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The role of neutrophil-lymphocyte ratio and red blood cell distribution width in the classification of febrile seizures

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Abstract. – OBJECTIVE: Most febrile seizures occur outside of hospitals, and in most cases, information about the characteristics of the seizures is obtained from the parents. This makes it difficult to differentiate between simple and complex seizures. The aim of this study is to evaluate the significance of the Neutrophil-Lymphocyte Ratio (NLR) and the red blood cell (erythrocyte) distribution width (RDW) in distinguishing between simple and complex febrile seizures.

PATIENTS AND METHODS: The files of 142 patients between the ages of 6 months and 5 years who were admitted to the Emergency Department with the diagnosis of first febrile seizure were reviewed retrospectively. Complete blood count and C-reactive protein (CRP) parameters obtained from the venous blood samples collected from the patients at admission were evaluated.

RESULTS: The average values of NLR for simple and complex seizure groups were 2.38 ± 1.60 and 3.42 ± 1.77 respectively, and the difference was statistically significant ($p < 0.001$). The average values of RDW for simple and complex seizure groups were 16.15 ± 1.37 and 16.27 ± 1.53, respectively; the difference was not significant ($p = 0.631$). We used receiver operating characteristic (ROC) analysis and chose a cutoff value of 2.315 for the NLR, and we found that the sensitivity and specificity were 62.7% and 53.8%, respectively (area under the curve [AUC]: 0.665, $p = 0.001$, confidence interval [CI] 0.573-0.756).

CONCLUSIONS: We suggest that NLR may provide clinicians with an insight into differentiating between simple and complex febrile seizures; however, it does not produce a clear-cut distinction. We found that the RDW ratio is not useful in this differentiation.

Key Words
Febrile seizure, Children, Neutrophil-lymphocyte ratio, Red blood cell distribution width, Epilepsy, Fever, Convulsion.

Introduction

Febrile seizures affect children between 6 months and 6 years of age and are seen in 2%-5% of children[1]. Complex seizures constitute 25%-30% of these seizures[1,2]. Complex seizures are defined as seizures by fever with at least one of the following characteristics: seizure duration longer than 15 minutes, recurrence within 24 hours, and showing focal characteristics of and/or accompanied by neurological abnormalities[3].

The American Academy of Pediatrics recommended that no further diagnostic evaluations are required, except determining the source of fever, in the treatment approach to simple febrile seizures[4]. On the other hand, in the etiology, usually a more detailed diagnostic approach is selected for complex febrile seizures because of the higher risk of recurrence and the possible presence of serious pathologies that should be treated immediately. Additionally, Vestergaard et al[5] observed that the sudden and unexpected death rate was doubled within two years after complex febrile seizures when compared to the normal population, whereas this ratio was similar between the simple febrile seizure group and the normal population.

Most febrile seizures occur outside of hospitals, and information on the character of the seizures is usually obtained from the parents. Currently, there are no objective parameters to distinguish between these two types of seizures. Hence, objective diagnostic indicators to determine the type of seizures in non-hospital seizures are needed. Goksugur et al[6] suggested that NLR and RDW may be used to objectively make this distinction.

Neutrophil-Lymphocyte Ratio (NLR) is an inexpensive, easily accessible, and easily calculable parameter that has been used for evaluation of

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systemic inflammation. It has been shown that there is a relationship between NLR and chronic inflammation in cardiovascular diseases, hepatic cirrhosis, diabetes mellitus, familial Mediterranean fever, and malignancies[7-11]. NLR increases in inflammatory conditions, and this increase is seen as an indicator of systemic inflammation.

Several researches[12-16] revealed that the Red blood cell Distribution Width (RDW) increases in liver disease, cerebrovascular disease, sepsis, and cancer. Although the reasons for this association between RDW and these diseases has not been clearly defined, it has been thought that it is occurring on an inflammatory basis, as it is with NLR.

In our study, we investigated the significance of NLR and RDW values as objective data for the differentiation of simple and complex febrile seizures.

Patients and Methods

This retrospective study was conducted in a tertiary hospital's Emergency Department. The hospital admits a total of approximately 300.000 adult and pediatric emergency patients annually. The number of admissions in the Pediatric Emergency Department is approximately 110.000. The study was planned and conducted according to the ethical standards detailed in the Declaration of Helsinki and approved by Ethical Committee of Kocaeli University.

In our study, the files of patients who were admitted to the Emergency Department of Kocaeli Derince Education and Research Hospital, Kocaeli, Turkey with complaints of seizures accompanied by fever, from January 1, 2013 through December 31, 2014, were reviewed retrospectively. Patients from the ages of 6 months to 6 years diagnosed with their first febrile seizure were included in the study. Also, detailed personal and family histories of all patients, physical examination findings, and etiologic investigations conducted were reviewed.

The patients with prior afebrile seizure history, structural or developmental central nervous system (CNS) abnormalities, metabolic disorders, findings of CNS infection, or toxic encephalopathy were excluded.

All patients included in the study were referred to a pediatric neurologist during working hours (weekdays 08:00 to 17:00) or to a pediatrician if admitted outside of the working hours, and then evaluated by a pediatric neurologist the following week.

Patients were divided into two groups: the simple febrile seizure group and complex febrile seizure group. Simple febrile seizures were defined as seizures accompanied by fever (fever in the emergency department > 38.3 °C), which lasted less than 15 minutes, occurred only once in 24 hours, and were not accompanied by focal neurological signs. Complex febrile seizures were defined as seizures accompanied by fever in the emergency room, lasted longer than 15 minutes, occurred more than once in 24 hours, and were accompanied by focal neurologic findings or postictal paresis.

Laboratory Analysis

White blood cell count (WBC), hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), red blood cell count (RBC), RDW, platelet count (PLT), neutrophil and lymphocyte counts, biochemical parameters, and CRP levels were evaluated from peripheral venous blood samples collected in EDTA tubes during admission. NLR was calculated by dividing absolute neutrophil counts into absolute lymphocyte counts.

Statistical Analysis

Statistical analysis was performed by using the SPSS Statistics 17.0 for Windows (SPSS Inc., Chicago, IL, USA) program. Compliance with the normal distribution of the dependent variable was evaluated by the Kolmogorov-Smirnov (K-S) test. Parametric data (quantitative) was expressed as numbers and percentages; qualitative data were expressed as a mean ± standard deviation. Independent samples *t*-test was used for comparison of independent data. The Mann-Whitney U-test was used for evaluation of parametric data without binomial distribution. When appropriate, X^2-test was used for the comparison of categorical data. Receiver operating characteristic (ROC) curve analysis was used for calculating the optimal cut-off values, sensitivity, and specificity of NLR. A value of $p < 0.05$ was considered significant for all tests.

Results

A total of 142 patients were included in the study. There were no significant differences between the groups regarding age and gender. The demographic characteristics of patients with complex febrile seizures and simple febrile seizures are shown in Table I.

Table I. Age and gender of the patients.

	Simple Seizure (n: 91)	Complex Seizure (n:51)	*p*-value
Age (months)	27.2 ± 15.3	25.7 ± 10.51	0.544
Gender			
– Male	42 (46.2%)	31 (60.8%)	0.094
– Female	49 (53.8%)	20 (39.2%)	

Values are expressed as mean ± standard deviation.

We found that NLR and percentage of neutrophils were significantly lower, while the number and percentage of lymphocytes were significantly higher in the simple seizure group compared to the complex seizure group (Table II).

According to ROC curve analysis, in the differentiation of simple and complex seizures we found the optimal cut-off value for NRL to be 2.315 (sensitivity 62.7%, specificity 53.8%, AUC: 0.665) (Figure 1).

Discussion

In our study, we investigated the significance of NLR and RDW as objective data for the differentiation of simple and complex febrile seizures.

As a result, we found that NLR may provide clinicians with insights to differentiate between simple and complex febrile seizures; however, it does not produce a clear-cut distinction. We found that the RDW ratio is not useful in this differentiation.

In our study, we showed that the average age of the patients in the complex seizure group was lower than in the simple seizure group, but the difference was not statistically significant. Our results agree with Goksugur et al[6] and with the literature.

We found that the frequency of febrile seizures was higher in boys. Similarly, in the works of Goksugur et al[6] and Sfaih et al[17], the frequency of febrile seizures was higher in boys. Our results are consistent with the literature[18].

We found a statistically significant difference in NLR values between the simple and complex seizure groups. This difference was also significant in the study of Goksugur et al[6], which is the only related report in the literature.

In our paper, we determined the ideal cut-off value as 2.315 in the ROC curve, although this ratio was higher than the cut-off value determined

Table II. Relationships between laboratory findings of the febrile seizure groups.

	Simple Seizure (n: 91)	Complex Seizure (n:51)	*p*-value
WBC ($\times 10^3/mm^3$)	13.25 ± 6.03	14.24 ± 5.6	0.339
RBC (10^6/ml)	4.44 ± 0.35	4.45 ± 0.44	0.789
Hb (g/dl)	11.6 ± 0.93	11.5 ± 0.9	0.690
Hct (%)	34.89 ± 2.77	34.66 ± 3.26	0.669
RDW (%)	16.15 ± 1.37	16.27 ± 1.53	0.631
MPV (fl)	6.64 ± 0.74	7.0 ± 1.21	0.057
Neutrophil number ($\times 10^3/mm^3$)	7.34 ± 4.23	8.5 ± 3.57	0.072
Lymphocyte number ($\times 10^3/mm^3$)	3.86 ± 2.04	3.16 ± 1.81	0.039
CRP (mg/dl)	14.92 ± 20.93	19.3 ± 21.99	0.242
NLR	2.38 ± 1.60	3.42 ± 1.77	0.001
Neutrophil (%)	53.26 ± 17.1	64.46 ± 14.46	< 0.001
Lymphocyte (%)	32.71 ± 15.76	23.28 ± 11.15	< 0.001
MCV (fl)	78.69 ± 4.98	77.99 ± 4.39	0.402
PLT (109/L)	287.31 ± 80.7	255.01 ± 99.9	0.051

Values are expressed as mean ± standard deviation.

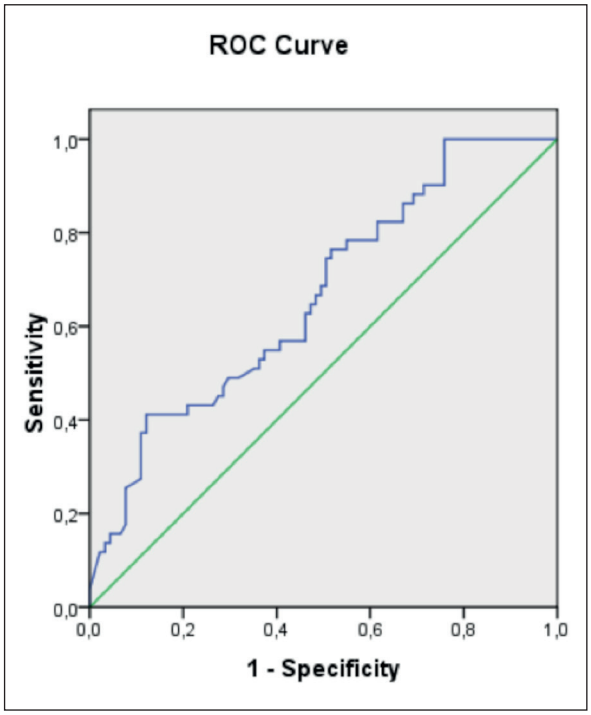

Figure 1. ROC curve analysis of neutrophil lymphocyte ratio (NLR) in differentiating simple and complex febrile seizures. Area under the curve (AUC, 0.665; confidence interval [CI], 0.573-0.756).

by Goksugur et al[6] (1.98); sensitivity and specificity were similar. We believe that the difference between the cut-off values in these two studies may have resulted from our study's being conducted with more patients. We found no statistically significant differences regarding average values of RDW between the two groups. On the other hand, Goksugur et al[6] reported a statistically significant difference between the average RDW values between the groups. These differences may be due to several factors. Despite the recommendations of the International Council for Standardization in Haematology for standardization in the measurement of RBC distribution curves published about twenty-five years ago, there is a lack of standardization among the manufacturers regarding RDW measurements. Buttarello et al[19] in their study, conducted with 220 healthy participants, detected a bias between 1%-24% in median RDW values and reference range. Independent research has shown that RDW measurements of Sysmex, Mindray, and Beckman Coulter hemocytometers are in accordance with each other and higher than the measurement of the Siemens devices; the measurements of the Abbott brand devices are the lowest among all devices[19-21]. In our investigation, all measurements are performed using the Abbott (Abbott CELL-DYN 3700, Abbott Diagnostics Division, Abbott Laboratories, IL, USA) device. Goksugur et al[6] reported that they made all the measurements with the same hemocytometer, but they did not specify a brand.

Also, RDW may increase in several conditions such as iron deficiency, folate deficiency, vitamin B12 deficiency, sickle cell anemia, hemolytic anemia, chronic liver disease, and myelodysplastic syndrome[22].

Although we excluded patients with metabolic diseases and the RDW values of the included patients were within normal range, we can't exclude the lack of any substrate deficiency that causes higher RDW levels; we do not know the ferritin, folic acid, and vitamin B12 levels of the patients due to the retrospective nature of the study. We believe the difference between the two studies may have resulted from RDW's predisposition to be influenced by many factors.

The pathogenesis of CNS pathologies has been investigated in many studies. In the literature, serum inflammatory mediators have been reported to increase in several diseases such as cerebral ischemia, Parkinson's disease, Alzheimer's disease, traumatic brain injury, and multiple sclerosis[23-28]. For example, the association between seizures and the inflammatory process activated by increased cytokine production in Rasmussen encephalitis has been clearly shown[29,30]. Also, there are studies indicating immune system activation in febrile seizures; and fever, the most common cause of febrile seizures, is a component of inflammation and multiple febrile seizures are predisposing causes of temporal lobe epilepsy[31,32]. Experimental studies have shown that interleukin-1β (IL-1β) plays an important role in the development of febrile seizures and epileptogenesis[33-35]. Vezzani et al[36] showed that this cytokine lowers the seizure threshold and worsens the seizure activity.

Fukuda et al[35] showed that IL-1β plays an important role in prolonged febrile seizures and the development of temporal lobe epilepsy in mice[35]. Marchi et al[37] showed that seizures followed an early rise in IL-1β levels in mice treated with pilocarpine. This indicates that increased IL-1β level is not a result of seizure development.

In our study, we found that NLR is significantly higher in complex febrile seizures when compared to simple febrile seizures. We believe that this difference is associated with the inflammatory process developing by increase of IL-1β in febrile seizures. Particularly, the cut-off value of 2.315 had 62.7% sensitivity and 53.8% specificity in this differentiation. Therefore, we suggest that NLR is a useful parameter in the differentiation of simple and complex febrile seizures. Nevertheless, it is clear that the current sensitivity and specificity levels are far from assuring a definitive and objective differentiation.

RDW shows the diversity of the distribution of the size of erythrocytes and has long been used to determine the etiology of anemia[38]. Several studies[39-41] show that RDW also has a diagnostic and prognostic value in non-hematologic diseases such as cardiovascular diseases, autoimmune diseases, and cancer. Although the relationship between RDW and pathogenesis of these diseases unknown, the findings indicate that this relationship develops by inflammation. In our study, although we found that RDW increased above the normal values in patients with febrile seizures, we did not find a significant difference between the RDW levels for differentiating between simple and complex seizures. Since it might be affected by many parameters including the measurement methods, prospective researches including more patients are needed to understand the value of RDW in differentiating simple and complex seizures.

The retrospective design and the small sample group are the main limitations of our report.

Conclusions

We suggest that NLR may provide clinicians with insights into differentiating between simple and complex febrile seizures; however, it does not provide a clear-cut distinction. We found that the RDW ratio is not useful in this differentiation. Prospective studies including more patients are needed to understand the value of RDW in differentiating between simple and complex seizures.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Waruiru C, Appleton R. Febrile seizures: an update. Arch Dis Child 2004; 89: 751-756.
2) Berg AT, Shinnar S. Complex febrile seizures. Epilepsia 1996; 37: 126-133.
3) Nelson KB, Ellenberg JH. Prognosis in children with febrile seizures. Pediatrics 1978; 61: 720-727.
4) Subcommittee on Febrile Seizures, American Academy of Pediatrics. Neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics 2011; 127: 389-394.
5) Vestergaard M, Pedersen MG, Ostergaard JR, Pedersen CB, Olsen J, Christensen J. Death in children with febrile seizures: a population-based cohort study. Lancet 2008; 372: 457-463.
6) Goksugur SB, Kabakus N, Bekdas M, Demircioglu F. Neutrophil-to-lymphocyte ratio and red blood cell distribution width is a practical predictor for differentiation of febrile seizure types. Eur Rev Med Pharmacol Sci 2014; 18: 3380-3385.
7) Sahan E, Polat S. Neutrophil to lymphocyte ratio is associated with more extensive, severe and complex coronary artery disease and impaired myocardial perfusion. Turk Kardiyol Dern Ars 2014; 42: 415.
8) Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int Arch Med 2012; 5: 2.
9) Uslu AU, Deveci K, Korkmaz S, Aydin B, Senel S, Sancakdar E, Sencan M. Is neutrophil/lymphocyte ratio associated with subclinical inflammation and amyloidosis in patients with familial mediterranean fever? Biomed Res Int 2013; 2013: 185317.
10) Biyik M, Ucar R, Solak Y, Gungor G, Polat I, Gaipov A, Cakir OO, Ataseven H, Demir A, Turk S, Polat H. Blood neutrophil-to lymphocyte ratio independently predicts survival in patients with liver cirrhosis. Eur J Gastroenterol Hepatol 2013; 25: 435-441.
11) Kayadibi H, Sertoglu E, Uyanik M, Tapan S. Neutrophil lymphocyte ratio is useful for the prognosis of patients with hepatocellular carcinoma. World J Gastroenterol 2014; 20: 9631-9632.
12) Hu Z, Sun Y, Wang Q, Han Z, Huang Y, Liu X, Ding C, Hu C, Qin Q, Deng A. Red blood cell distribution width is a potential prognostic index for liver disease. Clin Chem Lab Med 2013; 51: 1403-1408.
13) Chen B, Ye B, Zhang J, Ying L, Chen Y. RDW to platelet ratio: a novel noninvasive index for predicting hepatic fibrosis and cirrhosis in chronic hepatitis B. PLoS One 2013; 8: e68780.
14) Kim J, Kim YD, Song TJ, Park JH, Lee HS, Nam CM, Nam HS, Heo JH. Red blood cell distribution width is associated with poor clinical outcome in acute cerebral infarction. Thromb Haemost 2012; 108: 349-356.
15) Jo YH, Kim K, Lee JH, Kang C, Kim T, Park HM, Kang KW, Kim J, Rhee JE. Red cell distribution width is a prognostic factor in severe sepsis and septic shock. Am J Emerg Med 2013; 31: 545-548.
16) Koma Y, Onishi A, Matsuoka H, Oda N, Yokota N, Matsumoto Y, Koyama M, Okada N, Nakashima N, Masuya D, Yoshimatsu H, Suzuki Y. Increased red blood cell distribution width associates with cancer stage and prognosis in patients with lung cancer. PLoS One 2013 11; 8: e80240.
17) Sfaihi L, Maaloul I, Kmiha S, Aloulou H, Chabchoub I, Kamoun T, Hachicha M. Febrile seizures: an epidemiological and outcome study of 482 cases. Childs Nerv Syst 2012; 28: 1779-1784.
18) Behrman, Kliegman, Jenson. Febrile seizure. Nelson Essential of Pediatric. 15th edition. Philadelphia, Elsevier, 2004; p. 838.
19) Buttarello M, Plebani M. Automated blood cell counts: state of the art. Am J Clin Pathol 2008; 130: 104-116.
20) Qiao R, Yang S, Yao B, Wang H, Zhang J, Shang H. Complete blood countreference intervals and age- and sex-related trends of North China Han population. Clin Chem Lab Med 2014; 52: 1025-1032.
21) Lippi G, Pavesi F, Bardi M, Pipitone S. Lack of harmonization of red blood cell distribution width (RDW). Evaluation of four hematological analyzers. Clin Biochem 2014; 47: 1100-1113.
22) Kartal Ö, Kartal AT. Can we trust RDW for differentiation of febrile seizure types?. Eur Rev Med Pharmacol Sci 2015; 19: 345-346.
23) Aalbers MW, Rijkers K, Majoie HJ, Dings JT, Schijns OE, Schipper S, De Baets MH, Kessels A, Vles JS, Hoogland G. The influence of neuropathology on brain inflammation in human and experimental temporal lobe epilepsy. J Neuroimmunol 2014 15; 271: 36-42.
24) Corps KN, Roth TL, McGavern DB. Inflammation and neuroprotection in traumatic brain injury. JAMA Neurol 2015; 72: 355-362.
25) Hemmer B, Kerschensteiner M, Korn T. Role of the innate and adaptive immune responses in the course of multiple sclerosis. Lancet Neurol 2015; 14: 406-419.
26) Mallucci G, Peruzzotti-Jametti L, Bernstock JD, Pluchino S. The role of immune cells, glia and neurons in white and grey matter pathology in multiple sclerosis. Prog Neurobiol 2015; 127: 1-22.

27) Perry VH. The influence of systemic inflammation on inflammation in the brain: implications for chronic neurodegenerative disease. Brain Behav Immun 2004; 18: 407-413.
28) Perry VH, Nicoll JA, Holmes C. Microglia in neurodegenerative disease. Nat Rev Neurol 2010; 6: 193-201.
29) Ramaswamy V, Walsh JG, Sinclair DB, Johnson E, Tang-Wai R, Wheatley BM, Branton W, Maingat F, Snyder T, Gross DW, Power C. Inflammasome induction in Rasmussen's encephalitis: cortical and associated white matter pathogenesis. J Neuroinflammation 2013; 10: 152.
30) Rasmussen T, Olszewski J, Lloydsmith D. Focal seizures due to chronic localized encephalitis. Neurology 1958; 8: 435-445.
31) Abou-Khalil B, Andermann E, Andermann F, Olivier A, Quesney LF. Temporal lobe epilepsy after prolonged febrile convulsions: excellent outcome after surgical treatment. Epilepsia 1993; 34: 878-883.
32) Cendes F, Andermann F, Dubeau F, Gloor P, Evans A, Jones-Gotman M, Olivier A, Andermann E, Robitaille Y, Lopes-Cendes I, Peters T, Melanson D. Early childhood prolonged febrile convulsions, atrophy and sclerosis of mesial structures, and temporal lobe epilepsy: an MRI volumetric study. Neurology 1993; 43: 1083-1087
33) Dubé C, Vezzani A, Behrens M, Bartfai T, Baram TZ. Interleukin-1β contributes to the generation of experimental febrile seizures. Ann Neurol 2005; 57: 152-155.
34) Dubé CM, Ravizza T, Hamamura M, Zha Q, Keebaugh A, Fok K, Andres AL, Nalcioglu O, Obenaus, A, Vezzani A, Baram TZ, Dube M, Ravizza T, Hamamura M, Zha Q, Keebaugh A, Fok K, Andres AL, Nalcioglu O, Obenaus A, Vezzani A, Baram TZ. Epileptogenesis provoked by prolonged experimental febrile seizures: mechanisms and biomarkers. J Neurosci 2010; 30: 7484-7494.
35) Fukuda M, Hino H, Suzuki Y, Takahashi H, Morimoto T, Ishii E. Postnatal interleukin-1beta enhances adulthood seizure susceptibility and neuronal cell death after prolonged experimental febrile seizures in infantile rats. Acta Neurol Belg 2014; 114: 179-185.
36) Vezzani A, Moneta D, Richichi C, Aliprandi M, Burrows SJ, Ravizza T, Perego C, De Simoni MG. Functional role of inflammatory cytokines and antiinflammatory molecules in seizures and epileptogenesis. Epilepsia 2002; 5 43 Suppl: 30-35.
37) Marchi N, Fan Q, Ghosh C, Fazio V, Bertolini F, Betto G, Batra A, Carlton E, Najm I, Granata T, Janigro D. Antagonism of peripheral inflammation reduces the severity of status epilepticus. Neurobiol Dis 2009; 33: 171-181.
38) Evans TC, Jehle D. The red blood cell distribution width. J Emerg Med 1991; 9: 71-74.
39) 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: 635-641.
40) Lou Y, Wang M, Mao W. Clinical usefulness of measuring red blood cell distribution width in patients with hepatitis b. PLoSOne 2012; 7: e37644.
41) Hu ZD, Chen Y, Zhang L, Sun Y, Huang YL,Wang QQ, Xu YL, Chen SX, Qin Q, Deng AM. Red blood cell distribution width is a potential index to assess the disease activity of systemic lupus erythematosus. Clin Chim Acta 2013; 425: 202-205.