The importance of red cell distribution width on gastric cancer:  
A preliminary study

Dilek Erdem1, Emre Erdem1, Yasemin Turgut Kurt1, Turgut Kacan4, Bahiddin Yilmaz5, Meral Gunaldi6, Mahmut Buyuksimsek1
1Department of Medical Oncology, Bahcesehir University Medical School, Samsun Medical Park Hospital, Samsun,  
2Department of Nephrology, Ondokuz Mayis University Faculty of Medicine, Samsun,  
3Department of Internal Medicine, Samsun Education and Research Hospital, Samsun,  
4Department of Medical Oncology, Afyonkarahisar State Hospital, Afyon,  
5Department of Medical Oncology, Ondokuz Mayis University Medical School, Samsun,  
6Department of Medical Oncology, Istanbul Aydin University VM Medical Park Hospital, Istanbul,  
7Department of Medical Oncology, Cukurova University Medical School, Adana, Turkey

Value of red cell distribution in gastric cancer

Abstract
Aim: Red cell distribution width (RDW) is an elevated marker in several cancers like breast, colon, prostate and pancreatic cancer at the time of diagnosis. Gastric cancer (GC) is the fifth most common cancer and also the third leading cause of cancer deaths. We aimed to determine whether RDW values diagnosis in GC.Material and Method: This retrospective study included gastric cancer patients. Median age was 42-year old and sex- matched healthy controls. Blood samples were retrospectively obtained from the computerized patient database before surgery or chemotherapy/radiotherapy. Results: RDW, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio(PLR) were significantly higher in GC patients when compared to healthy subjects (RDW: 44.9 vs 41.4 p<0.0001, NLR: 3.40 vs 1.90 p<0.0001, PLR: 245.9 vs 131.1 p=0.007). There was no statistically significant association between these markers (RDW, NLR, and PLR) and stage, histopathological subgroups and metastasis stage at the time of diagnosis. Discussion: Elevated RDW is a simple, cheap and readily available marker and may be useful in GC at the time of early diagnosis especially. Also, NLR and PLR can accompany RDW in the assessment of GC.

Keywords
Gastric Cancer; Red Cell Distribution Width; Neutrophil to Lymphocyte Ratio; Platelet to Lymphocyte ratio

DOI: 10.4328/ACAM.6086   Received: 13.11.2018   Accepted: 13.12.2018   Published Online: 21.12.2018   Printed: 01.11.2019   Ann Clin Anal Med 2019;10(6): 658-61
Corresponding Author: Mahmut Buyuksimsek, Department of Medical Oncology, Cukurova University Medical School, Adana, Turkey.
GSM: +905368622026 E-Mail: mahmutbuyuksimsek@gmail.com
Value of red cell distribution in gastric cancer

Introduction
RDW is a component of complete blood count (CBC) reflecting erythrocyte anisocytosis which means the heterogeneity of erythrocyte volume [1]. Its main role was limited to the differential diagnosis in anemias in the past, but recent data show that elevated RDW is associated with a very wide spectrum of diseases leading mostly to inflammation but also oxidative stress and malnutrition [2,3]. Some inflammatory diseases are related to high levels of RDW such as inflammatory bowel disease, rheumatoid arthritis, hypertension, atherosclerosis, heart failure etc. [4,5]. Also, elevated RDW can predict mortality [6]. Malign tumors are known to trigger chronic inflammation which can also be an inducer for cancer itself [7]. Cancer-associated inflammation causes cellular and genomic damage by releasing a number of oxidative molecules and increase cancer risk that affects RDW [8]. In addition, some anti-inflammatory agents and antioxidants were shown to decrease the risk of cancer [9]. GC remains a major health problem worldwide and also it is the fifth most common cancer and the third leading cause of cancer deaths [10]. GC is a very heterogeneous disease that is due not only to tumor characteristics but also to host-related factors. Therefore the diagnosis is difficult in general [11]. With regard to these features of GC, we hypothesized that elevation of basic RDW related to cancer-induced chronic inflammation and nutritional status might be a biomarker and might be used in the early detection of GC. Also, there are factors leading to inflammation in peripheral blood count like NLR and PLR which may increase in several diseases including many cancer types [12-14]. Thus, we aimed to reveal the role of RDW in the diagnosis of GC and contribute this idea with examining NLR and PLR.

Material and Method
This is a retrospective study performed between November 2011 and May 2014 in which patients of Samsun Education and Research Hospital Medical Oncology Department were reviewed. The data were collected from hospital records and patient files of 68 patients with GC and 42 healthy controls were analyzed. The data were noted before surgery. The exclusion criteria involved cardiac disease, chronic obstructive lung disease, thromboembolism, chronic renal failure, hepatic disorders, hypertension, acute and chronic infections, stroke, hematologic disease, and other accompanying cancer. None of the patients were on anticoagulant therapy. The diagnosis of GC was made pathologically by endoscopic biopsy or surgically resected specimen. The cancer stage was determined in accordance with the TNM (tumor-node-metastasis) classification system (International Union against Cancer; UICC-7). Patients characteristics involved demographics, pathologic features, and hematological parameters. The healthy group involved the people with no known disease admitted to the internal medicine outpatient clinic for a check-up. The laboratory parameters were recorded at diagnosis and prior to the therapy, and collected from a computerized patient database. White blood cell count (WBC), neutrophil, lymphocyte, platelet count (PLT) and RDW were analyzed in the complete blood count using the same analyzer (Mindray BC6800). Standard tubes with constant amount of ethylenediaminetetraacetic acid were used. Our laboratory gives the standard deviation (SD) of RDW as femtolitre (fl). The normal range for RDW-SD was between 35.1-46.3 fl. Neutrophil counts were between 1.56-6.13 $\times 10^9$/mm$^3$ and lymphocyte counts were between 1.3-3.6 $10^9$/mm$^3$. NLR and PLR were calculated by dividing neutrophil and platelet count to lymphocyte count, respectively. The procedures followed were in accordance with the ethical standards and with the Helsinki Declaration of 1975, as revised in 2000. All people gave their informed consent prior to their inclusion in the study. The SPSS 19.0 software package was used for statistical analysis of the compiled dataset. The Kolmogorov-Smirnov test was used to determine the normality of data. Descriptive analyses for normally distributed variables were means and standard deviations and for abnormally distributed variables were medians with interquartile ranges. The Student’s t-test or Mann-Whitney U test were used to compare groups, with the cChi-Square test used for categorical variables. A p-value of less than .05 was considered statistically significant.

Results
The study included 68 GC patients and age- and sex-matched 42 controls. Their features and hematologic results are shown in Table 1. The median age among patients and healthy controls were 59.1 ± 11.5 (35-83) years and 56.3 ± 6.4 (44-70) years, respectively. There were 54 male (79 %) and 14 female (21 %) patients in GC group while healthy subjects included 28 males (67 %) and 14 females (33 %). GC patients had higher RDW (p<0.0001), NLR (p<0.0001) and PLR when compared to healthy subjects at the time of the diagnosis (p=0.007; Table 1). There was no correlation between RDW and stage (Table 2) and metastatic state at the time of diagnosis (Table 3).

Discussion
In the present study, we found a significant relationship between GC and elevation of RDW, NLR and PLR values at the time of diagnosis. Inflammation, anemia and oxidative stress are important factors for developing cancer. Elevated RDW is associated with oxidative stress, inflammation, and anemia [1,15]. Recent data show that the relation between RDW and age and mortality is supported by many studies [16]. And also most of inflammatory disease are related with high levels of RDW [4,5]. Although the exact mechanisms of how RDW levels are influenced by inflammation are unknown, four main causes step forward in this issue: impaired iron metabolism, decreased red blood cell (RBC) survival, erythropoietin response and the overproduction of selective cytokines such as CRP (C-reactive protein), tumor necrosis factor alpha and interleukin-6 [7]. Elevated RDW is as-

| Table 1. Hematological parameters at the time of diagnosis |
|------------------|------------------|------------------|------------------|
|                  | Healthy subjects | Patients         | p-value          |
|                  | (n=42)           | (n=68)           |                  |
| WBC (10$^9$/µL)  | 6868±1595        | 7570±3421        | 0.149            |
| Neutrophil (10$^9$/µL) | 3986±1431    | 4791±2998        | 0.062            |
| Lymphocyte (10$^9$/µL) | 2710±2813     | 1827±1002        | 0.020            |
| Hemoglobin (g/dl) | 13.5±1.4         | 11.4±1.5         | <0.0001          |
| MCV (fl)         | 85.6±4.5         | 81.5±7.9         | <0.0001          |
| MPV (fl)         | 11.3±12.1        | 9.4±1.1          | 0.20             |
| PDW               | 15.8±0.66        | 12.1±2.5         | <0.0001          |
| PLT (10$^9$/µL)  | 284±51.8         | 370±748          | 0.458            |
| RDW (%)          | 41.4±3.1         | 44.9±5.1         | <0.0001          |
| NLR               | 1.90±1.35        | 3.40±2.79        | <0.0001          |
| PLR               | 131.14±67       | 245.9±334.4     | 0.007            |

NLR: Neutrophil - Lymphocyte Ratio; PLR: Platelet - Lymphocyte Ratio; WBC: White blood cell count; MCV: Mean corpuscular volume; MPV: Mean platelet; volume; PDW Platelet distribution width; PLT: platelet; RDW: red cell distribution width
Value of red cell distribution in gastric cancer

Table 2. Hematological parameters of early and advanced stage of gastric cancer during diagnosis

|                      | Early stage (n=18) | Advanced stage (n=50) | p-value |
|----------------------|-------------------|-----------------------|---------|
| WBC (10³/µL)         | 7047±2037         | 7759±3790             | 0.829   |
| Neutrophil (10³/µL)  | 4253±1570         | 4984±3361             | 0.857   |
| Lymphocyte (10³/µL)  | 1825±848          | 1828±1060             | 0.813   |
| Hemoglobin (g/dl)    | 11.7±1.3          | 11.2±1.5              | 0.237   |
| MCV (FL)             | 80.0±9.6          | 81.8±7.3              | 0.541   |
| MPV (FL)             | 9.5±0.9           | 9.4±1.1               | 0.775   |
| PDW (10³/µL)         | 12.4±2.2          | 12.0±2.6              | 0.436   |
| PLT (10³/µL)         | 292.8±98.6        | 398.6±871.9           | 0.672   |
| RDW (%)              | 43.7±3.3          | 45.3±5.5              | 0.428   |
| NLR                  | 3.11±3.14         | 3.5±2.68              | 0.345   |
| PLR                  | 198.6±135.8       | 263±380               | 0.749   |

NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; WBC: White blood cell count; MCV: Mean corpuscular volume; MPV: Mean platelet volume; PDW: Platelet distribution width; PLT: platelet; RDW: red cell distribution width.

NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; WBC, White blood cell count; MCV, Mean corpuscular volume; MPV, Mean platelet volume; PDW, Platelet distribution width; PLT, platelet; RDW, red cell distribution width.

Table 3. Patients with or without metastasis during diagnosis

|                      | No metastasis (n=43) | Metastatic cancer (n=25) | p-value |
|----------------------|----------------------|--------------------------|---------|
| WBC (10³/µL)         | 6020±2385            | 8689±4546                | 0.160   |
| Neutrophil (10³/µL)  | 4121±1638            | 5942±4269                | 0.186   |
| Lymphocyte (10³/µL)  | 1770±951             | 1924±1098                | 0.770   |
| Hemoglobin (g/dL)    | 11.6±1.4             | 11±1.5                   | 0.075   |
| MCV (FL)             | 81.9±8.7             | 80.4±6.6                 | 0.363   |
| MPV (FL)             | 9.5±1.0              | 9.3±1.2                  | 0.376   |
| PDW (fL)             | 122±2.3              | 119±2.8                  | 0.476   |
| PLT (10³/µL)         | 281±93.2             | 524.6±1229.2             | 0.985   |
| RDW (%)              | 45.3±5.3             | 44.1±4.7                 | 0.500   |
| NLR                  | 3.15±2.76            | 3.82±2.85                | 0.227   |
| PLR                  | 216±182.8            | 297.5±497.4              | 0.726   |

NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; WBC, White blood cell count; MCV, Mean corpuscular volume; MPV, Mean platelet volume; PDW, Platelet distribution width; PLT, platelet; RDW, red cell distribution width.

Thirdly, we did not follow the change of RDW during the course of disease and lastly, the correlation between RDW and other inflammatory markers such as CRP were not studied because CRP is not a routine test for a GC patient.

Conclusion
Elevated RDW is seen to estimate as a good marker at the diagnosis of GC. High levels of NLR and PLR accompany with a high level of RDW. This state explains RDW’s inflammatory role in GC with this preliminary trial. These triplet markers can be strong diagnostic factors in GC when CBC is done routinely in future.

Acknowledgements
The submitted article has been accepted as an e-poster (e15502) in ASCO 2017.

Scientific Responsibility Statement
The authors declare that they are responsible for the article’s scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest
None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References
1. Simel DL, DeLong ER, Feuusen J, Weinberg JB, Crawford J. Erythrocyte anisocytosis. Visual inspection of blood films vs. automated analysis of red blood cell distribution width. Arch Intern Med. 1988; 148: 822-4.
2. Van Zebben D, Bieger R, van Wermeskerken RK, Castel A, Hermans J. Evaluation of microcytosis using serum ferritin and red blood cell distribution width. Eur J Haematol. 1990; 44: 106-9.
3. Lippi G, Plebani M. Red blood cell distribution width (RDW) and human pathology. One size fits all. Clin Chem Lab Med. 2014; 52: 1247-49.
4. Montagnana M, Cervellin G, Meschi T, Lippi G. The role of red blood cell distribution width in cardiovascular and thrombotic disorders. Clin Chem Lab Med. 2012; 50: 635-41.
5. Erdem E, Erdem D, Dilek M, Kaya C, Karatas A, Kut E, et al. Red cell distribution width and mean platelet volume in amyloidosis. Clin Appl Thromb Hemost. 2014; 20: 334-7.
6. Patell KV, Sembra RD, Ferrucci L, Newman AB, Fried LP, Wallace RB, et al. Red blood cell distribution width and mortality in older adults. Arch Intern Med. 2009; 169: 515-23.
7. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008; 454: 436-44.
8. Kundu JK, Surh YJ. Inflammation: gearing journey to cancer. Mutat Res. 2008; 659: 15-30.
9. Nelson JE, Harris RE. Inverse association of prostate cancer and non-steroidal anti-inflammatory drugs (NSAIDs) Results of a case-control study. Oncology Reports. 2000; 7: 169-70.
10. Zhu A, Sonnenberg A. Is gastric cancer again rising? J Clin Gastro. 2012; 46: 804-6.
11. MacDonald N. Cancer cachexia and targeting chronic inflammation: a unified approach to cancer treatment and palliative/supportive care. J Support Oncol. 2007; 5: 157-62.
12. Erdem E, Kaya C, Karatas A, Dilek M, Akpolat T. Neutrophil to lymphocyte ratio in predicting short-term mortality in hemodialysis patients. J Exp Clin Med. 2013; 30: 129-32.
13. Yao M, Liu Y, Jin H, Liu X, Lv W, Wei H, et al. Prognostic value of preoperative inflammatory markers in Chinese patients with breast cancer. Oncol Targets Ther. 2014; 7: 1743-52.
14. Kose M, Celik F, Kose SK, Arioz DT, Yilmazer M. Could the platelet-to-lymphocyte ratio be a novel marker for predicting invasiveness of cervical pathologies? Asian Pac J Cancer Prev. 2015; 16: 923-6.
15. Dogantekin A, Gurel A, Ustundag B, Ilhan S, Elkin ET. Oxidative stress and antioxidant parameters in neutropenic patients secondary to chemotherapy. Pak J Med Sci. 2016;32(2): 309-13.
16. Ay S, Eryilmaz M, Aksoy N, Okus A, Unlu Y, Sevinc B. Is early detection of colon cancer possible with red blood cell distribution width? Asian Pac J Cancer Prev. 2015; 16: 753-6.
17. Albayrak S, Zengin K, Tank S, Bakirtas H, Imamoglu A, Gurdal M. Red cell distribution width as a predictor of prostate cancer progression. Asian Pac J Cancer Prev. 2014; 15: 7781-84.
18. Yilmaz A, Malva FU, Ozturk G, Citgez B, Ozdenkaya Y, Ersavas C, et al. Effect of pre-operative red blood cell distribution on cancer stage and morbidity rate in patients with pancreatic cancer. Int J Clin Exp Med. 2014; 7: 3072-75.
19. Koma Y, Onishi A, Matsuoka H, Oda N, Yokota N, Matsumoto Y, et al. Increased red blood cell distribution width associates with cancer stage and prognosis in patients with lung cancer. PLoS One. 2013; 8: DOI: 10.1371/journal.pone.0080240.
20. Riedl J, Posh F, Königshagge O, Lottsch P, Reitter EM, Eigenbauer E, et al. Red cell distribution width and other red blood cell parameters in patients with cancer: association with risk of venous thromboembolism and mortality. PLoS One. 2014; 9(10). DOI: 10.1371/journal.pone.0111460.
21. Yamashita H, Kawai H. Systemic inflammatory response in gastric cancer. World J Surg. 2010; 34: 2399-400.
22. Dirican A, Kucukyaykab BB, Alacaciligol AG, Kucukyaykab Y, Erten C, Varol U, et al. Do the derived neutrophil to lymphocyte ratio and the neutrophil to lymphocyte ratio predict prognosis in breast cancer? Int J Clin Oncol. 2014; 20: 70-81.
23. Nakayama Y, Gotohda N, Shibasaki H, Nomura S, Kinoshita T, Hayashi R. Usefulness of the neutrophil/lymphocyte ratio measured preoperatively as a predictor of peritoneal metastasis in patients with advanced gastric cancer. Surgery Today. 2014; 11: 2146-52.
24. Chen J, Hong D, Zhai Y, Shen P. Meta-analysis of associations between neutrophil/lymphocyte ratio and prognosis of gastric cancer. World J Surg Oncol. 2015; 13: 122.
25. Ozkalemkas F, Ali R, Ozkocaman V, Ozcelik T, Ozan U, Ozturk H, et al. The bone marrow aspirate and biopsy in the diagnosis of unsuspected nonhematologic malignancy: a clinical study of 19 cases. BMC Cancer. 2005; 5: 144.

How to cite this article:
Erdem E, Erdem D, Kacar T, Kacan T, Yilmaz B, Gundali M, Buyuksimsek M. The importance of red cell distribution width on gastric cancer: A preliminary study. Ann Clin Anal Med 2019;10(6): 658-61.