Is immature granulocyte a new predictor in the diagnosis of peptic ulcer perforation?

Introduction: Peptic ulcer perforation (PUP) requires immediate treatment. Immature granulocyte (IG) takes part in the inflammation process and is a biomarker which can be easily tested in peripheral venous blood.

Aim: This study demonstrates that IG is a convenient biomarker in the diagnosis of PUP.

Material and methods: Medical records of patients treated in the years 2018–2020 were analysed retrospectively. The study recognized three groups of patients: 42 PUD patients (Group 1), 42 PUP patients (Group 2) and 45 individuals acting as a healthy control (HC, Group 3). Surgical repair was performed in all patients from the PUP group. Differences between the groups were analysed statistically. The receiver operating characteristic curve (ROC) was calculated in order to predict the likelihood of PUP diagnosis based on the immature granulocyte count (IGC) and immature granulocyte percentage (IG%).

Results: The average IGC was high in group 1 and group 2, while the IG levels remained low in the HC group. A statistically significant difference between the groups was confirmed (mean values, respectively; 1.62 ± 0.41, 0.68 ± 0.22, 0.37 ± 0.55, and P = 0.003). The following parameters were calculated for IGC and IG%: AUC: 0.637; sensitivity: 61.9%; specificity: 57.1%; P = 0.031, AUC: 0.693; sensitivity: 61.9%; specificity: 64.3%; P = 0.02, respectively.

Results: IG is convenient as a diagnostic biomarker in PUP patients admitted to the emergency department.

KEYWORDS: emergency department, immature granulocyte, peptic ulcer perforation

ABBREVIATIONS

ANOVA – analysis of variance
AUC – area under the receiver operating characteristic curve
BUN – blood urea nitrogen
CBC – complete blood count
CI – confidence interval
CRP – C-reactive protein
ED – emergency department
HC – healthy control
IG – immature granulocyte
IG% – immature granulocyte percentage
IGC – immature granulocyte count
LMR – lymphocyte-monocyte ratio
NLR – neutrophil/lymphocyte ratio
PLR – platelet lymphocyte ratio
PUD – peptic ulcer disease
PUP – peptic ulcer perforation
ROC – receiver operating characteristic
SBI – serious bacterial infections
WBC – white blood cell

INTRODUCTION

Peptic ulcer disease (PUD) is among the most common gastrointestinal disorders worldwide. In general population, the lifelong prevalence of PUD reaches 5–10% and its incidence is 0.1–0.3%.

Complications are still observed in 10–20% of these patients. The reported annual peptic ulcer perforation (PUP) incidence varies between 0.004 and 0.014 [1]. PUP is a serious complication seen at the PUD’s emergency department (ED) which requires rapid diagnosis and emergency surgical intervention [2]. Mortality associated with PUP is reported to be 10 times higher when compared to other abdominal emergencies [3]. Acute and severe abdominal pain, nausea, vomiting and classic peritonitis symptoms, involving abdominal guarding and rebound tenderness, indicate the diagnosis of PUP. However, it may be challenging to establish correct diagnosis in patients with an unknown PUD history [4]. Considering the widespread character of antulcer treatment, some changes in the admission procedure of patients with PUP have been introduced. Therefore, new diagnostic parameters are required to properly evaluate these patients in the ED [5].

The pathophysiology of PUP involves development of acute inflammatory response resulting from mucosal damage. The attempts to evaluate prognosis in inflammatory diseases involving the inflammatory response mechanism, biomarkers such as neutrophil–lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), procalcitonin and CRP were investigated [6]. Recent studies examining the early detection of inflammation and striving to enable accurate diagnosis of patients with medical emergencies have focused on such parameters [7]. However, it is not easy to distinguish between simple and complicated PUD despite the use of these biomarkers. Some studies have shown that immature granulocytes are an indicator of increased myeloid cell proliferation and their count increases in...
to the course of infection and inflammation [8]. Therefore, IGC (immature granulocyte count) and IG% (immature granulocyte percentage) are presented in reference literature as a new biomarker of inflammation which can be measured easily and quickly from the routine integer. As a consequence studies have demonstrated the inflammation which can be measured easily and quickly from the percentage (IG%) are presented in reference literature as a new biomarker of infection cases (I-G and IG%) in PUP diagnosis and PUD/PUP differentiation have been published yet. Therefore, in this study we aimed to demonstrate that IGC and IG% are convenient inflammatory biomarkers which can be applied to both the diagnosis of PUD and differentiation between PUP and PUD.

**MATERIALS AND METHODS**

**Study population**

Our work was designed as a single-center, retrospective, observational study. Patients who presented to the emergency department with abdominal pain and were diagnosed with PUD and PUP between January 1, 2018 and December 1, 2020 were included in the study. All patients were reviewed retrospectively through the hospital information record system. The patient population analysed in this study involved patients diagnosed with PUD and PUP who underwent endoscopy and were treated by surgical intervention; all diagnoses were made according to the ICD-10 (International Classification of Diseases) coding system used in the ED. The patients were categorized into three groups: PUD (Group 1), PUP (Group 2) and healthy control group (HC) (Group 3). Group 1 consisted of patients whose PU diagnosis was confirmed on endoscopic examination. Group 2 consisted of patients whose suspected PUD diagnosis was confirmed by radiological findings (in the form of subdiafragmatic free gas or BT on X-ray) laboratory results and clinical presentation and who were treated by surgical intervention afterwards. Group 3 was randomized from patients with demographic characteristics similar to our noncomorbid study groups that were admitted to the ED with nonspecific abdominal pain complaints. The following exclusion criteria were applied: patients under <18 years old, pregnant women, patients with haematological malignancies that could alter blood test results, patients treated with granulocyte colony stimulating factor as well as patients receiving immunosuppressive drugs or steroids. Information such as demographic data, complete blood count (CBC) results and biochemical parameters were recorded.

**CBC and biochemical laboratory analysis**

In order to evaluate CBC parameters, Sysmex XN 1000 (Sysmex Corp., Kobe, Japan) device was used during admission to the ED. Immature granulocyte count (IGC), immature granulocyte percentage (IG%), white blood cells (WBC), neutrophil lymphocyte and platelet counts were recorded. By proportioning these parameters, neutrophil–lymphocyte ratio (NLR), lymphocyte–monocyte ratio (LMR) and platelet–lymphocyte ratio (PLR) were calculated. In the biochemistry analysis, Blood Urea Nitrogen (BUN), CPR (C-reactive protein) creatinine, urea and glucose levels were examined.

**Statistical analysis**

Standard deviation and mean values were calculated for continuous variables; median and interquartile range were calculated for non-parametric data. Each of the independent variables was compared by applying the chi-square test and, if suitable, independent t-test. One-way ANOVA test was applied to more than two groups which demonstrated numerical independent variables in accordance with normal distribution. Descriptive statistical analysis of all variables was studied with the use of SPSS 21.0. The optimal cut-off value for IGC and IG% parameters to serve as diagnostic biomarkers in

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**Tab. I. Baseline characteristics of patients.**

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>PUD GROUP 1 (N = 42)</th>
<th>PUD GROUP 2 (N = 42)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.60 ± 19.68</td>
<td>49.90 ± 22.23</td>
<td>0.019</td>
</tr>
<tr>
<td>Male gender n (%)</td>
<td>33 (78.6)</td>
<td>36 (85.7)</td>
<td>0.369</td>
</tr>
<tr>
<td>Previous history n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (31.0)</td>
<td>10 (23.8)</td>
<td>0.463</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (9.5)</td>
<td>7 (16.7)</td>
<td>0.332</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>9 (21.4)</td>
<td>8 (19.0)</td>
<td>0.786</td>
</tr>
<tr>
<td>Chronic kidney failure</td>
<td>1 (2.4)</td>
<td>2 (4.8)</td>
<td>0.557</td>
</tr>
<tr>
<td>Smoking</td>
<td>0 (0)</td>
<td>8 (19.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Malignancy</td>
<td>8 (19.0)</td>
<td>2 (4.8)</td>
<td>0.043</td>
</tr>
</tbody>
</table>

**Tab. II. Comparison of demographic and laboratory parameters between groups.**

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>PUD GROUP 1 (N = 42)</th>
<th>PUP GROUP 2 (N = 42)</th>
<th>HEALTHY CONTROL GROUP 3 (N = 45)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.60 ± 19.68</td>
<td>49.90 ± 22.23</td>
<td>41.11 ± 12.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender n (%)</td>
<td>33 (78.6)</td>
<td>36 (85.7)</td>
<td>16 (35.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Laboratory findings (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC count (+10³/mm³)</td>
<td>10.97 ± 6.22</td>
<td>11.01 ± 5.25</td>
<td>9.36 ± 2.53</td>
<td>0.199</td>
</tr>
<tr>
<td>Neutrophil (+10³/mm³)</td>
<td>7.66 ± 5.67</td>
<td>8.53 ± 4.77</td>
<td>6.11 ± 2.35</td>
<td>0.390</td>
</tr>
<tr>
<td>Lymphocyte (+10³/mm³)</td>
<td>2.19 ± 1.04</td>
<td>3.13 ± 4.11</td>
<td>2.24 ± 0.88</td>
<td>0.148</td>
</tr>
<tr>
<td>Platelet (+10³/mm³)</td>
<td>243.92 ± 108.99</td>
<td>266.52 ± 67.05</td>
<td>266.33 ± 70.51</td>
<td>0.365</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>122.04 ± 64.94</td>
<td>142.51 ± 78.65</td>
<td>114.44 ± 42.72</td>
<td>0.110</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.14 ± 0.41</td>
<td>1.21 ± 0.74</td>
<td>0.97 ± 0.14</td>
<td>0.084</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>35.59 ± 23.31</td>
<td>22.83 ± 15.06</td>
<td>13.42 ± 5.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/mL)</td>
<td>7 (32.5)</td>
<td>16.5 (68.5)</td>
<td>5 (7)</td>
<td>0.001</td>
</tr>
<tr>
<td>IG (%)</td>
<td>1.62 ± 0.41</td>
<td>0.68 ± 0.22</td>
<td>0.37 ± 0.55</td>
<td>0.003</td>
</tr>
<tr>
<td>IG count (+10³/mm³) (IQR)</td>
<td>0.05 (0.12)</td>
<td>0.04 (0.06)</td>
<td>0.03 (0.03)</td>
<td>0.001</td>
</tr>
<tr>
<td>NLR</td>
<td>4.29 ± 3.62</td>
<td>8.01 ± 10.91</td>
<td>3.53 ± 3.18</td>
<td>0.006</td>
</tr>
<tr>
<td>PLR</td>
<td>131.71 ± 84.26</td>
<td>248.31 ± 208.99</td>
<td>140.41 ± 89.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LMR</td>
<td>2.94 ± 1.52</td>
<td>6.21 ± 1.64</td>
<td>3.49 ± 1.45</td>
<td>0.025</td>
</tr>
</tbody>
</table>

BUN—blood urea nitrogen, WBC—white blood cell, IG—immature granulocyte, CRP—C-reactive protein,
may lead to patient’s death [12]. Early diagnosis and immediate intervention can decrease the high mortality and morbidity risks observed in the ED. Therefore, rapid tests that can be easily detected in peripheral venous blood, are non-invasive and cost-efficient are required to achieve this goal. That is why recent studies have focused on NLR, PLR and various other inflammation markers. Some studies have demonstrated the NLR as a diagnostic marker of PUD [4]. PUD is a defect of the muscularis mucosae which extends along the gastric and duodenal wall, involving also its deeper layers. Systematic reviews of PUD show that one-year prevalence of PUD changes is estimated between 0.12% and 1.50% based on medical doctor diagnoses [13].

PUD can be complicated by bleeding, perforation and obstruction. Increased BUN/creatinine and elevated inflammation parameters are among the laboratory and radiological diagnostic indicators discussed in various studies [14]. In clinical practice, the use of NLR is becoming more popular in estimating the survival of patients with malignancies, coronary artery disease, acute appendicitis, acute cholecystitis, acute pancreatitis and community-acquired infections [15]. In our study, similarly to literature of the subject, NLR was found to be significantly higher in PUP Group when compared to other groups.

Tab. II. compares laboratory parameters between the groups. The average IGC level was found to be high in Group 1: 0.05 (0.12) and in Group 2: 0.04 (0.06), while it remained low in HC Group: 0.03 (0.03) and a statistically significant difference was found between the groups (P = 0.001). The average level of IG% was high in Group 1: 1.62 ± 0.41 and in Group 2: 0.68 ± 0.22, while it also remained low in HC Group: 0.37 ± 0.55 and a statistically significant difference was found between the groups (P = 0.003). NLR, PLR and LMR averages were discovered to be higher in PUP Group when compared to other groups and a statistically significant difference was found between the groups (P = 0.006, P < 0.001, P = 0.025, respectively). In the PUP Group, the average CRP level was 16.5 (68.53) – it was found to be statistically significant and higher than in other groups.

The efficiency of establishing correct PUP diagnosis based on IGC and IG% was calculated by designing ROC curves. Having applied a cut-off value of 0.05 for IGC and 0.045 for IG%, the following parameters were calculated: AUC: 0.637; sensitivity: 61.9%; specificity: 57.1%; P = 0.031 and AUC: 0.693; sensitivity: 61.9%; specificity: 64.3%; P = 0.02 respectively (Fig. 1., Tab. III.).

DISCUSSION

PUP is a high-risk clinical condition manifesting as acute abdomen which causes generalized or localized peritonitis, sepsis and may lead to patient’s death [12]. Early diagnosis and immediate intervention can decrease the high mortality and morbidity risks observed in the ED. Therefore, rapid tests that can be easily detected in peripheral venous blood, are non-invasive and cost-efficient are required to achieve this goal. That is why recent studies have focused on NLR, PLR and various other inflammation markers. Some studies have demonstrated the NLR as a diagnostic marker of PUD [4]. PUD is a defect of the muscularis mucosae which extends along the gastric and duodenal wall, involving also its deeper layers. Systematic reviews of PUD show that one-year prevalence of PUD changes is estimated between 0.12% and 1.50% based on medical doctor diagnoses [13]. PUD can be complicated by bleeding, perforation and obstruction. Increased BUN/creatinine and elevated inflammation parameters are among the laboratory and radiological diagnostic indicators discussed in various studies [14]. In clinical practice, the use of NLR is becoming more popular in estimating the survival of patients with malignancies, coronary artery disease, acute appendicitis, acute cholecystitis, acute pancreatitis and community-acquired infections [15]. In our study, similarly to literature of the subject, NLR was found to be significantly higher in PUP Group when compared to other groups.

IG are the progenitor forms of neutrophiles in their process of maturation in bone marrow. These cells are not detected in peripheral
venous blood of healthy individuals. Whenever inflammation develops, immature neutrophils are released from bone marrow into the circulation [16, 17]. The elevation of IG levels in circulation reflects a reaction of bone marrow against infections. In recent years it has been proven that it is possible to detect IG in peripheral blood thanks to technical advancements in automated hematological analysers [18–20]. The latest studies of IGC and IG% demonstrated that their levels increase in cases of infection and sepsis [21, 22]. However, to our knowledge no study focusing on IGC and IG% application in diagnosing PUP has been published yet. In this study we showed that IGC and IG% are useful biomarkers characterized by low sensitivity and high specificity in the diagnosis of PUP. Our study showed that these parameters can serve as predictors in the diagnosis of PUP, given the cut-off value of 0.05 for IGC and 0.045 for IG%. Similar studies reported that IG% was found useful in the diagnosis of acute appendicitis at a cut-off value of 0.6 (AUROC: 0.795, sensitivity: 55.5%, specificity: 96.1%) [23]. Another study found IG% to be a predictor of mortality with cut-off value >1%, 93.8% specificity and 100% sensitivity in patients with upper gastrointestinal bleeding [24]. In another study which examined a total number of 301 sepsis patients for the early diagnosis of sepsis, IG% allowed to exclude clinically diagnosed sepsis at a cut-off value of 2.0 with 90.9% specificity and 38.5% sensitivity [25]. In a study of serious bacterial infections (SBI) in pediatric population conducted by Güngör et al., the cut-off value was determined as 0.35 for IG%, the sensitivity for predicting SBI was found to be 75.4% and specificity was 76.6% [26].

This study had specific limitations. The data obtained for this research is limited since it is a retrospective study. In CBC, the IG level measurement did not apply before 2018, which affected the number of patients included in this study. Secondly, the IG level measurement was not standardized because the time between the onset of symptoms and the admittance to the ED was not fully known. This period may have affected the IG levels. Therefore this field requires further prospective studies to be carried out with regard to IG standardisation and ensuring repetitive measurements performed in specific periods of time.

CONCLUSION

As a result, we proved that IG is convenient as a diagnostic biomarker in PUP patients admitted to the ED.

REFERENCES

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The authors declare that they have no competing interests.

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