

# Utility of routine hematological and inflammation parameters for the diagnosis of cancer in involuntary weight loss

Cristian Baicus, MD, PhD<sup>1,2§</sup>

Simona Caraiola, MD<sup>1,2</sup>

Mihai Rimbas, MD<sup>1,2</sup>

Ruxandra Patrascu, MD, PhD<sup>1</sup>

Anda Baicus, MD, PhD<sup>2,3</sup>

for the GSSPI<sup>†</sup>

<sup>1</sup>Carol Davila University of Medicine, Colentina University Hospital, Departments of Internal Medicine and Gastroenterology, Soseaua Stefan cel Mare 19-21, sector 2, 020125 Bucharest, Romania

<sup>2</sup>Clinical Research Unit RECIF (Réseau d' Epidémiologie Clinique International Francophone), Bucharest, Romania

<sup>3</sup>"I. Cantacuzino" National Institute of Research and Development in Microbiology-Immunology Bucharest, Romania

§Corresponding author:

Dr. Cristian Baicus

Colentina University Hospital

3<sup>rd</sup> Department of Internal Medicine

Soseaua Stefan cel Mare 19-21

sector 2

020125 Bucharest, Romania

Tel: +40 788302355

Fax: +40 213180657

E-mail: [cbaicus@clicknet.ro](mailto:cbaicus@clicknet.ro)

† The Group for the Study of Involuntary Weight Loss (Grupul de Studiu al Scaderii Ponderale Involuntare ): C Baicus, C Badea, E Balanescu, M Balea, S Caraiola, G Constantin, I Constantinescu, L Dimitriu, D Georgescu, O Ghizdavu, A Haidar, M Ghita, M Iacob, RA Ionescu, P Leru, A Marian, RB Mateescu, A Nanu, A Nicolau, I Nicolescu, D Nitescu, R Patrascu, V Pompilian, M Rimbas, S Tanaseanu, G Ticu, D Ursica, Th Voiosu, R Voiosu, (Colentina Clinical Hospital), A Baicus ("I Cantacuzino" Institute)

## Acknowledgements

This work was supported by the National Council of Scientific Research in Higher Education (CNCSIS – UEFISCSU), Romanian Ministry of Education and Research, [grant number PNII – IDEI 10/2008].

## **Abstract**

### **Introduction**

A quarter of patients with involuntary weight loss (IWL) have cancer. Inflammation and anemia are associated with cancer, and recent studies showed that red blood cell distribution width (RDW) is a predictor of mortality, including cancer-related death. The aim of this study was to assess the ability of routine hematological and inflammation parameters to diagnose cancer in patients with IWL.

### **Material and methods**

253 consecutive patients with IWL admitted in a secondary care university hospital were included. Routine hematological and inflammatory parameters (hemoglobin, mean corpuscular volume, RDW, serum iron, erythrocyte sedimentation rate, C reactive protein and ferritin) were recorded for all patients. The investigative work-up was not standardized, but the patients were followed-up for 6 months, in order to avoid misclassification concerning the final diagnosis.

### **Results**

All parameters, excepting mean cellular volume, were statistically associated with cancer. The areas under the curve (AUC) were 0.708 (95% confidence interval [CI]: 0.627-0.790) for C reactive protein, 0.690 (95% CI: 0.620-0.760) for erythrocyte sedimentation rate, 0.651 (95% CI: 0.566-0.735) for serum iron, 0.607 (95% CI: 0.526-0.687) for hemoglobin, 0.598 (95% CI: 0.518, 0.679) for ferritin, 0.594 (95% CI: 0.517-0.671) for RDW and 0.561 (0.474, 0.649) for mean cellular volume. In multivariable analysis, only erythrocyte sedimentation rate remained associated with cancer.

### **Conclusions**

In patients with involuntary weight loss, the hematological and inflammation parameters were statistically different in patients with cancer and in those without cancer. However, in clinical practice they were modest diagnostic tests for cancer.

**Key words:** cancer; involuntary weight loss; red cell distribution width; hemoglobin; erythrocyte indices; erythrocyte sedimentation rate; C reactive protein; ferritin; area under curve (AUC); sensitivity and specificity.

## **Introduction**

Involuntary weight loss (IWL) is an important health problem, as 3-5% of the patients in internal medicine departments are admitted for this problem [1-3], and among them, a quarter have cancer [1,4].

In patients with IWL, anemia and high erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and ferritin were significantly associated with cancer in bivariate analysis [5-7]. On the other hand, in multivariable analysis, anemia and ESR remained independently associated with cancer in one study [6], while in another study both variables were eliminated from the multivariable model [5].

Red blood cell distribution width (RDW) has been intensely studied lately. A few studies and a meta-analysis [8] showed that RDW is a strong predictor of all cause mortality, including cancer-related death [9, 10], cardiovascular death (both in population studies [8-11], and clinical studies [12-15]) and death from chronic lower respiratory tract disease [9]. Apparently, there is also a strong, graded association of RDW with inflammatory biomarkers (serum C reactive protein, erythrocyte sedimentation rate and fibrinogen), independent of numerous confounding factors [16, 17].

We therefore conducted a study in order to assess the diagnostic accuracy of routine hematologic [hemoglobin, mean corpuscular volume (MCV), RDW] and inflammatory (ESR, CRP, ferritin) parameters in detecting cancer as a cause of IWL.

## **Material and Methods**

### **Setting and patients**

We prospectively enrolled adult inpatients with IWL admitted to the internal medicine departments of a secondary care university hospital. All consecutive patients, 18 years of age or more, were included if they fulfilled one of the following criteria: 1) documented IWL of at least 5% of usual body weight within the last 6 months; 2) declaration of a „very much” or „much” concerning the amount of weight loss, on a Lickert scale with five levels („very much”, „much”, „average”, „little” and „not at all”). The second criterion was applied only for the selection of patients for whom there was not baseline weight documentation, and the amount of weight loss could not be calculated in order to fulfill the first criterion. However, the scale was recorded for all patients, in order to assess the self-estimation of weight loss. The patients with voluntary weight loss or with a known malignancy were not included in the study. The study was conducted according to the Declaration of Helsinki, the protocol was approved by the ethics committee of Colentina University Hospital and all patients agreed to participate in the study and signed the informed consent before enrolling.

### **Study design**

The investigative work-up was not standardized; it was decided by every participating physician, depending on clinical and laboratory diagnostic clues in every particular patient. However, as one of the objectives of the study was the validation of several simple clinical and biological parameters, found as diagnostic for cancer in IWL patients in three previous studies [5, 6, 18], all patients had on admission a complete blood cell count (including MCV and RDW) and determination of blood erythrocyte sedimentation rate (ESR), serum C reactive protein (CRP), iron, albumin, alkaline phosphatase (ALP), alanin aminotransferase (ALAT) and lactate dehydrogenase (LDH) levels. All variables were recorded by every physician in a preformed questionnaire, and then registered by one of the authors into the database.

In order to avoid misclassification concerning the final diagnosis (cancer or not), the patients were followed up for six months, interrogating the final diagnosis, survival, state of health and further weight change.

### **Laboratory procedures**

The RDW, hemoglobin level and MCV were determined using the Sysmex XT 1800i counter (Sysmex Corporation, Kobe, Japan). The reference range for RDW was 11.5% to 14.5%. Serum albumin, iron, ALP, ALAT, LDH and CRP levels were measured using the Cobas 6000 Modular P 800 analyzer (Roche Diagnostics, Rotkreuz, Switzerland). ESR was measured by the Westergreen method. Throughout the study, the quality of results was validated by regular internal quality control procedures and participation in an external quality assessment scheme.

### **Statistical analysis**

The outcome was the cancer diagnosis as a cause of IWL, while the predictor variables were hemoglobin, MCV, RDW, ESR, CRP and ferritin.

Results were expressed as frequencies for categorical variables (further analyzed by Fisher's exact test), and median and extremes for non normal continuous variables (analyzed by Mann-Whitney U test and Kendall's rank correlation). For logistic regression, the variables were selected by the "enter" method. SPSS 16.0 software (SPSS Inc., Chicago, IL., USA) was used for the database construction and data analysis. Hypothesis testing was 2-tailed, with  $p < .05$  considered statistically significant.

### **Results**

#### **Patients: inclusion, work-up and follow-up**

255 consecutive patients with IWL were admitted from January 2009 to March 2010 (flow diagram presented in Figure 1). Two patients refused to participate, therefore 253 patients were included in the present study – 196 fulfilled the first inclusion criterion (baseline weight was known, so the amount of weight loss could be computed), while the other 57 fulfilled the second criterion.

All admitted patients had hospital work-up which included determination of mentioned hematological and inflammatory parameters; 226 (89%) were followed-up for 6 months, in order to diagnose possible cancer that was not discovered during the initial hospitalization. Of the 27 patients lost to follow-up, 6 had a certain diagnosis of cancer at the initial evaluation (four by histopathology, and two by a combination of computed tomography and elevated serum tumor markers). Concerning the 21 of these patients in whom no cancer was discovered during admission, hyperthyroidism was diagnosed in two, depression in four, sarcoidosis in one, Alzheimer disease in one, polyarteritis nodosa in one, polymyositis in one, and no clear cause for weight loss was found in 12 patients.

#### **Outcome**

Patient characteristics, together with the results of the routine hematological and inflammation tests are presented in Table 1.

Cancer was diagnosed in 67 patients with IWL (26.5%), proportion that corresponds to other IWL case series [4]. As seen in Table 1, higher RDW, ESR, CRP and ferritin, and lower hemoglobin and serum iron were associated with cancer, while age and MCV were not.

We looked for correlations between RDW and hematological and inflammatory parameters. Although statistically significant, the degree of correlation was weak (Kendall's coefficient = -0.268 with hemoglobin) or even negligible (-0.162 with MCV, -0.134 with serum iron, 0.184 with CRP and 0.173 with ESR). In a logistic regression model where all these variables were introduced (with "enter" as method of selection), only ESR remained associated with cancer (Table 2). We did not find any correlation between age and ESR (Kendall's coefficient=0.071,  $p=0.105$ ). RDW was

not statistically different between patients who were dead and patients who were alive at 6 month follow-up ( $p=0.083$ ).

### **The value of hemoglobin, MCV, RDW, ESR, CRP and ferritin in diagnosing cancer in patients with IWL**

In Table 3 there are presented the areas under receiver operator characteristic curves (AUC) for the same hematological and inflammatory parameters used for diagnosing cancer in patients with IWL. As one could see, the AUC of RDW is the smaller (0.594), along with MCV, while CRP and ESR are the best diagnostic tests (AOC = 0.708 and 0.690, respectively).

In Table 4 there are presented the cut-off values found for 90% sensitivities and specificities, together with the corresponding positive or negative likelihood ratios.

### **Discussion**

It is known that anemia and inflammation parameters are associated with cancer, and this was confirmed on a few series of IWL patients, at least in bivariate analysis [5, 6, 7]. Only two studies performed multivariable analysis [5, 6], and CRP and ferritin were not analyzed in multivariable models.

Concerning RDW, more articles about its association with all cause and specific causes of mortality were published; these studies, either performed on large cohorts or in clinical setting, showed that risk increased gradually with RDW.

Therefore, in our study we assessed the value of routine hematological and inflammation parameters as diagnostic tests in clinical practice for the diagnosis of cancer in a group of patients where cancer is always suspected – patients with involuntary weight loss.

Our study confirmed the fact that, in patients with involuntary weight loss, hemoglobin, RDW and inflammatory markers (ESR, CRP and ferritin) were statistically different in patients with cancer and in those without cancer.

Because the AUC of all tests were closer to 0.500 (a useless test) than to 1.00 (a perfect test), one could not choose a cut-off value for which the tests would have both good sensitivities and specificities. In this case, it would be wiser to use these parameters as multilevel tests, with more cut-off values in order to obtain good sensitivities (to exclude cancer) and specificities (to run in cancer). However, the cut-off values thus obtained were rather extreme values, and only a few patients could benefit from them; even for this cut-offs, the corresponding likelihood ratios, positive or negative, would not determine important shifts in posttest probabilities.

Although this study confirms the existence of a statistically significant correlation of RDW with inflammatory parameters, the magnitude of the correlation is rather small, and not strong, as claimed by two previous studies [16, 17]. The fact that, in multivariable analysis along with other hematological and inflammatory parameters as independent variables, RDW was not associated with cancer “supports the explanation that elevated RDW is a marker of pathophysiological processes such as inflammation or oxidative stress which are, in fact, risk factors for cardiovascular and cancer mortality” [19].

It is generally accepted that, the older the age, the higher the ESR, and there are formulas used to calculate the cut-off value for the normal ESR depending on age. However, in a previous study [6] we found only a negligible correlation between age and ESR, while in this study we did not find any correlation.

This study has several limitations. In order to be included, the patients had to fulfill one of two different criteria, which could have driven to different populations.

However, this did not happen, as the same proportion of cancers was diagnosed both

in patients included by the first criterion (53 of 196, 27%), and in those included by the second criterion (14 of 57, 25%),  $p=0.865$ . On the other hand, in the 196 patients for whom both variables were available (actual weight loss and self estimation of the weight loss by the Lickert scale), they were correlated (Kendall coefficient=0.400,  $p<0.001$ ), and we did not find any difference in self estimation between patients with and without cancer, like other authors did [20].

The study is a case series from a single center, and only inpatients were included. However, this is the second largest series of IWL, and the proportion of cancers is similar with that of other IWL series, either inpatients or outpatients.

Our study demonstrates that routine hematological and inflammation tests are modest tools for cancer diagnosis in patients with IWL, and in multivariable analysis, only ESR remains associated with cancer.

## References

1. Reife CM. Weight loss. In: Harrison's principles of internal medicine, Ed. XVI, McGraw-Hill, New York, 2005, p.233.
2. Nidiry JJ. A 2 step procedure determined diagnosis in patients with unexplained weight loss. *Evid Based Med* 2001;6:160.
3. Vanderschueren S, Geens E, Knockaert DJ et al. The diagnostic spectrum of unintentional weight loss. *Eur J Intern Med* 2005;16:160–4.
4. Baicus C, Caraiola S, Baicus A et al. Involuntary weight loss: case series, etiology and diagnostic. *Rom J Intern Med.*2009;47:87-92.
5. Hernandez JL, Matorras P, Riancho JA, Gonzales-Macias J. Involuntary weight loss without specific symptoms: a clinical prediction score for malignant neoplasm. *QJM* 2003;97:649-55.
6. Baicus C, Ionescu R, Tanasescu C. Does this patient have cancer? The assessment of age, anaemia, and erythrocyte sedimentation rate in cancer as a cause of weight loss. A retrospective study based on a secondary care university hospital in Romania. *Eur J Intern Med* 2006;17:28–31.
7. Metalidis, C., Knockaert, D.C., Bobbaers, H., Vanderschueren, S. Involuntary weight loss. Does a negative baseline evaluation provide adequate reassurance? *Eur J Intern Med* 2008;19:345-49.
8. Patel KV, Semba RD, Ferrucci L et al. Red cell distribution width and mortality in older adults: a meta-analysis. *J Gerontol A Biol Sci Med Sci.* 2010;65:258-65.
9. Perlstein TS, Weuve J, Pfeffer MA et al. Red blood cell distribution width and mortality risk in a community-based prospective cohort. *Arch Intern Med.* 2009;169:588-94.
10. Patel KV, Ferrucci L, Ershler WB et al. Red blood cell distribution width and the risk of death in middle-aged and older adults. *Arch Intern Med.* 2009;169:515-23.
11. Chen PC, Sung FC, Chien KL et al. Red blood cell distribution width and risk of cardiovascular events and mortality in a community cohort in Taiwan. *Am J Epidemiol.*2010;171:214-20.
12. Zalawadiya SK, Veeranna V, Niraj A et al. Red cell distribution width and risk of coronary heart disease events. *Am J Cardiol.* 2010;106:988-93.
13. Allen LA, Felker GM, Mehra MR et al. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. *J Card Fail.*2010;16:230-8.
14. Dabbah S, Hammerman H, Markiewicz W et al. Relation between red cell distribution width and clinical outcomes after acute myocardial infarction. *Am J Cardiol.*2010;105:312-7.
15. Ani C, Ovbiagele B. Elevated red blood cell distribution width predicts mortality in persons with known stroke. *J Neurol Sci.*2009;277:103-8.
16. Lippi G, Targher G, Montagnana M et al. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. *Arch Pathol Lab Med.* 2009;133:628-32.
17. Cakal B, Akoz AG, Ustundag Y et al. Red cell distribution width for assessment of activity of inflammatory bowel disease. *Dig Dis Sci.* 2009;54:842-7.
18. Bilbao-Garay J, Barba R, Losa-Garcia JE et al. Assessing clinical probability of organic disease in patients with involuntary weight loss: a simple score. *Eur J Intern Med.* 2002;13:240-245.

19. Means RT Jr. Higher red blood cell distribution width was associated with increased risk of mortality in adults  $\geq$  45 years of age. *Evid Based Med.* 2009;14:151.
20. Ramboer C, Verhamme M, Vermeire L. Patients' perception of involuntary weight loss: implications of underestimation and overestimation. *Br Med J.* 1985;291:1091.



Figure 1. Flow diagram of the study

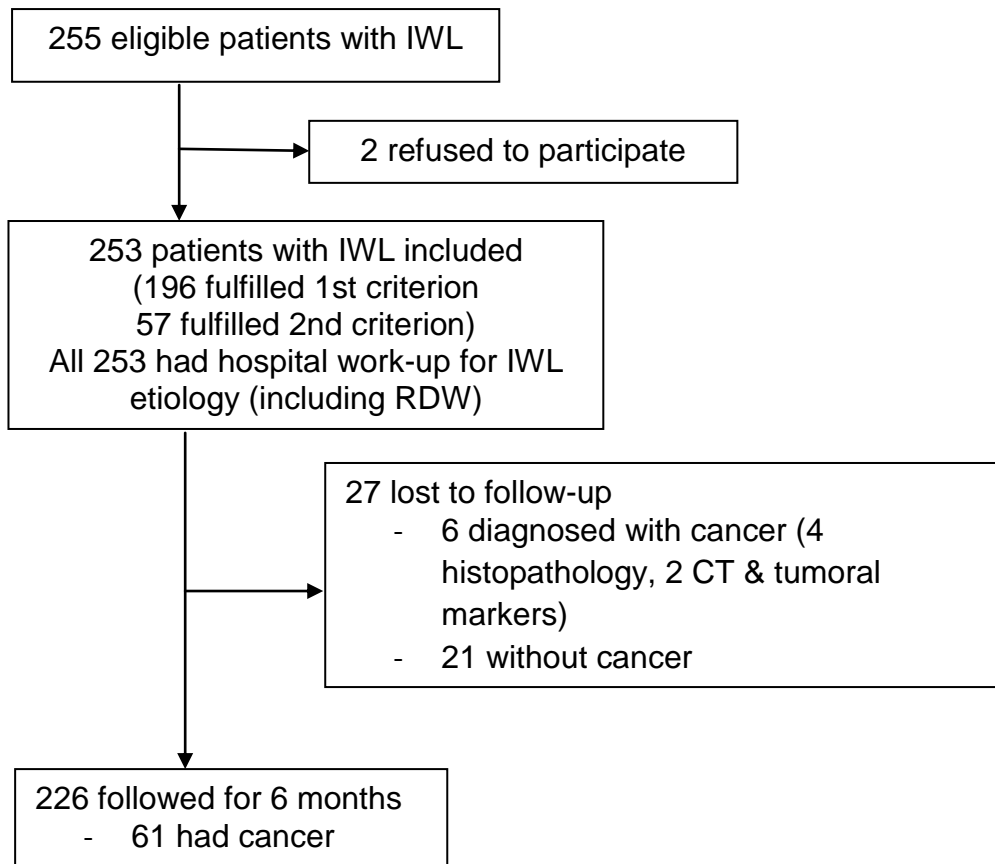


Table 1. Patients' characteristics.

Characteristic	All patients	Patients with cancer	Patients without cancer	p
Age (years)	68 (33, 94)	70 (44, 82)	68 (33, 94)	p=0.069*
Male sex	126/253 (49%)	31/67 (54%)	90/186 (48%)	p=0.479†
RDW <sup>§</sup> (%)	15 (11.5, 26.7)	15.1 (12.3, 19.6)	14.6 (11.5, 26.7)	<b>p=0.022*</b>
Hemoglobin (g/dl)	11.8 (6.1, 16.4)	11.2 (7.2, 15.5)	12.1 (6.1, 16.4)	<b>p=0.010*</b>
MCV <sup>¥</sup> (femtoliters)	88 (64, 125)	87.2 (64, 102)	88.6 (66, 125)	p=0.145*
Serum iron (mcg/dl)	51 (4, 197)	38 (4, 162)	54.5 (11, 197)	<b>p=0.001*</b>
ESR <sup>¥¥</sup> (mm/h)	43 (2, 140)	58 (10, 140)	35 (2, 140)	<b>p&lt;0.001*</b>
CRP <sup>§§</sup> (mg/L)	7.81 (1, 550)	41 (1, 550)	5.2 (1, 258)	<b>p&lt;0.001*</b>
Ferritin (mcg/L)	106 (5, 2000)	171 (10, 1105)	94 (5, 2000)	<b>p=0.019*</b>
Death at 6 months	44/226 (19%)	34/61 (56%)	10/165 (6%)	<b>p&lt;0.001†</b>
Cancer	67/253 (26%)			

\*Mann-Whitney *U* test

† Fisher's exact test

§ red cell distribution width

¥ mean of red blood cell volume

¥¥ erythrocyte sedimentation rate

§§ C reactive protein

(Results are expressed as frequencies for categorical variables, and median and extremes for non normal continuous variables)

Table 2. Hematological and inflammation parameters as predictors of cancer in patients with involuntary weight loss – logistic regression

<b>Variable</b>	<b>Odds ratio</b>	<b>95% CI</b>	<b>P value</b>
RDW <sup>§</sup> (%)	1.01	0.83, 1.24	0.897
Hemoglobin (g/dl)	1.07	0.86, 1.32	0.561
MCV <sup>¥</sup> (femtoliters)	0.97	0.92, 1.02	0.213
Serum iron (mcg/dl)	0.997	0.98, 1.00	0.660
ESR <sup>¥¥</sup> (mm/h)	1.02	1.01, 1.03	<b>0.011</b>
CRP <sup>§§</sup> (mg/L)	1.00	0.99, 1.00	0.654
Ferritin (mcg/L)	1.00	0.99, 1.00	0.740

<sup>§</sup> red cell distribution width

<sup>¥</sup> mean of red blood cell volume

<sup>¥¥</sup> erythrocyte sedimentation rate

<sup>§§</sup> C reactive protein

Table 3. AUC of hematological and inflammation parameters in the diagnosis of cancer in patients with IWL.

<b>Variable</b>	<b>AUROC</b>	<b>95% CI</b>
CRP <sup>§</sup> (mg/L)	0.708	0.627, 0.790
ESR <sup>¥¥</sup> (mm/h)	0.690	0.620, 0.760
Serum iron (mcg/dl)	0.651	0.566, 0.735
Hemoglobin (g/dl)	0.607	0.526, 0.687
Ferritin (mcg/L)	0.598	0.518, 0.679
RDW <sup>§</sup> (%)	0.594	0.517, 0.671
MCV <sup>¥</sup> (femtoliters)	0.561	0.474, 0.649

<sup>§</sup> red cell distribution width

<sup>¥</sup> mean of red blood cell volume

<sup>¥¥</sup> erythrocyte sedimentation rate

<sup>§§</sup> C reactive protein

Table 4. Cut-off values for sensitivities and specificities of 90%, with likelihood ratios.

Variable	Cut-off	sensitivity (%)	specificity (%)	likelihood ratio +	likelihood ratio -
RDW <sup>§</sup> (%)	≤12.8	90	12		<b>0.83</b>
	≥17.6	20	90	<b>2</b>	
ferritin (mcg/L)	≤16	<b>91</b>	14		<b>0.64</b>
	≥517	14.5	<b>90</b>	<b>1.45</b>	
hemoglobin (g/dl)	≥14.3	<b>92</b>	18		<b>0.64</b>
	≤8.9	19	<b>90</b>	<b>1.9</b>	
serum iron (mcg/dl)	≥101	<b>90</b>	17		<b>0.59</b>
	≤18.8	13	<b>90</b>	<b>1.3</b>	
ESR <sup>¥</sup> (mm/h)	≤15.5	<b>90</b>	31		<b>0.32</b>
	≥85	25	<b>90</b>	<b>1.2</b>	
CRP <sup>†</sup> (mg/L)	≤1.64	<b>91</b>	38		<b>0.23</b>
	≥105.5	16.5	<b>90</b>	<b>1.65</b>	

<sup>§</sup> red cell distribution width

<sup>¥</sup> erythrocyte sedimentation rate

<sup>†</sup> C reactive protein