RESEARCH ARTICLE

Diagnostic Power of Blood Parameters as Screening Markers in Gastric Cancer Patients

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Abstract

Background: Gastric cancer (GC) is the fifth most common cancer worldwide. Since development is usually asymptomatic, it is generally diagnosed at an advanced stage. The value of screening in patients with nonspecific symptoms for GC is controversial. Aim: The study aimed to evaluate whether hematological parameters (platelet count (PC), mean platelet volume (MPV), MPV/PC ratio, red blood cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR)) are useful markers to differentiate between gastric cancer patients and healthy individuals. Materials and Methods: Sixty-one patients with gastric cancer and sixty-one healthy individuals were enrolled to the survey and retrospective analysis of selected blood parameters were performed. Results: The mean values of PC, MPV, RDW, NLR, and PLR were significantly higher in GC patients compared to the control group. No statistical differences were observed in MPV/PC ratios. Likewise, no significant statistical differences were revealed in values of blood parameters among TNM stage groups. The RDW showed the highest diagnostic specificity and sensitivity. Conclusions: Hematological parameters: PC, MPV, RDW, NLR, PLR have diagnostic power and can discriminate patients with gastric cancer from patients without cancer. Blood parameters compared with clinical symptoms might alert physicians and patients and lead to performancce of upper gastrointestinal endoscopy, the gold standard in gastric cancer screening and therebly increase the early detection of cancer.

Keywords: Gastric cancer - platelet - mean platelet volume - red blood cell distribution width - neutrophil - lymphocyte

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Introduction

Gastric cancer (GC) is the fifth most common cancer worldwide, with 951,594 new cases diagnosed, accounting for 6.8% of all cancers and the third leading cause of deaths (723,000 deaths; 8.8% of the total deaths from cancer) in 2012 (Cancer Research UK, 2015). In Europe, more than 139,000 new cases of GC were diagnosed in 2012 making GC the sixth most common incident cancer (Ferlay et al., 2013).

Both genetic and environmental factors are involved in GC development (Fock et al., 2014). Recent epidemiological and clinical investigations have evidenced the relationship between inflammation and development of gastrointestinal cancers (Kim et al., 2009; Fichtner et al., 2015; Pietrzyk et al., 2015). Helicobacter pylori infection is considered to be the leading cause of gastric mucosa inflammation (Subhash and Ho, 2015). Gastritis is followed by the activation of neutrophils, leukocytes, macrophages, and platelets. Long-standing inflammation promotes the stomach wall ulceration and may initiate the cancer pathway: inflammation-metaplasia-dysplasia-cancer (Ernst, 1999; Fock, 2014).

Development of GC is usually asymptomatic; therefore, it is diagnosed at the advanced stage (Hartgrink et al., 2009). The value of screening in patients with nonspecific symptoms for GC is controversial; however, it is provided in geographical regions with high GC incidence rates, i.e. Japan, or Chile (Leung et al., 2008). By contrast, in countries with low incidence of GC, such as the United States, this strategy is recognized as costly and unwarranted, and it is dedicated to high-risk patients, i.e. individuals with chronic gastric atrophy, gastric polyps, partial gastrectomy, familial adenomatous polyposis, and hereditary nonpolyposis colon cancer (Fock et al., 2008).

Efforts to overcome the diagnostic problems and limitations should be the primary goal of modern medicine. Like in other cancers, an ideal would be a simple noninvasive blood-based test, which would allow for the diagnosis of GC at the stage, when curative intervention is still possible (Bornschein et al., 2010). Platelet count (PC), mean platelet volume (MPV) are routinely measured hematological parameters which higher levels were described in patients with malignancies of the pancreas

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and liver compared to healthy individuals (Cho et al., 2013). Recently, attention has been paid to red blood cell distribution (RDW), neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), critical players in systemic inflammation and cancer biology including cancer prediction, progression and survival prognosis (Cakal et al., 2009; Templeton et al., 2014; Tüzün et al., 2014; Kose et al., 2015).

Considering the importance of inflammatory pathway in gastric cancer development, we designed the survey and retrospectively evaluated whether hematological parameters are useful markers to differentiate between gastric cancer patients and healthy individuals. In particular, we focused on the level of PC, MPV, RDW, MPV/PC ratio, NLR, and PLR.

Materials and Methods

We retrospectively analyzed patients who have who have been initially diagnosed with gastric cancer (n=61) and were admitted to the Department of General, Oncological and Minimally Invasive Surgery of the 1st Military Clinical Hospital in Lublin, Poland between 2010-2015. Healthy individuals (n=61), served as a control group, were selected from patients of our hospital outpatient clinic. Exclusion criteria for both study groups (gastric cancer patients and control group) included: hypertension, diabetes mellitus, antiplatelet drug use, hepatic and renal failure, hyperlipidemia, and autoimmune disease. The extent of the GC's spread was described using the tumor-node-metastases (TNM) cancer staging system of the International Union for Cancer Control (UICC) (Sobin et al., 2010). TNM 1-2 stage group included 35 GC patients, while 26 GC patients were recruited to the TNM 3-4 stage group. Demographics and laboratory values of blood tests were extracted from the hospital medical database records. The evaluation of blood parameters was performed within 1 hour after venipuncture. The hematological parameters were measured by ABX Pentra XL 80 (Horiba Medical).

In our laboratory, normal values for studied blood parameters ranged as follows: PC: 150-400 x 10^9/l, MPV: 6.0-10.8fl, RDW: 11.0-15.0%, WBC: 4.0-10.0 x 10^9/l, neutrophil: 2.0-8.0 x 10^9/l, and lymphocyte: 2.0-4.8 x 10^9/l.

Statistical analysis was performed with the SPSS software (SPSS 15.0, Chicago, IL). The results were expressed as mean ± standard deviation (SD). Independent t-test was used to assess the difference in blood parameters between gastric cancer patients and control group. Receiver-operating characteristics (ROC) curve analysis was performed to identify cut-off values of studied blood parameters. A p-value less than 0.05 were considered to be statistically significant.

Results

Sixty-one patients with newly gastric cancer and sixty-one healthy individuals were enrolled to the survey. The demographics and laboratory blood parameters of GC patients and control group are shown in Table 1. The age and gender distribution did not differ significantly between the studied groups. Likewise, no significant statistical differences were revealed in values of blood parameters between TNM stage groups.

The mean value of PC, MPV, RDW, NLR, and PLR was significantly higher in GC patients compared to control group. No statistical differences were observed in MPV to platelet count ratio and WBC between gastric cancer patients and control group.

ROC analysis (Figure 1) showed the ideal cut-off value of PC was 252 x 10^9/l (AUC: 0.612, sensitivity: 61.5%, specificity: 53.8%) and 8.15fl as the cut-off value of MPV (AUC: 0.636, sensitivity: 61.5%, specificity:

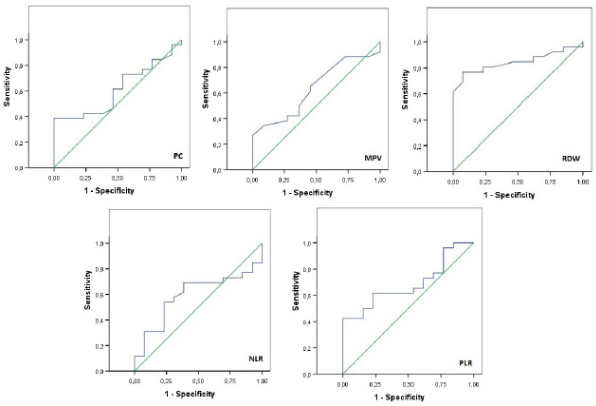

Figure 1. ROC Curve Analysis of PC, MPV, RDW, NLR, and PLR. PC: platelet count; MPV: mean platelet volume; RDW: red blood cell distribution width; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio

Table 1. Demographics and Laboratory Values for Blood Parameters of the Study Groups

	Gastric cancer patients (n = 61)	Control group (n = 61)	P-value
Age (years)	67 ± 11.34	65 ± 8.92	0.534
Gender (M:F)	35:26	30:31	0.507
PC (x 10^9/l)	294.77 ± 119.26	236.15 ± 46.37	0.018
MPV (fl)	8.34 ± 0.76	8.01 ± 0.49	0.030
MPV/PC ratio	0.032 ± 0.01	0.037 ± 0.01	0.069
RDW (%)	14.88 ± 3.91	12.23 ± 0.74	< 0.001
WBC (x 10^9/l)	6.88 ± 1.97	6.35 ± 1.59	0.202
NLR	3.05 ± 2.09	2.25 ± 0.87	0.020
PLR	187.75 ± 92.97	138.77 ± 39.32	0.002

Age and laboratory values of blood parameters are expressed as mean ± SD, PC: platelet count, MPV: mean platelet volume, MPV/PC: mean platelet volume to platelet count ratio, RDW: red blood cell distribution width, WBC: white blood cell, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio

54.5%). The cut-off value of RDW was 13.2% (AUC: 0.845, sensitivity: 76.9%, specificity: 92.3%). The cut-off value of NLR and PLR was 2.26 (AUC: 0.593, sensitivity: 53.8%, specificity 76.9%) and 163.83 (AUC: 0.686, sensitivity: 61.5%, specificity: 76.9%), respectively.

Discussion

To date, the lack of a single specific tumor marker for reliable detection of GC patients remains a fundamental problem in ensuring an excellent prognosis for effective GC treatment, which mainly relies on the early diagnosis. Previous studies have focused on exploring the usefulness of selected inflammatory indices: PC and MPV or NLR and PLR to distinguish between GC and healthy patients (Yamanaka et al., 2007; Lee et al., 2013; Kılınçalp et al., 2014; Demirkol et al., 2015). To provide more comprehensive information about inflammation and to diagnose GC patients Balta et al. suggested to evaluate PC and MPV together with other biomarkers (Balta et al., 2014). As far as we are aware, our investigation is the first to take this approach. Here, we evaluated the correlation between seven routinely measured hematological parameters, known as inflammatory indices, and GC. To maximize the effectiveness of the study and obtain the most reliable results, we excluded patients (and controls) with various pathologies, which could interfere with PC, MPV, MPV/PC ratio, RDW, NLR, and PLR. The exclusion criteria of our study emphasize the value of parameters considered for GC detection. In spite of that, we are aware that our study has still certain limitations, i.e. small number of individuals included, retrospective and single-center study.

The exact mechanism by which elevated values of PC, MPV, RDW, NLR and PRL in GC are noticed is not entirely evident. However, the probable explanation can be discussed. Persistent Helicobacter pylori infection that promotes inflammation is a one of crucial processes gastric carcinogenesis (Subhash et al., 2015). The prolonged inflammation can be hazardous to gastric epithelium and can induce cell damage. Altogether, these pathologies mirror the increase of inflammatory parameters in the total blood count (Fock et al., 2008; Fock, 2014).

The reports concerning the relationship between PC and GC are inconsistent. High PC is documented in 30-60% of gastrointestinal cancers cases. Significant raise (up to 5-10 times the average level) in PC is considered as an early indicator of cancer. Some reports showed that increase in PC value is an indicator of poor prognosis (faster disease progression and shorter overall survival) in GC patients (Ikeda et al., 2002; Kandemir et al., 2005; Voutsadakis et al., 2014). However, the PC value increase was no observed or even the decrease in PC value was recorded in GC patients (Osada et al., 2010; Kılınçalp et al., 2014). The biological mechanism for the PC increase in cancer is associated with oversecretion of cytokines, i.e. interleukin-6 (IL-6) stimulated by malignant tumor cells (Nash et al., 2002). Elevated cytokines level triggers the cascade of biochemical events and activates the hepatic thrombopoietin/thrombocytosis pathway (Lupia et al., 2012).

MPV is a straightforward and accurate marker of the functional status of platelets (Thompson et al., 2014). Our observations revealed elevated MPV level in GC patients compared to healthy controls, which is in agreement with the results announced by Osada et al. (2010) and Kılınçalp et al. (2014). On the contrary, low MPV values were reported in patients with advanced non-small cell lung cancer (NSCLC), as well as in individuals with solid tumors (lung, breast, gastric) with metastasis to the bone marrow (Aksoy et al., 2008; Inagaki et al., 2014). Divergent reports might be related to various pathological mechanisms. Generally, during cancer initiation, progression, and metastases, growing mass of malignant cells accelerate the secretion of pro-inflammatory and pro-angiogenic cytokines. These proteins play a central role in stimulation of platelets production and mediate the platelets activity (Nash et al., 2002). Several studies have described that more reactive platelets are characterized with increased MPV (Kisucka et al., 2003). Conversely, the reduction in MPV value may be interpreted as selective consumption of larger platelets as a result of the high platelets reactivity in response to stimuli (Inagaki et al., 2014).

Recently, MPV to platelet count ratio (MPV/PC ratio) has been preferentially proposed as a predictor of cancer patients (Inagaki et al., 2014). However, the relation between MPV/PC ratio and cancer is inconsistent. For example, Cho et al. reported significantly higher MPV/PC ratio in patients with hepatocellular carcinoma compared to control group (Cho et al., 2013). In contrast, reduction in MPV/PC ratio was detected in patients with advanced non-small cell lung carcinoma (Inagaki et al., 2014). In our study, the MPV/PC ratio between gastric cancer patients and the control group was comparable. We did not find the previous report assessing the MPV/PC ratio for patients with gastric cancer. MPV/PC ratio is an important marker for the inflammatory-derived pathologies, i.e. infective endocarditis or deep vein thrombosis (DVT) (Azab et al., 2011; Slavka et al., 2011; Han et al., 2013). Also, MPV/PC ratio is recommended to measure for differentiating iron deficiency anemia from the other types of anemia (Cho et al., 2013). Thus, the MPV/PC ratio would have potential clinical value in GC cancer patients' identification. However, further investigations should be conducted to clarify the pathogenic mechanisms of MPV/PC ratio in GC, and define the possibilities of this ratio use for cancer detection.

Red blood cell distribution width (RDW) is a parameter of the complete blood count that reflects the variability of red blood cell dimensions (anisocytosis) (Montagnana et al., 2002). The RDW is considered a detector of iron deficiency as well as an important inflammatory biomarker (Cakal et al., 2009; Borné et al., 2014; Tüzün et al., 2014). Recently, it has been demonstrated that RDW biomarker has a prognostic value in certain cancers (i.e. prostate cancer, clear renal cell carcinoma, breast cancer) (Seretis et al., 2013; Albayrak et al., 2014; Wang et al., 2014). In our study, the RDW was higher in GC patients compared to the control group. This result accords with earlier reports of Wang et al. who documented elevated RDW in patients with clear renal cell carcinoma (Wang et al., 2014). Ay

et al. (2015) found that the increased RDW is associated with colorectal cancer but not with colon polyps. In GC patients, RDW level might be influenced by inflammation and iron loss associated with chronic inflammatory status (Sategna Guidetti et al., 2015). Many studies documented that in response to increased levels of pro-inflammatory factors (i.e. interleukin-6, C-reactive protein, tumor necrosis factor-alfa), highly secreted in cancers, the erythropoietic activity and thereby iron metabolism and homeostasis are impaired (Vakkila et al., 2004; Lippi et al., 2009). However, the link between cancer cell metabolism and dysregulation of iron metabolism still raises many questions (Manz et al., 2016).

The other inflammatory markers evaluated in our study are neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR). These biomarkers have been recommended as clinically reliable diagnostic indicators in various types of malignancies (Shimada et al., 2010; Li et al., 2014). High NLR and PLR levels at diagnosis were associated with poor prognosis in patients with colon cancer, ovarian cancer, and gastric cancer (Gunor et al., 2009; He et al., 2013; Jiang et al., 2016). Our results agree with the finding of Aldemir et al. (2015), Yu et al. (2015) and Lian et al. (2015) who documented high values of NLR and PLR in GC patients. The direct mechanism is not entirely understood; however, one seems to be most presumably. Cancerogenesis is associated with neutrophil- and platelet-related inflammation and reduction of lymphocyte-dependent antitumor cellular immune response. These changes result in an increase of neutrophil and platelets levels and a decrease of lymphocyte level (Hsu et al., 2015). Other reports have shown that high preoperative values of NLR and PLR are predictors of survival in gastric cancer patients including early and late stages of disease (Yamanaka et al., 2007; Lee et al., 2013).

In conclusion, our results suggest that hematological parameters: PC, MPV, RDW, NLR, PLR have a diagnostic power and can discriminate patients with gastric cancer from patients without cancer. The RDW showed the highest diagnostic specificity and sensitivity. All blood parameters measured are available in routine blood tests, are easy to make by the vast majority of automated analyzers and does not increase the cost of diagnosis. Blood parameters compared with clinical symptoms might alert physician and patients and leads to perform the upper gastrointestinal endoscopy, the gold standard in gastric cancer screening and thereby increase the early detection of cancer.

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