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Does Mean Platelet Volume/Platelet Count Ratio and Red Rlood Cell Distribution Width Predict In-hospital Mortality in Patients Admitted for Acute Exacerbation of Chronic Obstructive Pulmonary Disease?

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Abstract

Background: The critical role of inflammation in increasing the frequency and the severity of the exacerbations has been demonstrated previously. Some previous research indicates that simple blood tests of inflammation such as neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) performed at admission might predict the severity of exacerbation and resultant outcomes. The purpose of the present study was to investigate the role of MPV/PLT and other parameters of complete blood count (CBC) in predicting in-hospital mortality in patients with AECOPD.

Materials and Methods: 171 patients admitted to the intensive care unit of our institute -a tertiary center- with acute exacerbation of COPD between May 2014 and August 2018 were retrospectively recruited in the study. Demographic and clinical data including age, gender, accompanying chronic diseases, spirometric data, and pretreatment laboratory test results were extracted from the institutional digital database. The study population was divided into two groups according to the development of in-hospital mortality as survivors or non-survivors.

Results: Thirty-six subjects died during the in-hospital course (non-survivors) and 135 survived (survivors). Non-survivors had higher C-reactive protein ($p<0.001$), NLR ($p=0.037$), PLR ($p=0.021$), mean platelet volume ($p<0.001$), and MPV/PLT ($p=0.004$) compared to survivors. Admission pH was significantly lower in no-survivors that survivors $p<0.001$. Logistic regression analysis revealed that among several variables, GOLD stage > 2 (OR: 2.222, 95 % CI: 1.196-4.128, $p=0.012$), admission CRP (OR: 1.158), RDW (OR: 2.327), pH (OR: 0.002), NLR (OR: 1.902), and MPV/PLT (OR: OR: 1.332) were independent predictors of in-hospital mortality in patients with AECOPD. ROC curve analysis indicated a cut of value of 43.57 (sensitivity 67%, specifity 66%) for CRP, 15.4 % for RDW (sensitivity 74 %, specifity 75 %), 3.18 for NLR (sensitivity 71 %, specifity 72 %), and 4.45 for MPV/PLT (sensitivity 67 %, specifity 68%) to predict in hospital-mortality in patients with AECOPD

Conclusions: MPV/PLT, as an emerging indicator of preexisting inflammation, and RDW indicating intermittent hypoxemia, independently predict in-hospital mortality in patients with AECOPD. Implementation of MPV/PLT and RDW in addition to GOLD stage, pH, NLR and CRP might be useful in identifying patients who will require advanced support during admission for AECOPD.

Key words: *Acute exacerbation of chronic obstructive pulmonary disease, in-hospital mortality, neutrophil–lymphocyte ratio, platelet–lymphocyte ratio, red blood cell distribution width , mean platelet volume/platelet count ratio*

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Introduction

Chronic obstructive pulmonary disease (COPD) is a frequent chronic respiratory disease identified with progressive airway limitation which is often accompanied by chronic inflammation. According to the results of the Global Burden of Disease Study, COPD was the third leading cause of mortality in the United States and the fourth leading cause in the United Kingdom in 2016 (1). Owing to the increments in the global burden of biomass exposure and environmental pollution, the prevalence of COPD is expected to increase in the next few decades (2).

Acute exacerbation of COPD (AECOPD) increases the rate of further exacerbations, deteriorates the quality of life and negatively influences the prognosis with a significant and prolonged impact exceeding 5 years following the index hospitalization (3, 4). Therefore, subjects with AECOPD, particularly when severe, often hospitalized in consideration of sophisticated monitorization of vital signs and implementation of assisted ventilation (5). However, despite the advanced assisted ventilation techniques and new treatment options, severe AECOPD is still associated with high mortality, reportedly accounting for 23.3% of all deaths of COPD patients (6).

The critical role of inflammation in increasing the frequency and the severity of the exacerbations has been demonstrated previously. Some previous research indicates that simple blood tests of inflammation such as neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) performed at admission might predict the severity of exacerbation and resultant outcomes (7, 8). In addition, increases in red cell distribution width (RDW) and mean platelet volume (MPV) in severe AECOPD has been shown previously. However, none of the studies mentioned before investigated the predictive role of mean platelet volume/ platelet count ratio (MPV/PLT) on in-hospital outcomes in patients with AECOPD. The purpose of the present study was to investigate the role of MPV/PLT and other parameters of complete blood count (CBC) in predicting in-hospital mortality in patients with AECOPD.

Materials and methods

All consecutive patients admitted to the intensive care unit of our institute -a tertiary center- with acute exacerbation of COPD between May 2014 and August 2018 were retrospectively recruited in the study. Informed consent was obtained from all subjects and the study protocol was approved by the local Ethics Committee. Inclusion criteria were as follows: Primary diagnosis of AECOPD confirmed with spirometric data, AECOPD complicated with cough, dyspnea, sputum purulence requiring intensive care unit admission for non-invasive or invasive ventilation support, having no acute clinical condition other than AECOPD. Patients with alternative acute clinical conditions were not enrolled in this study.

Data collection

Demographic and clinical data including age, gender, accompanying chronic diseases, spirometric data, and pretreatment laboratory test results (Cell-Dyn 3700 System; Abbott, Abbott Park, Illinois) and blood gas analysis were extracted from the institutional digital database. Information concerning the in-hospital mortality was also collected by the research staff. The study population was divided into two groups according to the development of in-

hospital mortality as survivors or non-survivors. MPV/PLT was calculated as MPV/(PLT X 〖10〗^5)

Statistical Analysis

Data were analyzed using the IBM Statistical Package for Social Sciences v20 (SPSS Inc., Chicago, IL, USA). A normal distribution of the quantitative data was checked using the Kolmogorov-Smirnov test. Parametric tests were applied to data of normal distribution and non-parametric tests were applied to data of questionably normal distribution. Independent samples t-test was used to compare the groups. Categorical variables were analyzed using Pearson chi-square test. Logistic regression analysis was carried to identify the contributors to in-hospital mortality. ROC curve analyses were performed to determine the cut-off values for selected variables to predict in-hospital mortality. A p-value < 0.05 was assumed statistically significant.

Results

A total of 171 patients (mean age 77 ± 11 years, 96 male) were enrolled in this retrospective study. Thirty-six subjects died during the in-hospital course and 135 survived. There were no significant differences between the survivors and non-survivors in terms of age, gender, COPD duration, GOLD stage, FEV 1/FVC, admission SpO2, smoking status, length of stay (LOS), and presence of hypertension, diabetes, coronary artery disease, and systolic heart failure. In addition, the groups were similar with regards to white blood cell count, and hemoglobin level. However, non-survivors had lower pH (7.29 ± 0.14 vs. 7.39 ± 0.16, p<0.001), and higher C-reactive protein (43 ± 9 vs. 35 ± 11, p<0.001), higher RDW value (16.9 ± 2.5 % vs. 14.1 ± 2.5 %, p<0.001) higher mean platelet volume (9.9 ± 1.3 fL vs 7.9 ± 2.1 fL, p<0.001). NLR (3.5 ± 1.9 vs 2.8 ± 1.4, p=0.037), PLR (128 ± 82 vs. 98 ± 57, p=0.021), and MPV/PLT (5.7 ± 0.4 vs. 3.7 ± 0.2, p=0.004) were also significantly higher in non-survivors compared to survivors (Table 1).

Logistic regression analysis revealed that among several variables admission CRP (OR: 1.158, 95 % CI: 1.049-1.279, p=0.004), RDW (OR: 2.327, 95 % CI: 1.507-3.594 , p<0.001), pH (OR: 0.002, 95 % CI: 0.001-0.283, p=0.014), GOLD stage > 2 (OR: 2.222, 95 % CI: 1.196-4.128, p=0.012), NLR (OR: 1.902, 95 % CI: 1.108-3.266, p=0.020), and MPV/PLT (OR: 1.332, 95 % CI: 1.054-1.683, p=0.016) were independent predictors of in-hospital mortality in patients with AECOPD (Table 2).

ROC curve analysis indicated a cut of value of 43.57 (sensitivity 67%, specifity 66%) for CRP, 15.4 % for RDW (sensitivity 74 %, specifity 75 %), 3.18 for NLR (sensitivity 71 %, specifity 72 %), and 4.45 for MPV/PLT (sensitivity 67 %, specifity 68%) to predict in hospital-mortality in patients with AECOPD (Figure 1).

Table 1. Demographic features, baseline spirometric data and laboratory measurements of the study group.

	Survivor n=135	Non-survivors n=36	p value
Age (years)	71 ± 12	69 ± 9	0.354
Gender(male)	73 (54%)	23 (63%)	0.326
COPD duration (years)	12.7 ± 4	12.6 ± 8	0.720
Current Smoking (n)	41 (30%)	14 (38%)	0.611
Diabetes (n)	31 (23%)	12 (33%)	0.195
HT (n)	53 (40%)	16 (44%)	0.753
CAD (n)	44 (32%)	13 (36%)	0.858
HF (n)	34 (25%)	12 (33%)	0.543
LOS (days)	11.5 ± 7	14.9 ± 9	0.169
Gold Stage > II	42 (31%)	22 (61%)	0.088
FEV 1/FVC (%)	56.7 ± 4.9	57.5 ± 5.3	0.316
SpO2 (%)	93.3 ± 1.3	93.1 ± 1.4	0.562
pH	7.39 ± 0.16	7.29 ± 0.14	<0.001
WBC (/mm3)	14.1 ± 6	13.7 ± 9	0.753
CRP (mg/L)	35 ± 11	43 ± 9	<0.001
RDW (%)	14.1 ± 2.5	16.9 ± 2.5	<0.001
Hemoglobin (g/dL)	12.1 ± 2.3	12.5 ± 2.6	0.250
PLT (/mm3)	225 ± 106	206 ± 119	0.006
MPV (fL)	7.9 ± 2.1	10.6 ± 1.3	<0.001
NLR	2.8 ± 1.4	3.5 ± 1.9	0.037
PLR	98 ± 57	128 ± 82	0.021
MPV/PLTx10^5	3.7 ± 0.2	5.7 ± 0.4	0.004

(Data are presented as mean ± standard deviation. CAD, coronary artery disease; CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease; FeV1, forced expiratory volume in one second; FVC, forced vital capacity; HF, Heart failure; HT, hypertension; LOS, length of stay; MPV, mean platelet volume; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PLT, platelet; RDW, red cell distribution width)

Table 2. Predictors of in-hospital mortality.

	OR	95%CI	p value
Age	0.639	0.266-1.532	0.315
Current smoking	0.990	0.957-1.024	0.542
Gold stage>II	2.222	1.196-4.128	0.012
MPV	1.197	0.862-1.663	0.283
CRP	1.158	1.049-1.279	0.004
pH	0.002	0.001-0.283	0.014
RDW	2.327	1.507-3.594	<0.001
NLR	1.902	1.108-3.266	0.020
PLR	1.004	0.994-1.014	0.452
MPV/PLT	1.332	1.054-1.683	0.016
LOS	1.005	0.970-1.041	0.779

(Abbreviations: Same as listed above)

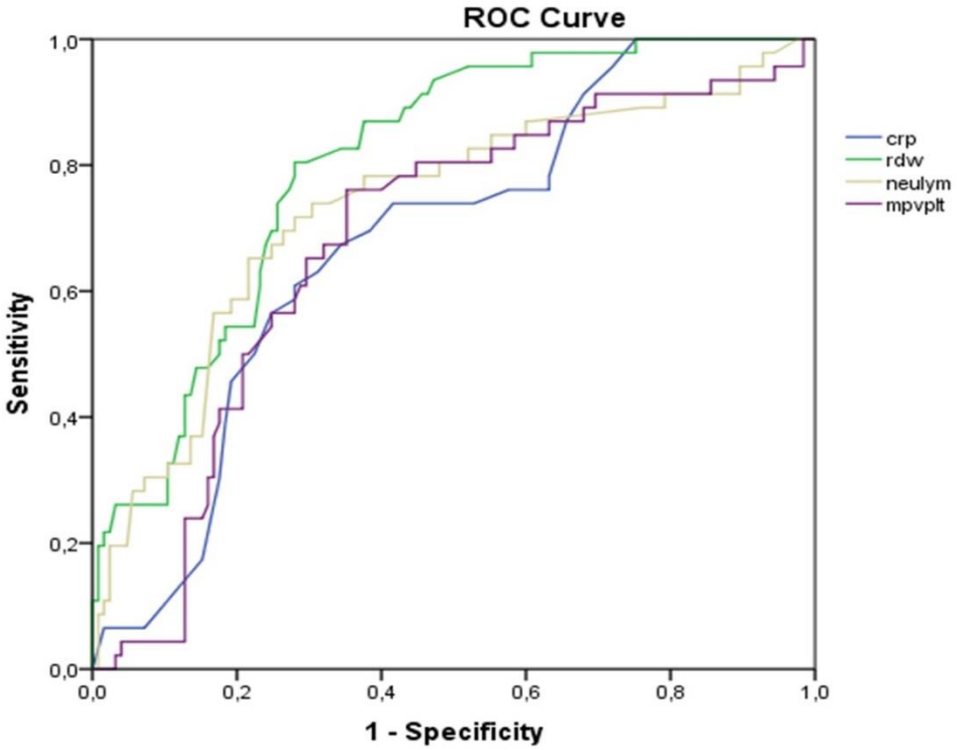

Figure 1. ROC curves demonstrating the predictive value of CRP, RDW, NLR, and MPV/PLT for in-hospital mortality.

Discussion

The present study demonstrates that admission CRP, MPV, NLR, PLR, and MPV/PLT are significantly higher and admission pH was significantly lower among non-survivors compared to survivors in AECOPD. Our findings also indicate that GOLD stage, admission pH, CRP, NLR, RDW, and MPV/PLT are predictive for in-hospital mortality in these patients.

COPD is at present one of the leading causes of death globally. As a consequence of the aging population and the lack of treatment options targeting prognosis, COPD is estimated to be the third leading cause of death by 2020 (9). As in many of the chronic diseases, the progressive clinical course of COPD is accentuated by acute exacerbations of respiratory impairment which are also responsible for most of the hospitalizations and deaths in patients with COPD (10). Therefore, determining subjects at high risk for death during AECOPD seems crucial for optimal utilization of healthcare resources and implementing advanced treatment options in these patients.

Several investigations have been carried out to identify simple blood tests which might have the potential to predict mortality in AECOPD. Bartziokas and colleagues have found that admission serum uric acid level was associated with 30-day mortality in AECOPD and

hospitalizations in the following 1 year (11). Blood tests employed to diagnose accompanying coronary artery disease- which is common in patients with COPD- were also studied in AECOPD. In a meta-analysis including ten studies, Pavasini et al. reported that cardiac troponin elevation was an independent predictor of increased risk of all-cause mortality in patients admitted for AECOPD (12). The contribution of inflammation to progression and development of exacerbations in COPD have also led to the search of simple blood markers for detecting exacerbations and mortality related to AECOPD. Progranulin and Interleukin (IL)-8 have been shown to predict the vulnerability to exacerbation in patients with COPD (13). In a recent trial conducted by Yao et al., NLR and PLR were found increased in non-survivors admitted for AECOPD. Moreover, they reported that NLR was a prognostic marker of increased mortality in the population of AECOPD (7). Their findings were consistent with the previous results of Rahimirad et al., where the authors revealed that higher NLR was positively associated with in-hospital mortality in AECOPD (14). More recently, a retrospective study including 906 subjects showed that admission NLR≥8.130 was predictive for 28-day mortality and subjects with an admission NLR ≥10.345 were more likely to need invasive mechanical ventilation (15). These findings confirm that inflammation plays a crucial role in AECOPD and with the more intense inflammation, the outcomes worsen. Our results identifying CRP, NLR and MPV/PLT as predictors of in-hospital mortality are consistent with the findings of previous studies demonstrating the role of inflammation in AECOPD. Furthermore, our findings reveal that RDW is also a powerful predictor for in-hospital mortality in AECOPD.

Intermittent hypoxemia occurring during AECOPD and right ventricular dysfunction developing as a consequence of the increasing pulmonary artery pressure are shown to be responsible for the increased RDW in AECOPD (16). Increase in RDW values has previously been demonstrated in patients with COPD compared to controls and was found in association with the severity of COPD (17). Recently, retrospective data reported by Epstein et al. revealed that increased RDW was an independent negative prognostic factor for adverse outcomes in patients with AECOPD (18). Our findings regarding the role predictive role of RDW for in-hospital mortality are in accordance with their results.

MPV/PLT ratio has emerged as a surrogate marker for several clinical conditions which explicit with acute or chronic inflammation. Ates et al. have shown in a previous study that MPV and MPV/PLT levels were higher in patients with sepsis and systemic inflammatory response syndrome compared to healthy controls, although, they could not establish a cut-off value for MPV/PLT to identify subjects with SIRS (19). Increased MPV/PLT was also demonstrated to be associated with atherosclerotic cardiovascular disease severity where inflammation plays a critical role both in development and progression of the disease (20, 21). The close relationship between airway inflammation and the frequency and severity of acute exacerbations in patients with COPD has been established previously (22-24). Besides their role in hemostasis, platelets also initiate inflammation by releasing various kinds of cytokines and adhesion molecules directly activating responses for monocytes, neutrophils, and T-lymphocytes (25). They also activate the complement system that augments the inflammatory responses. In patients with severe sepsis lower platelet counts have been reported in a substantial number of studies (26). With this background in mind, given the role of inflammation in severe AECOPD, we suppose that higher MPV/Platelet ratio measured at admission might indicate a preexisting chronic inflammatory state. We suggest

that, besides NLR, CRP, and RDW, MPV/PLT ratio might be employed to identify patients with high-risk for mortality in AECOPD.

The present study has some limitations to be mentioned. Retrospective design of the study and relatively small sample size should be kept in mind while interpreting the results. Sophisticated scoring systems such as DECAF were not implemented, thus, a correlation between admission MPV/PLT and these scores could not be studied.

Conclusion

MPV/PLT, as an emerging indicator of preexisting inflammation, and RDW indicating intermittent hypoxemia independently predict in-hospital mortality in patients with AECOPD. Implementation of MPV/PLT and RDW in addition to GOLD stage, pH, NLR and CRP might be useful in identifying patients who will require advanced support during admission for AECOPD.

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