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Monocyte-related hematological indices in acute exacerbations of chronic obstructive pulmonary disease – a new biomarker?

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Abstract

C-reactive protein (CRP) and leukocyte count are standard tools for recognizing inflammation in chronic obstructive pulmonary disease (COPD) patients. This study aimed to find out whether there is a pattern in monocyte-related hematological indices [monocyte to neutrophil ratio (MNR) and monocyte to lymphocyte ratio (MLR)], which could help differentiate COPD patients in need of hospitalization due to acute exacerbation of COPD and distinguish frequent COPD exacerbators from non-frequent COPD exacerbators. The study included 119 COPD patients and 35 control subjects, recruited at the Clinic for Respiratory Diseases Jordanovac, University Hospital Centre Zagreb, Croatia. A complete blood count was performed on Sysmex XN-1000, CRP on Cobas c501, and fibrinogen on the BCS XP analyzer. Data were analyzed with MedCalc statistical software. The COPD patients were divided into three groups: frequent exacerbators (FE), non-frequent exacerbators (NFE), and patients hospitalized for acute COPD exacerbations (HAE), and the control group consisted of healthy smokers (HS). A statistically significant difference was found in the values of MNR while comparing these groups of patients: FE *vs.* HAE ($p<0.000$), NFE *vs.* HAE ($p<0.000$), and HS *vs.* HAE ($p<0.001$); and for the values of MLR: FE *vs.* HAE ($p<0.022$), NFE *vs.* HAE ($p<0.000$), and HS *vs.* HAE ($p<0.000$). As MLR and MNR have shown the statistical difference comparing the group of HAE to NFE, FE, and HS, MLR and MNR could be valuable and available markers of acute COPD exacerbations and the need for hospitalization.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease characterized by persistent respiratory symptoms and airflow limitation. It is caused by significant exposure to harmful substances or gases, most frequently cigarette smoking [1]. COPD has become the third most common cause of death in the world [2] and has a big economic and social burden, with a prevalence of 11.7% globally [3].

As COPD is not a unique disease, there has been a need for distinguishing certain COPD phenotypes to achieve better management and disease prognosis. Miravitlles *et al*. proposed these four phenotypes of COPD [4]: infrequent exacerbators with either chronic bronchitis or emphysema; overlap COPD-asthma, frequent exacerbators (FE) with emphysema predominant; and FE with chronic bronchitis predominant. The COPD exacerbator phenotype is characterized by two or more exacerbations per year [4]. Frequent exacerbations cause acceleration in lung function and health status decline (measured by St. George's Respiratory Questionnaire), as

well as increased mortality and number of comorbidities [5]. It is reported that 13-47% of COPD patients are FE [6].

Acute exacerbation of COPD (AECOPD) is defined as a worsening of the patient's baseline dyspnea, cough, and/or sputum production, which must be treated with antibiotics or oral steroids. AECOPD is independently associated with a higher risk of mortality in patients with COPD [7], *i.e.*, mortality rates were 43-59% after 1 year [8,9]. Even a single COPD exacerbation leads to a significant increase in rates of decline in lung function, *i.e.*, pre- and post-bronchodilator forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) [10]. Reducing the frequency of exacerbations is one of the main goals of COPD therapy and follow-up.

Plasma fibrinogen (Fbg), C-reactive protein (CRP), and leukocyte count are the most frequently used inflammatory biomarkers in COPD, and it is known that patients with increased levels of these biomarkers (all three) are more prone to developing exacerbations [11].

A lot of effort is put into searching for a perfect COPD biomarker, but still, the history of previous exacerbations is strongly associated with future exacerbation risk, and no known biomarker provides additional information on exacerbation risk. In two large cohorts, the combination of soluble receptor for advanced glycation end-products and CRP best modeled total exacerbation frequency over the previous 12 months, and biomarkers CC16 and SP-D were each individually predictive of mortality. The conclusion of the analyses by Zemans *et al*. is that multiple biomarkers are much more strongly predictive than individual biomarkers, so approval of a panel of multiple biomarkers should be considered as biomarkers for COPD [12].

It is still necessary to find a biomarker that is widely available and affordable. That potential lies in hematological indices that are easily calculated from a standard complete blood count.

Hematological indices have been recognized through many studies as useful additional markers in many acute and chronic medical conditions. By now, the most studied is the neutrophil to lymphocyte ratio (NLR), which is associated with outcome prognosis in sepsis [13], solid tumors [14], and other inflammatory and chronic conditions. Platelet-related indices are a potential inflammatory marker in various inflammatory diseases, including COPD [15]. In this study, special attention was given to monocyte-related hematological indices which have shown a significant pattern in differentiating patients with AECOPD in need of hospitalization.

This study aimed to determine differences in monocyte-related hematological indices among four groups of patients – healthy smokers (HS), non-frequent exacerbators (NFE), FE, and patients hospitalized for AECOPD. Monocyte-related indices were compared to common inflammatory parameters (CRP, Fbg, white blood cells) as well, and so was the influence of most frequent COPD comorbidities. The goal of the analysis was to find whether there is an adequate biomarker in hematological indices that could help differentiate COPD phenotypes, exacerbation severity, and indication for hospitalization. To the authors' best knowledge, the indices we have evaluated have not been studied in these groups of patients so far.

Materials and Methods

Subjects

The study was retrospective and included a total of 154 individuals - 119 COPD patients and 35 HS in the control group. The COPD patients were divided into three groups – 41 FE, 41 NFE and 37 patients with known diagnosis of COPD hospitalized for acute COPD exacerbation (HAE). FE are, as earlier explained, patients with two or more COPD exacerbations per year.

The Ethics Committee of University Hospital Centre Zagreb and University of Zagreb School of Medicine (Zagreb, Croatia) approved the study. The study was conducted at the University Hospital Centre Zagreb, Clinical Department for Lung Diseases Jordanovac, from May to October 2013. All patients provided written informed consent for participation. The study was conducted following the Declaration of Helsinki of the World Medical Association and was registered at ClinicalTrials.gov before the enrolment of the first patient: NCT02092675 (http://clinicaltrials.gov).

The study was cross-sectional: the 154 subjects' data were collected according to the chronological order of the ambulatory visits and hospitalizations due to the AECOPD at the Clinical Department for Lung Diseases Jordanovac, University Hospital Centre Zagreb. A total of 35 out of 154 were cigarette smokers with no diagnosis of COPD or other lung disease.

COPD was diagnosed by a specialist pulmonologist according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, and patients were screened for eligibility and recruited during ambulatory visits at the outpatient clinic or during hospitalization for the AECOPD. GOLD criteria for COPD diagnosis, alongside signs and symptoms, include a FEV1/FVC value of <0.70. Consecutive patients, male or female, age >40 years with objectively confirmed COPD were included. Patients had to be active smokers or ex-smokers with 10 or more pack-years history and have adequate COPD therapy with no changes within the previous month.

Exclusion criteria were the change in COPD medications within the previous month, malignant diseases, acute cardiovascular events or clinically manifest cardiovascular disease, other non-regulated chronic diseases (arterial hypertension, diabetes mellitus), acute inflammatory conditions, and women of reproductive age.

The control group consisted of HS with the same inclusion and exclusion criteria as for COPD patients, except they do not have a COPD diagnosis.

Methods and laboratory tests

For the analysis of complete blood count, platelet parameters, and total leukocyte and lymphocyte count, we used blood samples collected in ethylenediaminetetraacetic acid tubes. Blood for CRP measurement in serum was collected into the tubes without additive.

Leukocyte, lymphocyte, and platelet counts, as a part of a complete blood count, were performed on the Sysmex XN-1000 analyzer (Sysmex Corporation, Kobe, Japan). Leukocyte, lymphocyte, and platelet counts are provided after the instrument has separated them according to the different signals, and mean platelet volume (MPV) and platelet distribution width were calculated by the software. Procalcitonin test was analyzed by the electrochemiluminescence immunoassay method on Cobas 6000 - module e601 (Roche Diagnostics, Mannheim, Germany). Immunoturbidimetry was a method used for CRP determination on the Cobas c501 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The measurement of Fbg was performed on a BCS XP analyzer (Siemens Healthcare Diagnostics, Marburg, Germany).

Statistical analysis

A Kolmogorov-Smirnov test was used for normal distribution testing. All data were non-parametric, so they were presented as

median with interquartile range, while only age was presented as median with minimum and maximum. Differences between controls and COPD patients were tested by a Mann-Whitney Rank Sum test, while Kruskal-Wallis one way analysis of variance on rank test was used in case of comparison between three or more groups of participants, and Pearson correlation was used for measuring relationships between variables. Data were considered statistically significant if $p<0.05$. Statistical analysis was performed by SPSS for Windows version 21.0 (IBM Corp., Armonk, NY, USA).

Results

The baseline characteristics of study participants are shown in Table 1. The study included 119 COPD patients and 35 HS as controls. A total of 35 out of 154 (22.7%) were healthy cigarette smokers. COPD patients were divided into three subgroups: 37 (24,0%) hospitalized for acute exacerbations, 41/154 (26,6%) NFE and 41/154 (26,6%) FE.

Well-known inflammatory parameters – CRP, leukocyte count, and Fbg showed increased levels in COPD patients compared to controls ($p<0.0001$) and were statistically significantly different between the groups of our patients. As expected, HAE patients had significantly higher CRP and Fbg values than all other groups of patients.

The only statistically significant difference in leukocyte values was in the NFE group compared to the HAE group ($p=0.024$). No statistically significant difference was found in HS *vs.* NFE ($p>0.999$), in HS *vs.* FE ($p>0.999$), HS *vs.* HAE ($p=0.150$) as well as NFE *vs.* FE ($p>0.999$). There was no statistically significant difference in FE *vs.* HAE ($p=0.168$).

When platelet to lymphocyte ratio (PLR) was compared, a statistically significant difference was found comparing these groups of participants: HS *vs.* HAE ($p<0.000$), NFE *vs.* HAE ($p<0.000$), and FE *vs*. HAE ($p<0.000$), while no statistically significant difference was found comparing the other groups: HS *vs.* NFE ($p<0.116$), HS *vs.* FE ($p<0.105$), NFE *vs.* FE ($p<1.000$).

No statistically significant difference was found in the values of hematological index platelet to mean particular volume (platelet/MPV) while comparing the following groups of our participants: NFE *vs.* HS ($p<1.000$), NFE *vs.* FE ($p<1.000$), HS *vs.* FE ($p<1.000$), and FE *vs.* HAE ($p<0.214$). A statistically significant difference was found in platelet/MPV between these groups of participants: NFE *vs.* HAE (p 0.008), and HS *vs.* HAE ($p<0.034$).

Regarding the NLR the results were as follows: HS *vs.* HAE ($p<0.000$), NFE *vs.* HAE ($p<0.000$) and FE *vs.* HAE ($p<0.000$), while no statistically significant difference was shown between HS *vs.* NFE ($p<0.371$), HS *vs.* FE ($p<0.259$), and NFE *vs.* FE ($p<1.000$).

The focus of our work is the following values: we have found a statistically significant difference in the values of a hematological index monocyte to neutrophil ratio (MNR) while comparing these groups of our participants: FE *vs.* HAE ($p<0.000$), NFE *vs.* HAE ($p<0.000$) and HS *vs.* HAE ($p<0.001$) (Figure 1).

A statistically significant difference was found in the values of hematological index monocyte to lymphocyte ratio (MLR) while

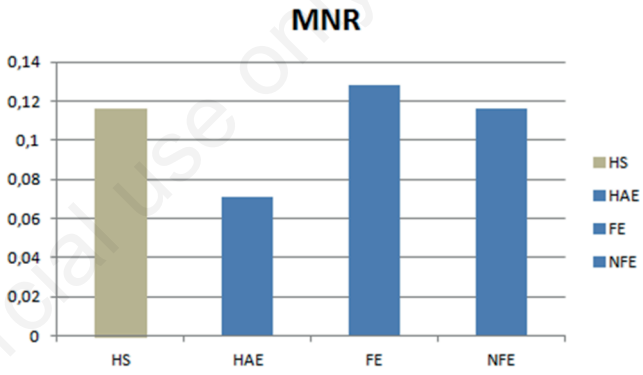

Figure 1. Monocyte to neutrophil ratio (MNR) values are statistically significantly different in the group of patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease (HAE) compared to the groups of frequent exacerbators (FE), non-frequent exacerbators (NFE), and healthy smokers (HS) ($p<0.05$).

Table 1. Baseline characteristics, inflammatory and monocyte-related parameters of controls and patients with chronic obstructive pulmonary disease.

Parameter	Controls (HS), n=35	NFE, n=41	FE, n=41	HAE, n=37
Age (years)	58 (45-74)	68 (49-88)	68 (48-88)	73 (61-90)
Sex, n/total				
Males	19/35	28/41	31/41	23/37
Females	16/35	13/41	10/41	14/37
Smoking status, n/total				
Smoker	35/35	17/41	15/41	12/37
Ex-smoker	0/35	24/41	26/41	24/37
CRP (mg/L)	1.7 (0.8-3.4)	2.7 (1.6-4.1)	5.6 (2.5-14.8)	24 (10.2-95.5)
Fbg (g/L)	3.7 (3.2-4.7)	4.1 (3.7-4.9)	4.8 (3.8-6.1)	5.1 (4.2-7.7)
WBC ($\times 10^9$/L)	7.9 (6.7-9.2)	7.8 (6.6-8.8)	8.0 (6.9-9.6)	9.5 (7.2-14.0)
Lymphocytes ($\times 10^9$/L)	2.2 (1.9-2.7)	1.9 (1.5-2.2)	1.9 (1.45-2.2)	0.9 (0.58-1.2)
Monocytes ($\times 10^9$/L)	0.6 (0.5-0.7)	0.6 (0.5-0.7)	0.7 (0.6-0.8)	0.5 (0.375-0.8)
MNR	0.116 (0.093-0.135)	0.116 (0.098-0.157)	0.128 (0.101-0.165)	0.071 (0.034-0.099)
MLR	0.25 (0.222-0.313)	0.333 (0.255-0.414)	0.353 (0.310-0.512)	0.556 (0.382-1.042)

Smoking status is presented as absolute numbers and all other data are presented as the median (interquartile range), except for age that is presented as median (minimum-maximum). Data were analysed by Mann-Whitney Test. HS, healthy smokers; NFE, non-frequent exacerbators; FE, frequent exacerbators; HAE, hospitalized for acute exacerbation of chronic obstructive pulmonary disease; CRP, C-reactive protein; WBC, white blood cells; MNR, monocyte to neutrophil ratio; MLR, monocyte to lymphocyte ratio.

comparing the same groups of participants: FE *vs.* HAE (p<0.022), NFE *vs.* HAE (p<0.000) and HS *vs.* HAE (p<0000) (Figure 2).

There was no statistically significant difference between FE and NFE (p=1.000) regarding MNR and MLR.

Concerning comorbidities, no significant difference in MLR nor MNR values distribution was found between the groups of patients with different comorbidities (p=0.05). Groups according to comorbidities were as follows: no comorbidities, arterial hypertension, diabetes mellitus, cardiovascular disease. No statistically significant difference was found neither when the comorbidities were clustered as arterial hypertension + diabetes mellitus, arterial hypertension + cardiovascular diseases, nor arterial hypertension + cardiovascular diseases + diabetes mellitus.

Statistically significant correlations between CRP, Fbg, and MLR values are found in all participants of this study – in healthy controls as well as in every COPD patient's group – HAE, NFE, and FE. There was no statistically significant correlation between the MNR and CRP, nor between the MNR and Fbg. There was no statistically significant difference in MNR and MLR distribution amongst the groups of different comorbidities (cardiovascular disease, AH, DM, no comorbidities group).

Discussion

This study demonstrated that MNR and MLR have a significant pattern across the subgroups of our patients and the HS as a control group. This pattern could have a role in differentiating patients with AECOPD in need of hospitalization, *i.e.*, to distinguish COPD exacerbation from other differential diagnoses in the emergency department. To the authors' best knowledge, MNR and MLR have not been the focus of research in patient groups like the ones in this work.

By now, the most studied is the NLR. The studies have shown that the NLR is a predictor of both AECOPD and mortality, could be used in defining COPD exacerbation endotypes, and has been used in other diseases except COPD [16,17].

Lymphocyte to monocyte ratio was studied and found to be a potentially useful marker in patients with urological and colorectal cancers as a prognostic marker in mood disorders as an inflammatory marker [18-20]. Lymphocyte to monocyte ratio was found to be more sensitive than PLR in differentiating glioblastoma (due to the systemic inflammation component) from brain metastasis. Elevated MLR and NLR may be unfavorable prognostic factors for clinical outcomes in patients with hyperglycemia during pregnancy.

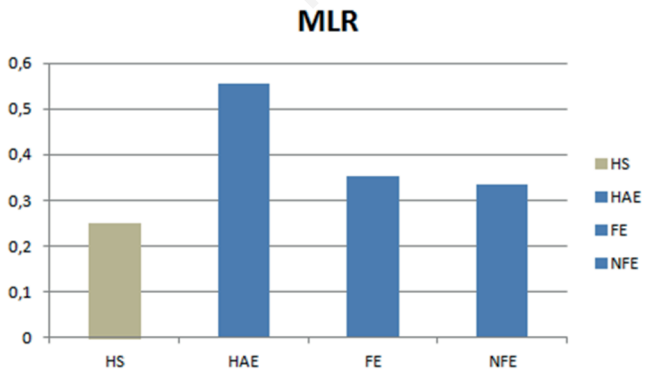

Figure 2. Monocyte to lymphocyte ratio (MLR) values are statistically significantly different in the group of patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease (HAE) compared to the groups of frequent exacerbators (FE), non-frequent exacerbators (NFE) and healthy smokers (HS) (p<0.05).

Neutrophil to monocyte and NLR were found potentially useful in predicting lupus nephritis [21]. In one study, the neutrophil count/(monocyte count + lymphocyte count) is shown to be more powerful than the NLR in discriminating tuberculosis from non-tuberculosis infectious lung diseases [22]. In a study by Rahimirad *et al*., LMR did not show a significant relation to in-hospital death in AECOPD, while the NLR ratio was associated with in-hospital mortality [23]. In a South Korean study by Lee *et al*. [24], there has been evaluated a reference value for LMR, NLR, PLR, and MPV among 12,160 samples from patients without any medical history. The mean LMR value was 5.31, but it is still necessary to adjust normal values based on race, age, and sex in further studies.

A statistically significant correlation between CRP and MLR values was proven in a study on knee osteoarthritis [25], and the correlation was shown in our study as well, while neither CRP nor Fbg shows a statistically significant correlation with MNR values in our study or in the earlier published studies.

The results of our study demonstrated a significant MLR and MNR pattern in HAE patients compared to the other two groups of COPD patients (FE, NFE) and the control group of HS. This could mean that MLR and MNR could be a good biomarker of AECOPD and the need for hospitalization due to AECOPD. These findings may help in differentiating AECOPD from other causes of acute dyspnea in COPD patients, such as pulmonary thromboembolism, pneumonia, or congestive heart failure, when considered together with CRP, Fbg and relevant clinical parameters.

We did not find a statistically significant pattern in any of the hematological indices analyzed to differentiate NFE from FE, which was one of the motivating ideas for this work.

The results we obtained are compared to the known inflammatory biomarkers, across the groups of participants and the groups of patients with different comorbidities, independent of COPD exacerbations.

As CRP and Fbg are well known for their role as biomarkers in inflammatory conditions, our results are in concordance with known data: CRP and Fbg levels are higher in the HAE group compared to other groups of patients, and CRP levels are higher in FE compared to NFE and other groups of participants, though Fbg and leukocyte count had no significant difference in FE *vs.* NFE groups. As Perera *et al*. concluded, FE have persistently higher systemic inflammatory markers [26].

Concerning PLR, we have confirmed what was already proven in earlier research: PLR values are higher in the AECOPD compared to stable disease and healthy controls, and PLR values were even higher in life-threatening acute respiratory failure [27,28]. PLR could also be considered a novel COPD exacerbation biomarker.

The major limitation of our study was the limited sample size; consequently, there were a relatively small number of subjects in each group. The study is a single-center one; and only spot parameters were analyzed with no follow-up values. Due to this limitation, it was not possible to set a cut-off value for MLR and MNR, which could be used in clinical routine for the decision of hospitalization. HS, as a control group, were on average younger than COPD patients (57.8 and 69.6 years, respectively), had a lower body mass index, and fewer comorbidities. There were more male than female participants (101 *vs*. 53, respectively). Patients hospitalized for AECOPD were older than HS, NFE, and FE (73, 57.8, 68, and 67.9 years, respectively).

Conclusions

In conclusion, the results of our study have demonstrated a statistically significant difference in MNR and MLR between hospitalized patients with AECOPD and patients with stable COPD (FE and NFE). This could mean that MLR and MNR could be valuable and available biomarkers for the prediction of AECOPD and the need for hospitalization. To our knowledge, this is the first study to identify the MLR and MNR as novel and reliable potential predictors for AECOPD. Further prospective studies are needed.

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