "Alexandrovska" between January 2019 and January 2022. Approval for the study was obtained from the Ethics Committee of the University Hospital "Alexandrovska". This study encompassed hospitalized patients diagnosed with heart failure (HF) who met the established diagnostic criteria for the condition. [6, 7].

Baseline data on hospitalized patients were collected through interviews, medical records, and direct measurements. This encompassed:

1. Demographic baseline information: Gender, Age, Body mass index (BMI), Blood pressure, History of cardiovascular disease (CVD), and Comorbidities.

2. Echocardiography was conducted within 48 hours of admission using ultrasound equipment (GE Vivid 95) to measure left ventricular ejection fraction (LVEF) using the biplane Simpson method.

3. ECG-related parameters: Heart rate (HR), QRS interval.

4. Blood tests for routine laboratory parameters: Hematology, Biochemical parameters.

After discharge, all heart failure (HF) patients were prescribed guideline-directed HF medication unless contraindicated. They were scheduled for follow-up visits at 1, 6, 12 and 24 months post-discharge. The study's endpoint event was defined as all-cause mortality and survival. The Hamilton Depression Rating Scale (HAM-D or HDRS) is a widely used tool for evaluating depression symptoms. It has been employed in numerous important studies on depression and its treatment. The scale is typically administered by clinicians following either a structured or unstructured interview with the patient to assess their symptoms. A total score is obtained by summing the individual responses from each item.

- Scores below 7 usually indicate no depression or remission.
- Scores ranging from 7 to 17 suggest mild depression.
- Scores between 18 and 24 reflect moderate depression.
- Scores of 25 or higher indicate severe depression.

The statistical analysis was conducted as follows:

Statistical analysis was performed using SPSS version 23.

Normally distributed data were reported as mean ± standard deviation (SD), while categorical variables were expressed as frequency or percentage. Differences between groups were assessed using the chi-square test for categorical variables, one-way analysis of variance for normally distributed continuous variables, and Mann–Whitney U tests for skewed continuous variables.

Kaplan–Meier curves were employed to evaluate differences in the risk of endpoint events between groups, with log-rank tests used to determine statistical significance. Variables with a significance level of $P < 0.10$ in the univariate Cox regression analysis were included in the multivariate regression analysis, utilizing bidirectional elimination (entry and exit criteria set at $P < 0.05$ and $P > 0.10$, respectively). Cox regression analysis was utilized to identify predictors for mortality in HF patients with depression, with hazard ratios and 95% confidence intervals (CI) used to express the degree of association. Cut-off points were determined using ROC analysis, and the area under the receiver operating curve (AUC) was calculated.

RESULTS

We screened 332 patients, hospitalized patients with heart failure (HF). The enrolled sample consisted of 114 patients who underwent study eligibility screening. The study cohort comprised 51 (44.7%) men and 63 (55.3%) women. The average age at enrollment was 70.6 ± 9.6 years. Most patients were classified as New York Heart Association (NYHA) Class II/III prior to the index admission, and around 60% exhibited a left ventricular ejection fraction (LVEF) above 50%. (Table 1).

Table 1. Distribution of depression, accessed by HAMD scale, in subgroups HF patients.

Severity of depression	HFpEF	HFmEF	HFrEF
Mild	26 (37.7%)	6 (26.1%)	7 (28%)
Moderate	31 (44.9%)	9 (39.1%)	10 (40%)
Severe	10 (14.5%)	7 (30.4%)	5 (20%)
Very severe	2 (2.9%)	1 (4.3%)	3 (12%)

Table 2. CVD, risk factors and comorbidities in subgroups HF patients with depression.

Comorbidities	HFpEF	HFmEF	HFrEF	p
Mean age	69.3±9.2	74.5±8.2	70.4±11.2	0.044
Male	34.8%	60.9%	59.1%	0.096
Arterial hypertension	97.1%	100%	95.5%	0.254
Insulin-dependent DM	10.1%	13.0%	4.5%	0.014
Non-insulin-dependent DM	30.4%	30.4%	27.3%	0.523
Coronary artery disease	20.3%	26.0%	40.9%	0.004
Dyslipidemia	34.8%	34.8%	27.3%	0.654
Peripheral artery disease	2.4%	13.0%	27.2%	0.016
Chronic kidney disease	11.6%	34.8%	50.0%	0.031
Previous myocardial infarction	7.7%	8.7%	27.3%	0.008
Aortocoronary bypass	5.8%	4.3%	2.1%	0.012
Previous stroke	11.6%	39.1%	31.8%	0.001
Mitral stenosis	2.8%	0%	13.5%	0.002
Mitral insufficiency	88.4%	100%	95.5%	0.023
Aortic stenosis	10.1%	4.3%	9.0%	0.032
Aortic insufficiency	36.2%	43.5%	59.1%	0.007
Secondary tricuspidal insufficiency	87.3%	91.3%	90.9%	0.123
Anemia	24.6%	43.5%	36.4%	0.048
NYHA III	98.5%	87.0%	81.8%	0.025
NYHA IV	1.5%	13.0%	18.2%	0.011
Atrial fibrillation	36.1%	73.8%	68.2%	0.045
Alcohol abuse	49.3%	52.2%	50.9%	0.231

During the follow-up period, a total of 36 patients (31.6% of the sample) died. 15 (41.7%) of these patients were with HFrEF, 9 (25.0%) with HFmEF and 12 (33.3%) with HFpEF.

HFpEF and depression

In the cohort of HFpEF, the presence of valvular heart disease is associated with increased mortality. Valvular heart defects associated with reduced survival in these patients include mitral stenosis (16.9%, p=0.008), aortic stenosis (25.0%, p=0.041), and secondary tricuspid regurgitation (59.2%, p=0.020). Men have higher mortality than women in this group, 58.3% vs. 41.7% (p=0.032). Patients with insulin-treated diabetes mellitus (DM) have increased mortality (25.0% vs. 7.0% with non-insulin-dependent DM, p=0.040). The presence of coronary artery disease (CAD) increases mortality in patients with depression and HFpEF (33.3% vs 17.6% without CAD, p=0.007), especially in those with a history of myocardial infarction (MI) (16.7% vs 1.8%, p=0.021) and following aortocoronary bypass (ACB) surgery (8.3% vs 0%, p=0.028). Peripheral artery disease is also associated with higher mortality in depressive patients with HFpEF (8.3% vs. 0%, p=0.028). Using ROC analysis, we found that patients with a pulmonary pressure of 50 have a higher risk of mortality (sensitivity 65%, specificity 85%, AUC 0.71, p=0.039). Anemia with hemoglobin below 117g/l in women (sensitivity 67%, specificity 75%, AUC 0.69, p=0.045) and below 125 g/l in men (sensitivity 64%, specificity 81%, AUC 0.72, p=0.033) is factor corresponding with reduced survival in this cohort. With multivariate Cox regression analysis, we create a model of factors associated with reduced survival in patients with HFpEF and depression. (Table 3)

Table 3. The model of factors which increase mortality in patients with HFpEF and depression.

Predictor	HR	CI	P
Secondary tricuspidal regurgitation (fig.1)	2.87	1.33-4.45	0.027
Pulmonary pressure > 50 mmHg (fig.2)	3.58	1.56-5.66	0.035
Previous myocardial infarction	4.25	2.21-8.56	0.032
Insulin-dependent DM	5.56	2.36-7.86	0.015

Fig. 1. Kaplan-Maier curve showed reduced survival of patients with secondary tricuspidal regurgitation

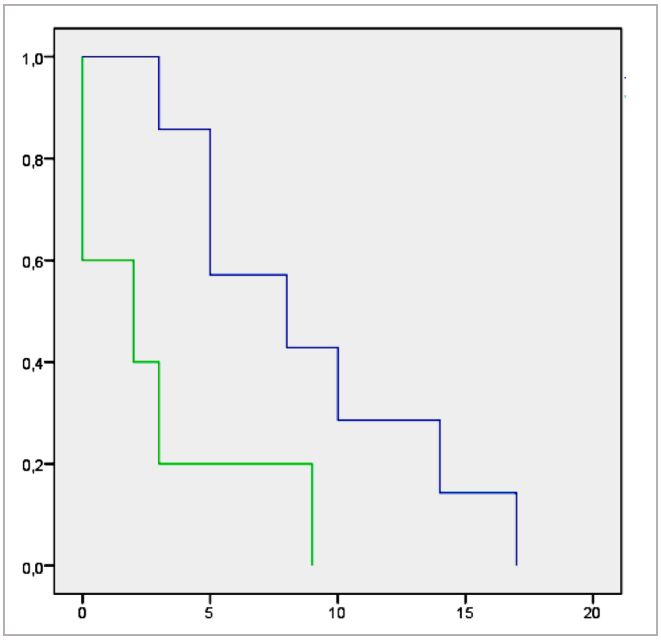
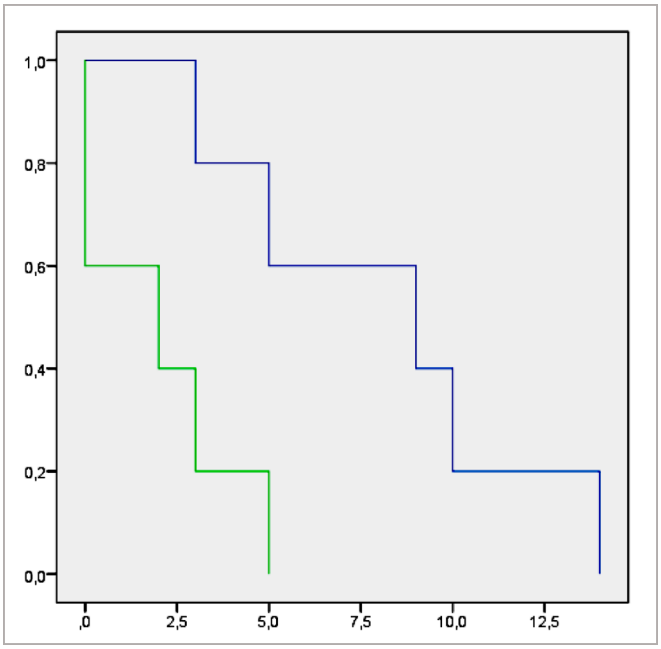


Fig. 2. Kaplan-Maier curve showed reduced survival of patients with pulmonary pressure above 50 mmHg



HFmEF and depression

In this group, we found that alcohol consumption increased the risk of mortality in patients with HFmEF and depression by 33.3% vs 21.4% (p=0.032). The presence of atrial fibrillation also reduces the survival of these patients (48.7% vs 18.5%, p=0.002). Patients with previous strokes have a higher mortality rate (44.4% vs. 21.2%, p=0.023). Comorbidities like COPD were associated with reduced survival (22.2% vs. 0% (p=0.045). End-systolic volume >75 ml corresponds with a higher mortality rate (sensitivity 65%, specificity 74%, AUC=0.75, p=0.044). Anemia with hemoglobin below 110 g/l (sensitivity 92%, specificity 70%, AUC=0.69, p=0.006) is also factor correlated with mortality in this cohort. In this group, alcohol consumption (HR 2.55, 95%CI 1.47-6.21, p=0.012) and ESV > 75 ml (HR 4.42, 95%CI 2.16-10.87, p=0.024) were predictors of reduced survival on multivariate Cox regression analysis.

HFrEF and depression

Elderly patients >66 years with HFrEF and depression have a higher mortality rate (sensitivity 87%, specificity 72%, AUC=0.77, p=0.045). Presence and severity of CAD were a risk factor for mortality of these patients - 14.3% with single vessel disease vs 6.7% without CAD (p=0.025); 15.8% with two-vessel disease vs 5.2% (p= 0.014) and 26.7 with three vessel disease vs 12.3% without CAD (p=0.011), CKD is another comorbidity that reduce survival in this cohort of patients. Many echocardiographic parameters were associated with mortality in this group: left atrial (LA) length> 58 (sensitivity 80%, specificity 62%, AUC=0.89, p=0.017).; systolic PA pressure > 40 mmHg (sensitivity 83%, specificity 86%, AUC=0.86, p=0.011); PLAX right ventricular outflow tract (RVOT) >34 (sensitivity 77%, specificity 77%, AUC=0.78, p=0.043). With multivariate COX regression analysis we found that age >66 (HR 5.31, 95%CI 2.24-8.69, p=0.015); CKD (HR 6.25.31, 95%CI 3.11-11.77, p=0.007) and pulmonary hypertension with systolic PA pressure>40 mmHg (HR 3.71, 95%CI 1.66-7.44, p=0.032);

DISCUSSION

Depression has emerged as a significant consideration in patients with heart failure (HF), offering valuable insights for prognosis stratification in individuals with HF and associated comorbidities. While current HF guidelines do not advocate for routine depression screening in HF patients, contemporary guidelines on cardiovascular disease prevention underscore the importance of assessing mental health as a modifier of risk. This is especially pertinent in HF patients with depression, as evidenced by recent studies. Coping with the stigma of psychiatric illness is a contemporary problem, and it is related not only to the patients, their relatives, the general practitioners and the medical staff working in the mental health system but also to the whole society. [14]

Many studies indicated that depressive symptoms were associated with poorer prognosis in HF. Rutledge's et al. revealed that concurrent depression was a negative prog-

nostic indicator for overall mortality in patients with heart failure (adjusted relative risk: 2.10, 95% CI 1.71–2.58). [3] Similarly, another meta-analysis involving 9 studies and 4012 heart failure patients found that those experiencing depression exhibited a significantly elevated risk of all-cause mortality compared to non-depressed counterparts (HR = 1.51, 95% CI: 1.19–1.91). Subgroup analyses indicated that major depression posed a substantially greater risk of all-cause mortality in HF patients (HR = 1.98, 95% CI: 1.23–3.19) than mild depression, which showed no significant association with mortality risk (HR = 1.04, 95% CI: 0.75–1.45). [10] Similarly, a 20-year follow-up study revealed that major depression significantly heightened the risk of all-cause mortality in HF patients compared to those without depression (adjusted HR = 1.64, 95% CI: 1.27–2.11, P = 0.001), underscoring depression's independent role as a long-term prognostic risk factor in HF patients.[12] Only one study provided a univariate hazard ratio (HR) for cardiovascular mortality. Additionally, three studies presented multivariate HRs for cardiovascular mortality. Following adjustment for cardiovascular risk factors, depressive symptoms did not exhibit a significant impact. [13] According to a study involving 238 people, 75 of which had a close relative with a psychiatric illness and 154 did not have such, all respondents tend to correctly refer to the relevant specialist, recognizing the main specifics in the work of psychologists and psychiatrists; express a realistic view that not all persons with mental illness are dangerous, share their endorsement of receiving drug therapy when necessary. [14]

The aim of our study is to analyze the mortality of patients with depression and heart failure compared to their ejection fraction and to identify the factors in each subgroup that are associated with increased mortality.

This is the first study to examine mortality and prognostic factors in the individual subgroups of HF. CAD is crucial in determining the prognosis of patients with HF with preserved and reduced ejection fraction, also, the severity of CAD corresponds with a higher mortality rate. Secondary pulmonary hypertension serves as a common predictor of mortality in patients with HF with preserved and reduced ejection fraction. Conversely, anemia is a common factor in increasing mortality in HFpEF and HFmEF. Diabetes, especially insulin-dependent, affects survival in patients with HFpEF, while it does not impact prognosis in other subgroups. Advanced age and chronic kidney disease are determining factors for survival in patients with HFpEF. Only in the HFmEF group is the combination of depression with alcohol abuse associated with increased mortality. Men with depression and HFpEF exhibit significantly higher mortality compared to females. Atrial fibrillation and previous stroke are factors associated with higher mortality in patients with HFmEF. Valvular heart diseases correspond with reduced survival in HFpEF patients.

Our extensive literature review overwhelmingly indicates the significant burden of mortality and morbidity associated with depression in patients with heart failure. This highlights the importance of increasing clinician awareness regarding the use of user-friendly screening tools to effectively assess depressive symptoms in these individuals. Furthermore, it underscores the necessity for further evaluation and appropriate referral to specialized clinicians for individuals demonstrating a high likelihood of depression. The data from the obtained algorithms would be useful for the timely detection of high-risk patients and their timely active treatment, which would improve the prognosis of patients with heart failure and depression.

CONCLUSION

This is the first study examining mortality in patients with depression and the subgroups of heart failure. The data obtained can be extremely useful in improving the prognosis and timely treatment of patients with HF and depression. The resulting predictors of each group can allow healthcare professionals to identify high-risk patients and take proactive measures for their treatment.

REFERENCES:

1.Duan J, Huang K, Zhang X, Wang R, Chen Z, Wu Z, et al. Role of depressive symptoms in the prognosis of heart failure and its potential clinical predictors. *ESC Heart Fail.* 2022 Aug;9(4):2676-2685. [PubMed]

2. Grigorov E, Naseva E, Getov I. Study of patients' willingness-to-pay for pharmacotherapy of ischemic heart disease. *Arch Balk Med Union.* 2011 Sep;46(3):177-179.

3.Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure: a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol.* 2006;48(8):1527–37. [PubMed]

4. Sokoreli I, Pauws SC, Steyerberg EW, de Vries GJ, Riistama JM, Tesanovic A, et al. Prognostic value of psychosocial factors for first and recurrent hospitalizations and mortality in heart failure patients: insights from the OPERA-HF study. *Eur J Heart Fail.* 2018 Apr; 20(4): 689–696. [PubMed]

5. O'Connor CM. Depression in heart failure: Beyond a SADHART. *JACC Heart Fail.* 2018 Oct;6(10):885-886. [PubMed]

6.Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et

al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2016 Aug;18(8):891–975. [PubMed]

7. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013 Oct 15;62(16):e147-239. [PubMed]

8. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, et al. The global health and economic burden of hospitalizations for heart failure: Lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol.* 2014 Apr 1;63(12):1123-1133. [PubMed]

9. Koehler J, Stengel A, Hofmann T, Wegscheider K, Koehler K, Sehner S, et al. Telemonitoring in patients with chronic heart failure and moderate depressed symptoms: Results of the Telemedical interventional monitoring in heart failure (TIM HF) study. *Eur J Heart Fail.* 2021 Jan;23(1):186-194. [PubMed]

10. Sbolli M, Fiuzat M, Cani D, O'Connor CM. Depression and heart failure: The lonely comorbidity. *Eur J Heart Fail.* 2020 Nov;22(11):2007-2017. [PubMed]

11. Fan H, Yu W, Zhang Q, Cao H, Li J, Wang J, et al. Depression after heart failure and risk of cardiovascular and all cause mortality: a meta analysis. *Prev Med.* 2014 Jun;63:36-42. [PubMed]

12. Freedland KE, Carney RM, Rich MW, Steinmeyer BC, Skala JA, Davila Roman VG. Depression and multiple Rehospitalizations in patients with heart failure. *Clin Cardiol.* 2016 May;39(5):257-62. [PubMed]

13. Diez-Quevedo C, Lupón J, González B, Urrutia A, Cano L, Cabanes R, et al. Depression, antidepressants, and long-term mortality in heart failure. *Int J Cardiol.* 2013 Aug 20;167(4):1217-25. [PubMed]

14. Dimitrova M, Dilkov D, Marinova Y, Grigorov N. [Associative and family stigma research in people with psychiatric disorders – in benefit of the general practitioners and their patients.] [in Bulgatian] *General Medicine.* 2020; 22(6):37-44. [Internet]

Please cite this article as: Pancheva R, Pencheva V, Manov E, Kolev V, Stoimenov B. Predictors of mortality among depressive patients with HFpEF, HFmEF, HFrEF. *J of IMAB.* 2024 Oct-Dec;30(4):5910-5915.
[Crossref - https://doi.org/10.5272/jimab.2024304.5910]

Received: 30/04/2024; Published online: 06/12/2024

Address for correspondence:
Blagovest Stoimenov,
Department of Propaedeutics of Internal Diseases, UMHAT "Alexandrovska";
Medical Faculty, Medical University - Sofia;
1, St Georgi Sofiiski Str., Sofia, Bulgaria;
E-mail: stoimenov90@gmail.com,