UNIVERSITY OF MEDICINE AND PHARMACY

“CAROL DAVILA”, BUCHAREST

DOCTORAL SCHOOL

FIELD - MEDICINE

Mean platelet volume: a prognostic parameter in patients with heart failure

SUMMARY OF DOCTORAL THESIS

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2024

SUMMARY

I. GENERAL PART - CURRENT STATE OF KNOWLEDGE

Despite all medical efforts and discoveries, heart failure (HF) remains one of the most important and frequent public health problems, with still very high mortality and morbidity and high hospitalization rates, especially for elderly patients. In Romania, 1 out of 3 patients are rehospitalized or die in the first year after the last hospitalization for HF [1], and most hospitalizations for HF are due to its decompensation under the influence of some precipitating factors [2].

Although diagnostic and treatment methods are increasingly complex, the hospitalization rate and mortality are still very high, which is equal to a large consumption of financial resources.

In these general conditions and especially for Romania, through the present study, I aimed to identify a predictive factor that could be used to assess the risk of rehospitalization and mortality in the first year from the last admission of a patient with decompensated HF.

The parameter I set out to investigate is the mean platelet volume (MPV). This is very easy to obtain (by collecting whole blood, being part of the usual blood count) and not expensive, being measured by electrical impedance by hematological auto analyzers. It is expressed in phentoliters (fL), and its normal values are between 7.2-11.7 [3].

Since HF is currently associated with a negative prognosis representated by increased mortality and reduced quality of life, by proving the existence of a possible prognostic parameter such as MPV included in any blood count, could provide in the future salutary solutions for prophylactic intervention in terms of management in patients with decompensated HF.

Identifying the cut-off value above which MPV could predict a negative prognosis in patients with decompensated HF, would represent an easy and inexpensive prognostic tool available to any medical practitioner.

The correlation between MPV and decompensated HF is poorly understood, and the mechanisms are unclear, with limited studies showing that MPV could be an indicator of platelet activation in patients with acute HF [4].

Regarding the current state of knowledge in the medical literature regarding MPV as a possible negative prognostic factor in patients with HF, studies are limited, there being three in this respect: the study conducted by Hayati Kandis et al. [5], the study conducted by Budak et al. [6], the study conducted by Hakki Kaya and his collaborators [7].

One of the studies cited in the current medical literature that focused on the prognostic impact of MPV on patients with HF is the study conducted by Hayati Kandis et al. [5], on a population of 207 patients with HF, of whom 136 with decompensated HF and 71 with NYHA classes I-III HF, and whose results showed the following: 1) the MPV value is much higher in patients with decompensated HF compared to those with stable HF, 2) an increased MPV on admission could be a possible predictor of in-hospital and 6-month mortality in patients with decompensated HF.

The study conducted by Budak et al. [6] on a group of 319 patients with HF, which was subdivided into 2 groups, namely a group of 190 patients admitted to emergency for acute HF and a group of 129 patients with chronic HF stable, showed a positive correlation between BNP and MPV values, by highlighting that the patients with decompensated HF had elevated MPV values.

Another study cited in the medical literature that focused on the prognostic impact of MPV in the population of patients with HF was the one conducted by Hakki Kaya and his collaborators [7] on a group of 197 patients with NYHA classes I-III HF in sinus rhythm (SR) and concluded that MPV could be a possible independent predictor of hospitalization, based on two possible hypotheses.

a) The first hypothesis

An increases MPV value, as an independent predictor of hospitalization in patients with HF, could be explained by the increase in platelet activation as a consequence of the activation of compensatory neurohormonal mechanisms (increase in catecholaminergic activity, renin-angiotensin system activity, and inflammatory activity - expressed by an increased release of cytokines), all these mechanisms being triggered in patients at high risk of decompensation [8, 9].

This hypothesis is supported by several studies, among which I mention: 1) the study conducted by Karabacak and his collaborators [10] which investigated the impact of treatment with Carvedilol and Nebivolol on MPV values in patients with HF of non-ischemic etiology, and whose results pointed out that beta-blockers reduce mortality and hospitalization in patients with heart failure by reducing catecholaminergic activity [11], and this latter effect leads to a decrease in the MPV level in the patient with HF; 2) the study conducted by Alper and his collaborators which revealed that resynchronization therapy in patients with HF significantly reduced the level of MPV, the pathophysiological explanation of this phenomenon being the reverse remodeling of left ventricle secondary to the effect of resynchronization therapy, the reverse remodeling itself contributing to the reduction of activity catecholaminergic and inflammatory and thus reducing the MPV level by decreasing platelet activity [12].

b) The second hypothesis

The increase in mean platelet volume as an independent predictor of hospitalization in patients with heart failure could be explained by episodes of paroxysmal atrial fibrillation, which may occur during hospitalization. This hypothesis is supported by previous studies that showed that the average platelet volume value is higher in patients with permanent and paroxysmal atrial fibrillation (AFib) compared to patients with sinus rhythm [13, 14].

II. THE SPECIAL PART

Working hypothesis and general objectives

Based on the information mentioned above, I have launched the following working hypotheses:

1) Patients with decompensated chronic HF might have a higher MPV value compared to patients with stable chronic HF.

2) The increased value of MPV at admission could represent a new indicator of prognostic estimation in patients with HF, by correlating it with 3-months and 6-months hospitalization, prolonged duration of hospitalization as well as with 1-year mortality from cardiac causes.

3) Patients with chronic HF and AFib rhythm on admission, history of stroke, history of ischemic heart disease (IHD), history of diebetes mellitus (DM) or associated non-cardiac complications (nitrogen retention, hyponatremia, hyperkalemia, anemia, sepsis), could have a higher MPV value.

4) Increased MPV at admission could correlate with left ventricle systolic dysfunction translated by left ventricle ejection fraction (LVEF) below 50%.

5) The increased value of MPV at admission could correlate with an increased value of NT pro BNP in patients with HF.

6) Increased MPV value at admission could correlate with increased red cell distribution width (RDW) value in HF patients.

The main objective of my study will be to test the working hypothesis according to which MPV could represent a new prognostic factor for patients with HF, by identifying a relationship between its value and the rate of hospitalizations at 3 and 6 months, the rate of mortality at 1 year, as well as the extended length of hospitalization.

The secondary objectives of my study will be represented by testing the working hypotheses presented at points 3), 4), 5) and 6).

General research methodology

In order to test the above-mentioned working hypotheses, I carried out the research in a retrospective manner, in the Cardiology Department of the "Bagdasar-Arseni" Emergency Hospital, the target population being patients with chronic heart failure (HF), both stable as well as decompensated.

The research was divided into 2 studies, the first study being a concept pilot study conducted on 130 patients and focusing on patients with chronic decompensated HF (NYHA class IV HF/ APE), and the second study was conducted on a larger group of patients with chronic HF (260 patients) including patients with decompensated chronic HF and patients with stable chronic HF (NYHA class II HF). Both studies focused on the research parameter of interest, namely the average platelet volume (MPV).

The inclusion criteria were:

1) patients with both decompensated chronic HF - defined by NYHA functional class III/IV HF or acute cardiogenic pulmonary edema (APE), as well as patients with stable chronic HF - defined by NYHA class II HF, regardless of left ventricular ejection fraction.

2) patients in whom MPV was available.

3) patients for whom data on hospitalization and mortality at 1 year were available.

The exclusion criteria were:

1) patients without defining criteria for chronic HF.

2) patients in whom MPV was not available.

3) patients for whom data on hospitalization and mortality at 1 year were not available.

4) diseases with a survival time of less than 1 year.

5) neoplasias.

6) chronic kidney disease.

7) acute coronary syndrome (acute myocardial infarction with / without ST segment elevation).

8) acute stroke.

9) acute pulmonary thromboembolism (PE) or deep vein thrombosis (DVT).

10) autoimmune diseases.

11) thrombocytopenia.

In the case of both studies, the following data were collected:

1) demographic (age, sex, background).

2) anthropometric data (weight, height, body mass index).

3) personal pathological history data.

4) data related to the cardiac visa medication used.

5) associated comorbidities (hypertension (HT), diabetes mellitus (DM), dyslipidemia, history of myocardial infarction (MI), history of PE or DVT, history of stroke, sepsis).

6) laboratory data (NT pro BNP at admission and at discharge, presepsin at admission, erythrocyte sedimentation rate (ESR) at admission, fibrinogen at admission, serum creatinine (Cr) at admission and at discharge, serum ionogram at admission – sodium, potassium, complete blood count at admission – hemoglobin (Hb), erythrocyte indices (mean erythrocyte volume (MEV), mean hemoglobin concentration (CHEM), mean erythrocyte hemoglobin (HEM), red cell distribution width (RDW), leukocyte count, platelet count, mean platelet volume (MPV).

7) echocardiographic data (HF with reduced LVEF defined as LVEF below 50% or HF with preserved LVEF defined as LVEF above 50%, left atrial diameter (LA), left ventricular diameter (LV), presence or absence of pulmonary hypertension (PH)).

8) electrocardiographic data (cardiac rhythm at admission and discharge, left bundle branch block/major right bundle branch block).

9) data related to the duration of hospitalization.

10) data related to rehospitalization and mortality (dichotomized by yes or no).

Rehospitalizations were tracked either by consulting the hospital's computer system (Hippocrates) or by telephone, in cases where hospitalizations for HF decompensation were made in another hospital.

Death at 1 year was documented by phone call or by consulting the hospital IT system if the event occurred during one of the readmissions at 1 year after the initial admission.

My study was carried out in accordance with the conditions found in the October 2008 Declaration of Helsinki and as it did not involve the testing of experimental procedures or treatments on patients/animals, but only the retrospective collection of some clinical and paraclinical data respecting patient confidentiality, the present study does not require the approval of the Ethics Commission of the "Carol Davila" University of Medicine and Pharmacy, Bucharest. According to the Ethics Commission of the "Carol Davila" University of Medicine and Pharmacy, ethics guidance, approval is only required for interventional studies involving interventions or drug testing on human/animal subjects.

Referring to the signed agreement of the patients regarding the collection of their medical data for didactic/scientific purposes, it should be noted that all the medical sheets of the Cardiology Clinic of "Bagdasar-Arseni" Emergency Hospital have the signed consent of the patients since admission.

Access to the hospital's medical archive was obtained with the consent of the Manager and Medical Director "Bagdasar-Arseni" Emergency Hospital.

In the case of both studies, the above-mentioned clinical and paraclinical data were collected in the form of a database created by means of the Microsoft Excel 1997-2003 program.

The statistical analysis of the data from the first study was performed using the statistical analysis software SPSS version 18.0. For the main study parameter MPV, the following statistical procedures were performed: mean and standard deviation, and confidence interval for a p-value of 1%.

Using the Student's T-test, I compared the mean MPV value in the group of patients who had this variable with that of the group of patients who did not have this variable.

Pearson's coefficient was used to analyze the correlation between NT pro BNP and MPV.

Boxplots that looked at the distribution of MPV values were used for the graphical representations of the results in the first study.

Statistical results from the second study were obtained by applying linear and logistic regression models using Python version 3.10.

The linear regression model was applied to the continuous dependent variables: NT pro BNP, presepsin, RDW, the transverse dimension of LA, the transverse dimension of LV, LVEF value, creatinine value, Hb value, and the regression model logistic regression was applied to binary dependent variables: class II/III/IV NYHA HF, APE, sinus rhythm (SR), atrial fibrillation

(AFib), reduced LVEF, preserved LVEF, dilated LA, dilated LV, PH, smoking status, sepsis, history of stroke/ IHD, DM, a medication used (loop diuretic, mineralocorticoid antagonist (MRA) medication, angiotensin converting enzyme inhibitor (ACEI)).

In the case of linear regression, to obtain the significance of the independent variable (MPV) and to find out whether there is a relationship between it and a continuous dependent variable, we estimated a model in the form of the following **mathematical formula**: $\boldsymbol{y = \beta_0 + \beta_1 \times x}$

Where *y* is the continuous dependent variable, *x* is the MPV (independent variable), β_0 and β_1 are the parameters to be estimated in the collected data sample. Starting from this model, an interpretation can be obtained regarding the relationship between *x* and *y*, testing the significance of β_1, which in turn tells us if there is a statistically significant relationship between *x* and *y*.

For logistic regression, the model is similar to that applied in the case of linear regression, and is defined by the following **mathematical formula**: $\boldsymbol{score = \beta_0 + \beta_1 \times x}$

Where the *score* is the probability that an event will occur (dependent binary variable), *x* is the MPV value, and β_0 and β_1 are the parameters that will be estimated in the collected data sample (β_0 = the coefficient for the dependent variable, β_1 = the coefficient for the MPV).

The interpretation of this model is similar to the one applied using linear regression, except that in order to find out the probability in percentage of an event to occur, the value of the *score* obtained using the above-mentioned mathematical formula must be converted into probability using the following **equation**: $\boldsymbol{probability = \frac{1}{1+e^{-score}}}$, where *e* is the number of Euler (2.71828).

The graphical representations of the statistical results from the second study are boxplots, histograms, and density distribution representations.

In the case of both studies, the *p* threshold below which the results are considered to be statistically significant is below 0.05.

Study 1 - Mean platelet volume – a possible predictor for patients with decompensated chronic heart failure

Study 1 was designed as a retrospective pilot study, which focused on a group of 130 patients, having as inclusion criteria patients with chronic decompensated HF in the category of which patients with class IV NYHA HF entered, as well as patients with APE.

The results of the first study were published in the scientific journal entitled International Journal of General Medicine [15] and involved information that focused on the following: demographic data, the relationship between certain laboratory data and the MPV value, the relationship between the comorbidities of the study group and the MPV value, relationship between ECG changes and MPV value, correlation between MPV value at admission and hospitalization at 6 months, respectively mortality of patients with chronic decompensated HF at 1 year after the initial discharge.

The statistical results of the first study revealed the following findings:

1) the NT pro BNP value at discharge was statistically significantly correlated with an increased MPVvalue at admission.
2) there were no statistically significant correlations between MPV values and serum sodium and potassium, serum creatinine, or presepsin values.
3) patients with microcytic anemia, history of myocardial infarction, and atrial fibrillation rhythm had increased values of MPV (of at least 9 fL).
4) patients with chronic decompensated HF who were hospitalized at 6 months or died at 1 year had an MPV value of at least 9.1 fL.

Study 2 - Mean platelet volume as a predictor for patients with heart failure - hypothesis based on statistical models

The second study is a continuance of the first study, being also carried out in a retrospective manner, but on a larger number of patients, namely 260, the target study sample being patients with chronic decompensated HF (NYHA class III/IV HF/acute pulmonary edema (APE)) to which patients with stable chronic HF (NYHA class II HF) were also added, the parameter of interest being also the mean platelet volume (MPV).

The working hypotheses from which I have started in the second study were the following:

- if based on the MPV value we can estimate the probability of an event in patients with HF (rehospitalization at 3 months, at 6 months, death at 1 year, in-hospital death, prolonged duration of hospitalization).

- if patients with chronic decompensated HF (NYHA class IV HF/APE) have higher MPV values compared to patients with stable chronic HF (NYHA class II HF).

- if there is a relationship between MPV value and certain variables in the study population (LVEF, NT pro BNP, sepsis, Hb value, serum Cr value, RDW value, cardiovascular (CV) disease history (stroke/IHD), LA dilatation, LV dilatation, the presence of HP, the Afib rhythm, SR rhythm, history of type 2 DM, the medication used at home –ACEI, MRA, loop diuretics).

Starting from the working hypotheses listed above, the statistical analysis of my study looked for whether there is a plausible relationship between the MPV value and certain categories of variables, applying the regression model. Therefore, my study focused on the relationship between MPV and the following variables of interest:

-qualitative variables represented by the type of HF (chronic decompensated HF represented by NYHA classes III-IV HF/APE, stable chronic HF represented by NYHA class II HF), hospitalization at 3 months, hospitalization at 6 months, death at 1 year, death in-hospital, the rhythm of AFib, SR, CV disease history (stroke/MI), history of DM, medication used -ACEI, MRA, DA, smoker/non-smoker status, presence of HP.

-quantitative variables represented by the duration of hospitalization, presepsin value, NTproBNP value, Hb value, serum Cr value, RDW value, FEVS value, LA diameter, LV diameter.

The statistical results of the second study were published in the journals Applied Sciences [16] and Life [17] and confirmed the results of the first study, namely that HF patients who were hospitalized at 6 months or died at 1 year had higher MPV values, the cut-off value of MPV above which I have observed these results, being over 9 fL. However, compared to the first study, the second study brings additional elements, namely:

1) the study sample was larger therefore the statistical power was more relevant;

2) in addition to patients with chronic decompensated HF (NYHA classes III-IV HF/APE) we also included patients with stable chronic HF (NYHA class II HF);

3) the statistical models used were different and more innovative, namely the logistic and linear regression models, based on which mathematical models were obtained and through which we could estimate the probability of an event according to the MPV value;

4) patients with a higher MPV value had a higher probability of having decompensated chronic HF compared to patients with stable chronic HF;

5) in addition to demonstrating that HF patients who were hospitalized at 6 months or died at 1 year had a higher MPV value (above 9 fL), I also have demonstrated that HF patients with an

increased MPV value were more likely to be readmitted at 3 months and to have a prolonged in-hospital stay;

6) I have identified a statistically significant relationship between the MPV value and certain variables in the study (sepsis, RDW, AFib rhythm, HP, reduced LVEF, dilated LA, dilated LV, specific medication for HF (ACEI, MRA), cardiovascular history (IHD), history of DM).

Corroborating all the results from the second study, its conclusions highlight the prognostic correlation between the MPV value and HF, namely that patients with chronic decompensated HF had a higher value of MPV (over 9 fL) compared to patients with stable chronic HF, and that patients with HF who had an MPV value above 9 fL, had an worse prognosis in terms of readmissions at 3 months, 6 months, mortality at 1 year and prolonged hospitalization.

Final conclusions

The final conclusions that can be drawn from both studies reflect the prognostic relevance of mean platelet volume (MVP) in the heart failure (HF) patient population and are presented in detail in the following paragraphs:

1) The cut-off value of MPV above which we observed that patients with HF had a negative prognosis is 9 fL.
2) Patients with chronic decompensated HF (NYHA class IV HF or APE) had higher MPV values (above 9 fL) compared to patients with stable chronic HF (NYHA class II HF) who had low MPV values (below 9 fL).
3) By applying the logistic regression model I was able to estimate the probability of a patient to have class II/III/IV NYHA HF or APE based on the MPV value, noting that an MPV value above 9 fL was associated with a higher probability of a patient to have NYHA class IV HF or APE.
4) Patients with HF who were hospitalized at 3 months, respectively at 6 months or died at 1 year, had a higher MVP value (over 9 fL) compared to patients who were not hospitalized or did not die (under 9 fL).
5) Based on the logistic regression models, I was able to estimate the probability of hospitalization or mortality depending on the MPV value, noting that as the MPV value increases (above 9 fL) the probability of 3 and 6-months hospitalization and of 1-year death also increases.

6) Regarding the duration of hospitalization, based on the linear regression model, I have identified a statistically significant linear relationship between this variable and the MPV, namely that there is a tendency of in-hospital stay of HF patients to increase as the value of the MPV increases.
7) Regarding in-hospital death, I did not identify a statistically significant relationship between this variable and the MPV value, the possible explanation being the reduced statistical power provided by the small number of HF patients who died in the hospital.
8) Between the NT pro BNP value and the MPV value I have identified a statistically significant relationship, highlighted in the first study by the positive correlation between the NT pro BNP value at discharge and the MPVvalue at admission (Pearson coefficient of 0.249), and in the second study, by the linear regression model which showed that there is a relevant linear relationship between the NT pro BNP value at admission and the MPV value at admission (as the MPV value increases, so does the NT pro BNP value).
9) Patients with HF and sepsis had a higher value of MPV (over 9 fL) compared to patients without sepsis.
10) Between the presepsin value and the MPV value I did not observe a statistically significant relationship, the explanation of this result being the small number of patients with HF for whom the presepsin value was available.
11) Although in the first study I have observed that patients with microcytic anemia had an increased MPV value compared to those without microcytic anemia (9.16 fL versus 8.79 fL), in the second study I did not identify a statistically significant relationship between the MPV value and hemoglobin value.
12) I did not observe a statistically relevant relationship between the MPV value and the presence of dyselectrolytemia or the value of serum creatinine at admission.
13) Regarding the relationship between the specific medication for HF patients and the MPV value at admission, the results were varied; in contrast to patients on or not on ACEI treatment in which MPV values did not differ, in HF patients on loop diuretics or MRA treatment, MPV values were higher (at least 9 fL) compared to HF patients who were not taking medication loop diuretics or MRA.
14) I did not identify a statistically relevant link between the MPV value and the smoking status, or the personal history of hypertension or stroke.

15) The results of my study identified the existence of a significant relationship between the MPV value and patients with a personal history of type 2 diabetes or (ischemic heart disease (IHD), noting that diabetic patients or those with a history of IHD had a higher VPM value compared to those non-diabetic or without a history of IHD (MPV of at least 9 fL versus below 9 fL).
16) Regarding the presence of atrial fibrillation (Afib) rhythm or sinus rhythm (SR), I have found that patients in AFib rhythm had higher MPV values (above 9 fL) compared to those in SR (below 9 fL) and that based on the logistic regression model, I was able to estimate the probability of an HF patient having AFib or SR rhythm depending on the MPV value (the probability of HF patients to have AFib increases as the MPV value increases, and the probability of HF patients to have SR increases as the MPV value decreases).
17) Regarding the relationship between left ventricle ejection fraction (LVEF) and MPV value, the results of my study indicated that HF patients with reduced LVEF had higher MPV values compared to those with preserved LVEF (MPV above 9 fL versus below 9 fL) and that there is a statistically relevant linear relationship between the MPV value and LVEF, highlighted by the application of the linear regression model (as the MPV value increases, the LVEF value decreases and vice versa).
18) Patients with HF and dilated LA as well as those with HF and dilated LV had higher values of MPV compared to those with non-dilated LA, respectively non-dilated LV (above 9 fL versus below 9 fL), there being a statistically significant linear relationship between the value of the transversal dimension of the LA, respectively of the LV and the MPV value (the increase of 1 unit of the MPV value correlates with an increase of the LA dimension by 2.3 mm, respectively by 1.6 mm of the LV dimension).
19) Regarding the relationship between the MPV value and the presence or absence of pulmonary hypertension (PH), by applying the logistic regression model, I have found a statistically significant link between the two variables, namely that as the MPV value increases (above 9 fL), the probability of patients with HF to have PH, increases.
20) Regarding the relationship between MPV and red cell distribution width (RDW) in patients with HF, by applying the linear regression model, I have found that there is a statistically relevant linear relationship between the two variables, namely that as the value of MPV increases (over 9 fL), the RDW value also increases (over 13%).

21) Considering that I have identified a statistically significant relationship between the MPV value and the RDW value, the results of my study identified a relevant correlation between the RDW value and the type of HF (NYHA class IV HF/APE), hospitalization, and mortality, namely that patients with an increased RDW value (over 14%) were more likely to have NYHA class IV HF/APE, to be rehospitalized, or to die.

Limits of studies

As the study was conducted in a retrospective manner, there were the following limitations:

1) The retrospective collection of medical data could have been influenced by human errors of collection or interpretation.

2) certain variables of interest were not available in a large number of patients, which influenced the results of the study (for example presepsin was available only in a number of 39 patients).

3) the possibility of improper collection or storage of the blood samples due to which the values of MPV and other biological variables could have been influenced.

Personal contributions

The evolution of a patient with heart failure (HF) is unfavorably influenced by certain negative prognostic elements represented either by decompensation, frequent hospitalizations or by mortality, therefore, the identification of a parameter such as mean platelet volume (MPV) that could predict these negative events, could represent an element of novelty in the medical field.

The strength point of my research is given by the fact that my statistical results concluded that MPV can be used as a prognostic parameter in the HF patient population, a notion underlined by the following arguments: 1) patients with chronic decompensated HF (NYHA class IV HF/APE) had higher MPV values compared to patients with stable chronic HF (NYHA class II HF), who had lower MPV values; 2) HF patients who were hospitalized at 3 months, 6 months or died at 1 year had a higher MPV value compared to those who did not experienced the mentioned events.

The statistical data from my study according to which patients with decompensated chronic HF had higher MPV values compared to patients with stable chronic HF confirm the results of the study conducted by Hayati Kandis et al. [5], but the novelty of my study compared to that of Hayati Kandis is the statistical methodology used, namely the application of logistic regression models through which we were able to estimate the probability that a patient has decompensated or stable chronic HF based on MPV value.

Regarding the relationship between mortality at 1 year and the value of MPV identified in patients with HF in my study, it partially highlights the results of the study carried out by Hayati Kandis and his collaborators, the difference in the mentioned study being given by the dependent variable followed, namely 6-months death. However, similar to the results obtained in the study by Hayati Kandis, my study revealed that HF patients who died had higher MPV values compared to those who did not die.

Regarding the statistical link between hospitalization (at 3 and 6 months) and the value of MPV, as well as that between the number of days of hospitalization and the value of MPV, the results of my study showed that there is a statistically significant relationship between the mentioned variables and the increased value of MPV. The elements of novelty that my research offers to the medical literature regarding this aspect are represented by the following: 1) there are no studies in the current medical literature that have targeted the relationship between the mentioned variables and the MPV value, the only studies that pursued the idea according to which MPV could be a prognostic parameter in the HF patient population, are the study conducted by Hayati Kandis (5) (who studied the relationship between death at 6 months and MPV value in HF patients) and the study conducted by Hakki Kaya [7] (which studied the relationship between hospitalization in general and the value of MPV); 2) the statistical analysis used in my study (logistic and linear regression models) allowed me to estimate the percentage probabilities that a patient with HF will be rehospitalized at 3 months, respectively at 6 months, have a certain number of days of hospitalization, or die at 1 year, depending on the value of MPV.

Regarding the relationship between the value of NT pro BNP and the value of MPV, my study identified a statistically relevant link between the two variables, confirming the results of the study by Budak et al. [6], namely that there is a positive correlation between the value of BNP and the value MPV in patients with HF. Compared to the mentioned study, the novelties brought by my research are represented by the following: 1) by applying the linear regression model, my research demonstrated a linear relationship between the value of NT pro BNP and the value of MPV, that is, an increase of 1 unit of MPV correlates with an increase in NT pro BNP value by

2677 pg/ml; 2) if in my second I identified a statistically significant link between the value of NT pro BNP at admission and the value of MPV at admission, in my first study, I have demonstrated a positive correlation between the value of NT pro BNP at discharge and the value of MPV at admission, using the coefficient of Pearson.

The statistical results of my research identified a relevant link between sepsis and the increased value of MPV, confirming the data of a study conducted by J. Van Der Lelie [18] which showed that patients with infectious syndrome had a high MPV. The novelty of my research compared to the study mentioned above, is the target study population (HF patients), as well as the statistical analysis used (logistic regression model) according to which I was able to estimate the probability in percenteges of a patient with HF to have sepsis, based on the value VPM.

Regarding the relationship between the MPV value and LVEF, my research identified a statistically significant link between the two variables, highlighting the statistical data of two studies cited in the medical literature, regarding this aspect, namely the one conducted by Nassiba M. [19] which was focused on the prognostic impact of MPV in HF patients with preserved LVEF, and the one performed by Fujita S. [20] who focused on the impact of MPV on HF patients regardless of LVEF value. The novelties brought by my research compared to the previously mentioned studies, are represented by the following: 1) compared to the study conducted by Nassiba M., my study included patients with HF regardless of the LVEF value, revealing that patients with reduced LVEF had a value of higher MPV compared to patients with preserved LVEF; 2) compared to the two cited studies, the novelty brought by my research is given by the statistical analysis used (logistic regression models) according to which I had the possibility of estimating the probability of a patient with HF to have reduced or preserved LVEF based on the MPV value (HF patients with MPV values above 9 fL were more likely to have reduced LVEF, and HF patients with MPV values below 9 fL were more likely to have preserved LVEF).

If there are studies available in the medical literature regarding the prognostic relationship between MPV and LVEF, regarding the prognostic relationship between MPV value and echocardiographic variables represented by LA, LV, or PH in HF patients, there are no available studies, and my research brings novelties in this sense, by applying the logistic regression model based on which I was able to estimate the probability of a the patient with HF to have dilated LA, dilated LV, or PH, depending on the value of MPV.

The results of my research identified a statistically significant correlation between the value of MPV and the presence of AFib rhythm, confirming the data from the study conducted by Yucel Colkesen [21] and the one conducted by Okan Turgut [14], according to which patients with AFib rhythm have an increased MPV. The novelty brought by my study, regarding this aspect, is the targeted study population (patients with HF), along with the statistical methodology used (logistic regression model), on the basis of which I was able to estimate the probability in percentages of a patient with HF to have AFib rhythm, depending on the value of MPV.

Another novelty brought by my research is that regarding the statistical link between MPV and RDW, as studies related to this aspect are absent, being available only those related to HF and MPV or HF and RDW, taken separately. Using the linear regression model, the data from my study indicated a statistically significant linear relationship between an increased MPV value and RDW value, that is, a tendency for RDW value to increase as MPV value increases.

If I extrapolate the statistical results from my study that the increased value of MPV (over 9 fL) correlates with a poor prognosis in patients with HF and that there is a statistically significant positive correlation between the value of RDW and MPV in patients with HF, it can be understood why the statistical results of my research also revealed that an increased value of RDW (over 14%) in HF patients correlated with a negative prognosis represented by hospitalization and mortality. Therefore, the results of my research on the prognostic relationship between MPV value and RDW value in HF patients are promising.

In the light of the above, I would like to mention that the strength points of my study are represented by: 1) the identification of a statistically significant correlation between the MPV value and certain qualitative variables (NYHA class IV HF/APE, hospitalization, mortality, the presence of sepsis, the presence AFib rhythm, the presence of dilated LA, the presence of dilated LV, the presence of PH) and quantitative (increased RDW value, increased NT pro BNP value, prolonged number of days of hospitalization, reduced value of LVEF); 2) identifying the cut-off value of MPV above which I have observed that patients with HF had a negative prognosis or had decompensated, and which is 9 fL.

Based on these observations found in my study, it can be said that mean platelet volume could represent a possible negative prognostic parameter for heart failure patients and that based on its value we can identify heart failure patients at risk of having an unfavorable outcome or to decompensate.

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