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ORIGINAL ARTICLE

Prognostic Value of Hematological Inflammatory Markers in Patients with Pleural Effusion Due to Heart Failure

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SUMMARY

Background: **Pleural effusions due to heart failure are associated with a high 1-year mortality. Several hematological parameters have been shown to provide prognostic information in patients with cardiovascular diseases. The objective was to assess whether hematological markers can also provide prognostic information in patients with pleural effusion caused by heart failure.**
Methods: **This was a retrospective study of patients with pleural effusion due to heart failure who underwent a diagnostic thoracentesis. The hematological parameters evaluated were as follows: neutrophils, lymphocytes, neutrophil-to-lymphocyte ratio, platelet count, platelet-to-lymphocyte ratio, mean platelet volume (MPV), and MPV-to-platelet ratio. Patients were divided into two groups: those who died within 1 year and survivors of more than 1 year. Differences and possible correlations were analyzed with non-parametric tests. Diagnostic values were estimated. Survival analysis was performed using the Kaplan-Meier method. Cox regression analysis was performed to identify independent variables.**
Results: **Twenty five of 55 (45%) patients died within 1-year from thoracentesis. Patients who died in this period were older, aged 83 years (73 - 87, median and interquartile range, IQR) vs. 74 (65 - 82); with lower platelet count: 181 x 10^3 (140 - 258 x 10^3) vs. 241 x 10^3 (198 - 324 x 10^3); and higher MPV/platelet: 48.1 (34.9 - 75.6) vs. 35.6 (27.1 - 42.9). In the regression analysis only the MPV/platelet had statistical significance (p = 0.002). MPV/platelet > 50 had a specificity of 87% for 1-year mortality, and a ratio > 30 had a sensitivity of 84%.**
Conclusions: **Simple hematological parameters such as platelet count and MPV/platelet, may provide useful prognostic information for predicting 1-year mortality in patients with pleural effusion due to heart failure.**
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INTRODUCTION

In the past few years, many investigations into the prognosis of cardiovascular disease by evaluating easily accessible hematological markers have been performed [1]. Routine hematological parameters used in clinical practice such as neutrophils, lymphocytes or platelets seem to be able to offer prognostic information. Probably the most widely analyzed marker has been the neu-

trophil-to-lymphocyte ratio (NLR). NLR is able to predict the risk for cardiac arrhythmias and for mortality in patients with coronary disease [1] and the risk of death in patients with acute or advanced heart failure [2]. This ratio has been extensively studied as a prognostic marker in several malignant and inflammatory diseases [3-5]. Other hematological markers also appear to be useful. It has been reported that the platelet-to-lymphocyte ratio (PLR) predicts outcome in heart failure patients undergoing heart transplantation [6]. There is an association between PLR and mortality in patients with cardiogenic pulmonary edema [7]. Low platelet count has been associated with risk for all-cause death and heart failure rehospitalization in patients with acute heart failure [8]. Also, the value of the mean platelet volume (MPV) and, in particular, its ratio to platelet count seems to be useful for predicting cardiac mortality in older patients with acute coronary syndrome [9].Pleural effusion is a highly common clinical problem with a significant variety of etiologies, both malignant and benign. Congestive heart failure is the leading cause of nonmalignant pleural effusion [10-12]. Despite being a pleural effusion of benign origin, the 1-year mortality is significantly high [11], and the availability of parameters to predict this early mortality may be of great clinical interest. However, the potential prognostic role of these hematological biomarkers in this group of patients has not been evaluated. Our objective was to assess whether hematological markers that have shown prognostic usefulness in cardiovascular disease can also provide prognostic information in patients with pleural effusion caused by heart failure.

MATERIALS AND METHODS

We conducted a retrospective study of patients who underwent a diagnostic thoracentesis between January 2014 and December 2017 at a pleural medicine unit of a university hospital. Only the first diagnostic thoracentesis for each patient was considered. The exclusion criteria were patients with more than one possible diagnosis and those without full follow-up during the study period. Patients with a final diagnosis of pleural effusion due to heart failure were included in the study. The diagnosis was established according to standard clinical practice [13] by experienced attending medical specialists, and confirmed by two of the authors (EGP, MJSS) by reviewing the clinical history and evolution. All patients were followed up until death or the end of the follow-up period (April 2019).

Laboratory data of blood tests were obtained from the electronic medical records for each patient. Hematological values chosen for the analysis in this study were those of the date closest to thoracentesis (within 24 hours in all cases). The researchers who collected the data did not know the evolution of the patients. The following hematological parameters were evaluated: neutrophils, lymphocytes, NLR, platelets count, PLR, MPV, and MPV-to-platelet ratio (MPV/platelet). The survival time was determined in months until death or until the end of the study (minimum follow-up 16 months). The date of death was obtained in official documents from the national health system database. The study, conducted according to the principles of the Declaration of Helsinki, was approved by the local ethics committee.

Statistical analysis was performed using SPSS 22.0 (IBM Corp.; Armonk, NY, USA) software. The distribution of the measured variables was non-normal. Consequently, data were presented as a median (25th - 75th interquartile range, IQR) or percentage (with 95% interval confidence). Comparisons were performed with the Mann-Whitney *U*-test, chi-squared test or Fisher's exact test, where appropriate. Possible relationships among survival and analyzed variables were calculated using Spearman's rank correlation coefficient (rho). Diagnostic values were reported in terms of sensitivity, specificity, predictive values, and accuracy. Survival analysis was performed using the Kaplan-Meier method, and the log-rank test was implemented to estimate the differences between groups. Cox regression analysis was performed to identify independent variables. A p-value < 0.05 was considered to be statistically significant.

RESULTS

A total of 55 patients were included in the study, 21 female (38%) and 34 male (62%) with a median age (25th - 75th IQR) of 79 years (70 - 86 years). Twenty-five patients (45%) died within the first year of follow-up after the diagnostic thoracentesis. Of the 30 patients who survived more than 1 year, 11 died during subsequent follow-up (median 31 months, IQR 18 - 49). The remaining 19 patients were alive at the end of the study period (median 30 months of follow-up, IQR 22 - 42). Patients with a survival of less than 1 year after the first diagnostic thoracentesis were older than the survivors (Table 1). The presence of bilateral pleural effusion did not achieve statistical significance for predicting 1-year mortality (Table 1).

The values of the evaluated hematological markers are detailed in Table 2. Patients with a survival of less than 1 year differed significantly from patients with a longer survival in platelet count and in the MPV/platelet ratio. Low values of platelets and high values of the MPV/platelet ratio were significantly associated with lower survival. A significant correlation was observed between survival and platelet count (rho = 0.35, p = 0.009) and between survival and MPV/platelet (rho = -0.39, p = 0.003).

Tables 3 and 4 show the diagnostic values (sensitivity, specificity, predictive values, and accuracy) of these two parameters to predict mortality during the first year of follow-up. Cutoff values were set at the point to obtain a sensitivity higher than 80% and a specificity more than 80% for each parameter. The combination of the

Table 1. Patient characteristics according to 1-year survival.

Parameter	Non-survivors (n = 25)	Survivors (n = 30)	p-value
Gender (female/male)	7/18	14/16	0.127
Age (years)	83 (73 - 87)	74 (65 - 82)	0.04 *
Bilateral effusion	14 (56%)	9 (30%)	0.06

*** Value with statistical significance.**

Table 2. Hematological markers according to 1-year survival.

Parameter	Non-survivors (n = 25)	Survivors (n = 30)	p-value
Neutrophils, µL	6,210 (4,395 - 7,490)	5,505 (4,032 - 7,603)	0.95
Lymphocyts, µL	1,000 (605 - 1,400)	1,010 (795 - 1,500)	0.52
NLR	5.27 (2.79 - 11.92)	5.84 (3.45 - 8.76)	0.99
Platelet, x 10^3/µL	181 (140 - 258)	241 (198 - 324)	0.02 *
PLR	0.20 (0.13 - 0.31)	0.25 (0.18 - 0.35)	0.19
Mean platelet volume (MPV), fL	9.0 (8.7 - 9.6)	8.6 (8.0 - 9.3)	0.06
MPV/platelet	48.1 (34.9 - 75.6)	35.6 (27.1 - 42.9)	0.006 *

Values are median (IQR). * Values with statistical significance. NLR - neutrophils to lymphocytes ratio. PLR - platelets to lymphocytes ratio. MPV/platelet - values x 10^3.

Table 3. Diagnostic values of platelet count for detecting 1-year mortality.

Value	Sensitivity	Specificity	PPV	NPV	Accuracy
< 182	48 (28 - 69)	83 (65 - 94)	71 (49 - 85)	66 (56 - 74)	67 (53 - 79)
< 300	84 (64 - 95)	33 (17 - 53)	51 (43 - 59)	71 (47 - 88)	56 (42 - 70)

Values are percentage and 95% confidence interval.

Table 4. Diagnostic values of the MPV/platelet ratio for detecting 1-year mortality.

Value	Sensitivity	Specificity	PPV	NPV	Accuracy
> 50	44 (24 - 65)	87 (69 - 96)	73 (50 - 88)	65 (56 - 73)	67 (53 - 79)
> 30	84 (64 - 95)	40 (23 - 59)	54 (45 - 62)	75 (52 - 89)	60 (56 - 73)

Values are percentage and 95% confidence interval.

different hematological parameters did not obtain better results than the biomarkers individually.

Overall survival of patients with an MPV/platelet above or below the median value was statistically different (Figure 1). Patients with a higher ratio had a significantly lower survival (log-rank, p = 0.004). In the multivariate analysis (Cox regression) including age and MPV/platelet ratio, 1-year mortality was significantly associated only with the MVP/platelet ratio (p = 0.002) and not with age (p = 0.06).

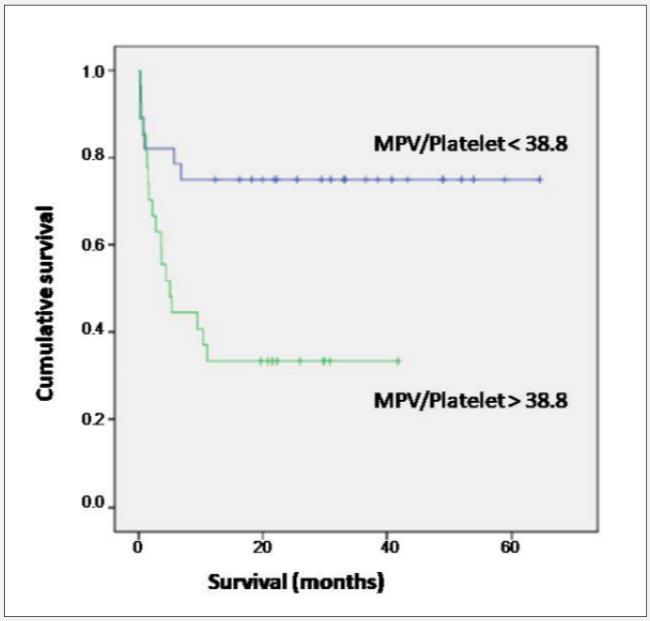

Figure 1. Kaplan-Meier curves illustrating survival according to MPV/platelet ratio below or above median value.

Significantly higher survival when the ratio is below median value (log-rank p = 0.004).

DISCUSSION

In this study, we have found that easily accessible hematological biomarkers provide prognostic information in patients with pleural transudate of cardiac origin. Pleural effusion due to congestive heart failure represents the most frequent cause of nonmalignant pleural effusions [10-12] and has a significantly high 1-year mortality (50% in the series by Walker et al. [11] and 45% in our series), not very different to that described in malignant effusions [14]. This mortality is higher than that reported for all cause 1-year mortality in patients hospitalized with acute heart failure in a large international registry; that was 23% [15]. From a clinical point of view, it may be of great interest to have markers that could identify patients at higher risk of dying in the next few months. This information could contribute to propose different measures in therapy or to consider the possibility of palliative treatments.

We evaluated several hematological inflammatory markers, inexpensive and easily available, that have been described of prognostic utility in patients with cardiovascular disease. In these patients, inflammation and hypoxia produce a stimulus in the bone marrow that causes a discharge of immature cells and increases other hematological cells in the systemic circulation [16]. Studies have shown that several hematological parameters such as NLR and MPV in the bloodstream are independent prognostic biomarkers of survival [16]. A high NLR has been repeatedly reported as an indicator of more negative events in patients with coronary diseases and heart failure, including all-cause mortality [1,2,17, 18]. Another evaluated ratio, the PLR, predicts mortality in patients with cardiovascular diseases [6,7]. We expected that these ratios would be different in our groups of patients with pleural effusion due to heart failure and different survival; however, neither NLR nor PRL can significantly differentiate the patients according to 1-year mortality. A radiological characteristic has been related with mortality in these patients. In a study of nonmalignant pleural effusions, bilateral involvement was associated with a higher 1-year mortality [11]. In our series, patients with shorter survival more frequently have bilateral pleural effusion, but at a borderline level of statistical significance.

Our patients did differ for 1-year mortality in age (lower survival in older patients, as reasonably expected), and, interestingly also differ in the platelet count and the MPV/platelet ratio. MPV values in both groups had a difference close to statistical significance. The role of platelet count as a prognostic marker has also been pointed out [8]. Platelets are extremely reactive blood components, and acute heart failure triggers platelet aggregation [8]. We have found that patients with a lower platelet count have a significantly higher 1-year mortality.

In normal conditions, there is a nonlinear inverse relationship between MPV and platelet count, and in several disorders this physiological proportion may be disrupted [19,20]. Literature data indicate that MPV can provide important information on the course and prognosis in many pathological conditions, such as cardiovascular, respiratory and inflammatory diseases, diabetes mellitus, or cancer [21]. Elevated MPV is associated with higher risks of cardiovascular disease and coronary heart disease including acute myocardial infarction and mortality, restenosis following coronary angioplasty [22,23], events after percutaneous coronary intervention [17], and heart failure-related hospitalization [24].

The combination of the MPV and platelet count could be even more interesting than the individual values. Our results demonstrate that the MPV/platelet ratio is an independent predictor of 1-year mortality in patients with pleural effusion due to heart failure. A few previous studies had already suggested that this ratio is able to predict adverse outcomes in patients with cardiovascular diseases [9,25-27], but its potential application to patients with pleural effusion of cardiac origin had yet to be evaluated.

When determining the diagnostic usefulness of biomarkers, the selection of the cutoff value is not universal and can be established according to different criteria [28]. In our study we calculate the points at a sensitivity and specificity of more than 80%, which we consider of clinical interest. We found that values of the MPV/platelet ratio above 30 have a sensitivity of 84% for predicting 1-year mortality, and values higher than 50 have a specificity of 87%. These results are similar but slightly better than those obtained with the platelet count and may help clinicians differentiate patients based on the risk of dying.

The results of this study have been obtained in patients who underwent a diagnostic thoracentesis indicated by their attending physicians in a real clinical scenario. Consequently, it is applicable to patients in a similar situation. The finding of a pleural effusion is frequent in patients with acute heart failure, but in many cases, effusions resolve after the initial therapy and the diagnostic thoracentesis is not required [13]. Therefore, our findings cannot systematically be applied to all patients with pleural effusion due to heart failure until their possible usefulness is demonstrated. In addition, this is a retrospective study, in a single center, and with a relatively small series of patients, so it may be necessary to confirm their results prospectively.

CONCLUSION

Pleural effusions due to heart failure undergoing diagnostic thoracentesis are associated with a high 1-year mortality. We have found that two simple hematological parameters, platelet count and MPV/platelet ratio, may provide useful prognostic information in these patients. Low platelet count ($< 182 \times 10^3$) is a predictor of survival shorter than 1 year with a specificity of 83%. An MPV/platelet value above 30 had a sensitivity of 84%, and values higher than 50 had a specificity of 87% for predicting 1-year mortality. This information may contribute in clinical decision making.

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Declaration of Interest:
The authors declare no conflict of interest.

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