

# Red blood cell distribution width and serum CA-125 level as prognostic markers in acute exacerbation of chronic obstructive pulmonary disease

Fang He<sup>1</sup> , Ping Zhao<sup>2</sup> , Yan Chu<sup>1</sup>, Na Zhao<sup>1</sup> and Jiexi Cheng<sup>1</sup>

## Abstract

**Objective:** Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a primary cause of hospitalization and death in COPD. Serum CA-125 and red blood cell distribution width (RDW) are related to AECOPD. We investigated correlations between serum markers and AECOPD.

**Methods:** In total, 132 patients with AECOPD were included from January 2017 to December 2019. Participants were followed for 1 year. Patients were assigned to the poor prognosis ( $n = 40$ ) or good prognosis ( $n = 92$ ) group. We collected serum samples and general clinical information and conducted routine blood tests. We used logistic regression, receiver operating characteristic (ROC), and area under the ROC curve (AUC) analyses to assess differences between groups.

**Results:** We found significant differences between groups (odds ratio, 95% confidence interval) for age (1.046, 1.005–1.09), RDW (2.012, 1.339–3.023), and cancer antigen 125 (CA-125; 1.022, 1.006–1.039); these remained risk factors for AECOPD prognosis in multivariate analyses. RDW and CA-125 in combination was significant in ROC curve analysis. The AUC of RDW, CA-125, and these combined were 0.691, 0.779, and 0.772, respectively. Patients with RDW  $> 12.75\%$  and CA-125  $> 15.65$  U/mL were predicted to have poor prognosis.

**Conclusions:** We found that RDW and CA-125 are potential prognostic indicators for AECOPD.

<sup>2</sup>Clinical Laboratory, Beijing Shijitan Hospital, Capital Medical University, Beijing, China

### Corresponding author:

Fang He, Respiratory Department, Beijing Chaoyang District Shuangqiao Hospital, Shuangqiao East Road, Chaoyang District, Beijing, 100121 China.  
Email: mrhippo@126.com

<sup>1</sup>Respiratory Department, Beijing Chaoyang District Shuangqiao Hospital, Beijing, China



**Keywords**

Red blood cell distribution width, cancer antigen 125, acute exacerbation of chronic obstructive pulmonary disease, prognostic indicator, serologic marker, patient outcome

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**Introduction**

Chronic obstructive pulmonary disease (COPD) is characterized by progressive, irreversible airflow limitation. COPD is one of the three main causes of death worldwide<sup>1,2</sup> and an important public health challenge. Acute exacerbation of COPD (AECOPD) is a primary cause of hospitalization and is associated with high mortality.<sup>3,4</sup> Hence, it is important to identify serological indicators that are readily available at the time of hospital admission to assess the prognosis of patients with AECOPD.

Red blood cell distribution width (RDW) is a clinical indicator of changes in red blood cell volume. A large number of studies have confirmed that an increase in RDW may lead to poor prognosis in cardiovascular diseases.<sup>5</sup> RDW is also associated with the prognosis of COPD.<sup>6-8</sup> The tumor marker cancer antigen 125 (CA-125) is mainly used in the diagnosis and screening of ovarian cancer. A few studies have indicated that serum CA-125 level is related to lung function in patients with COPD. However, few studies have investigated RDW combined with serum CA-125 level in the prognostic diagnosis of patients with AECOPD. In this study, we aimed to assess RDW value and CA-125 level as prognostic indicators of AECOPD. Our findings may provide a new method for the prognostic evaluation of patients with AECOPD.

**Methods**

We recruited inpatients who were diagnosed with AECOPD between January 2017 and December 2019. The inclusion criteria for AECOPD were in accordance with the 2007 revised Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Diseases in China. Patients complicated with primary heart valvular disease, arthritis, connective tissue disease, inflammatory bowel disease, renal failure, liver and blood system diseases or suspected malignancy were excluded from the analysis. Patients were followed up for treatment effect or death over a period of 1 year. Patients who died and those readmitted to the hospital within 90 days after discharge were assigned to the poor-prognosis group; the remaining patients were assigned to the good-prognosis group. Patients were assessed in subgroups of 10-year intervals.

Serum samples were collected within 24 hours of admission. We collected general clinical information and routine blood test results. The following parameters were examined: sex, age, smoking history, length of hospital stay, white blood cells, C-reactive protein, neutrophil absolute value, RDW, type B natriuretic peptide (BNP), CA-125, albumin, uric acid, and gamma-glutamyl transferase.

This study protocol was approved by the Beijing Chaoyang District Shuangqiao Hospital ethics review committee.

The patients in this study provided their verbal informed consent.

### Statistical analysis

IBM SPSS 25.0 software was used for data analysis (IBM Corp., Armonk, NY, USA). Measurement data conforming to a normal distribution are expressed as mean  $\pm$  standard deviation. We used an independent samples *t*-test and Wilcoxon rank-sum test for comparisons between the groups. Measurement data with a non-normal distribution are expressed using median (25th percentile, 75th percentile). Enumeration data are expressed as n (%), and comparisons between groups was performed using the  $\chi^2$  test. Logistic regression analysis was used in multivariate analysis. The diagnostic ability of each index was analyzed in receiver operating characteristic (ROC) curve analysis.  $P < 0.05$  indicated statistical significance.

### Results

A total of 132 (86 men, 46 women) were included in this study. Patient ages ranged from 55 to 103 years old. Forty patients were assigned to the poor-prognosis group, and 92 patients were assigned to

the good-prognosis group, with a significant difference in age ( $P < 0.05$ ) between groups (Table 1).

In a comparison of serologic markers between the two groups, we found significant differences in RDW, BNP, and CA-125 ( $P < 0.05$ ) (Table 2).

Single-factor logistic regression analysis was conducted for all indicators. We found significant differences for age (odds ratio [OR] 1.046, 95% confidence interval [CI] 1.005 to 1.09), RDW (OR 2.012, 95% CI 1.339 to 3.023), and CA-125 (OR 1.022, 95% 1.006–1.039) between the two groups (all  $P < 0.05$ ). These indicators were included in multifactor logistic regression analysis; RDW ( $P = 0.004$ ) and CA-125 ( $P = 0.040$ ) remained statistically significant. Thus, age, RDW, and CA-125 were independent risk factors for prognosis. Higher values of age, RDW, and CA-125 were associated with greater likelihood of a poor prognosis (Table 3).

Combined diagnostic indicators were included in the multivariate logistic regression function. RDW, CA-125, and these two indicators combined were statistically significant in ROC curve analysis of prognosis ( $P < 0.05$ ). The area under the ROC curve for RDW, CA-125, and for these

**Table 1.** Comparison of clinical data between the two groups.

		Good prognosis	Poor prognosis	$\chi^2$	<i>P</i> -value
Sex	Female	32 (34.8)	14 (35.0)	0.001	0.981
	Male	60 (65.2)	26 (65.0)		
Smoking	No	30 (32.6)	12 (30.0)	0.087	0.767
	Yes	62 (67.4)	28 (70.0)		
Length of hospital stay		11.77 $\pm$ 4.42	11.78 $\pm$ 6.09	0.003	0.997
Age		73.22 $\pm$ 9.57	77.35 $\pm$ 9.95	2.253	0.026
Age group, years	$\leq 60$	7 (7.6)	7 (17.5)	9.566	0.023
	$\leq 70$	16 (17.4)	14 (35)		
	$\leq 80$	38 (41.3)	10 (25)		
	$> 80$	31 (33.7)	9 (22.5)		

Note: Values in the table are n (%), unless otherwise indicated.

**Table 2.** Comparison of serologic markers between the two groups.

	Good prognosis	Poor prognosis	$\chi^2/t/Z$	P-value
WBC ( $10^9$ cells/L)	8.80 $\pm$ 3.82	8.61 $\pm$ 3.58	0.279 <sup>a</sup>	0.781
CRP (mg/L)	28.00 (8.25, 98.5)	39.50 (9.25, 102.75)	-0.473 <sup>b</sup>	0.636
Neutrophils ( $10^9$ cells/L)	6.58 $\pm$ 3.48	6.84 $\pm$ 3.75	-0.379 <sup>a</sup>	0.705
RDW (%)	12.75 $\pm$ 0.86	13.56 $\pm$ 1.40	-3.383 <sup>a</sup>	0.001
BNP (pg/mL)	73 (34.75, 173.25)	123.50 (79.75, 237.00)	-2.595 <sup>b</sup>	0.009
CA-125 (U/mL)	10.75 (7.20, 16.33)	19.95 (15.88, 39.75)	-5.085 <sup>b</sup>	<0.001
ALB (g/L)	37.81 $\pm$ 5.20	36.38 $\pm$ 7.32	1.271 <sup>a</sup>	0.206
UA ( $\mu$ mol/L)	262.08 $\pm$ 104.16	280.43 $\pm$ 105.68	-0.926 <sup>a</sup>	0.356
GGT (U/L)	23 (14, 40.75)	21 (14, 40.5)	-0.352 <sup>b</sup>	0.725
Creatinine ( $\mu$ mol/L)	62.5 (53, 77)	63.5 (55.25, 76.75)	-0.911 <sup>b</sup>	0.362
Urea nitrogen (mmol/L)	5.23 (3.98, 6.87)	4.68 (3.99, 6.93)	-0.594 <sup>b</sup>	0.552
ALT (U/L)	13 (11, 20)	16.5 (12, 23.50)	-1.535 <sup>b</sup>	0.125
AST (U/L)	18.5 (15, 24)	20.5 (16, 27.75)	-1.084 <sup>b</sup>	0.279

<sup>a</sup>Independent samples *t*-test. <sup>b</sup>Wilcoxon rank-sum test.

Values in the table are mean  $\pm$  standard deviation or median (25th percentile, 75th percentile).

WBC, white blood cells; CRP, C-reactive protein; RDW, red blood cell distribution width; BNP, type B natriuretic peptide; CA-125, cancer antigen 125; ALB, albumin; UA, uric acid; GGT, gamma-glutamyl transferase; ALT, alanine aminotransferase, AST, aspartate aminotransferase.

**Table 3.** Logistic regression analysis for prognostic ability.

	Single factor logistic regression analysis		Multivariate logistic regression analysis	
	OR (95% CI)	P	OR (95% CI)	P-value
Sex	1.010 (0.462, 2.199)	0.981		
Smoking	1.129 (0.505, 2.524)	0.768		
Length of hospital stay	1.000 (0.928, 1.078)	0.997		
Age	1.046 (1.005, 1.090)	0.029	1.048 (1.002, 1.096)	0.040
WBC	0.986 (0.891, 1.090)	0.779		
CRP	1.002 (0.997, 1.007)	0.489		
Neutrophils	1.020 (0.920, 1.131)	0.703		
RDW	2.012 (1.339, 3.023)	0.001	1.796 (1.212, 2.664)	0.004
BNP	1.001 (1.000, 1.002)	0.216		
CA-125	1.022 (1.006, 1.039)	0.006	1.017 (1.001, 1.033)	0.040
ALB	0.958 (0.897, 1.024)	0.207		
UA	1.002 (0.998, 1.005)	0.354		
GGT	1.000 (0.990, 1.012)	0.930		
Creatinine	1.001 (0.989, 1.014)	0.841		
Urea nitrogen	0.995 (0.853, 1.159)	0.946		
ALT	1.013 (0.995, 1.032)	0.158		
AST	1.010 (0.991, 1.030)	0.307		

OR, odds ratio; CI, confidence interval; WBC, white blood cells; CRP, C-reactive protein; RDW, red blood cell distribution width; BNP, type B natriuretic peptide; CA-125, cancer antigen 125; ALB, albumin; UA, uric acid; GGT, gamma-glutamyl transferase; ALT, alanine aminotransferase, AST, aspartate aminotransferase.

indicators combined was 0.691, 0.779, and 0.772, respectively. The cutoff values for RDW and CA-125 were 12.75 and 15.65. The prognostic ability of CA-125, and of RDW and CA-125 combined, was close to but superior to that of RDW alone (Table 4, Figure 1).

## Discussion

COPD is a common respiratory disease, especially in older people, with high morbidity and mortality.<sup>9</sup> Timely and accurate assessment of the severity of disease and

appropriate treatment measures are important to improve patient prognosis.

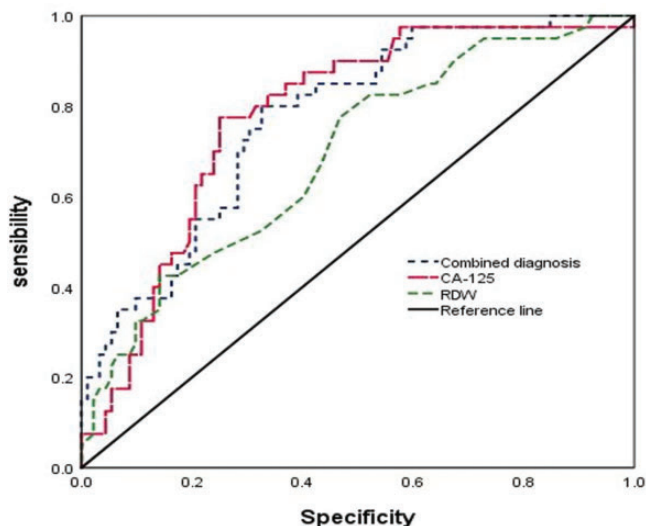
In this study, we found that age was a risk factor for prognosis in patients with AECOPD, as reported in other studies.<sup>10–12</sup> Older patients with AECOPD have poorer outcomes, which can be explained by a natural decline in lung function. Additionally, older patients often have multiple comorbidities, making them more vulnerable to exacerbation,<sup>10,13</sup> which contributes to a poor AECOPD prognosis.

RDW is a routine blood test that can quantitatively reflect the volume difference

**Table 4.** ROC curve analysis of prognostic ability for each index.

	AUC (95% CI)	SE	P	Boundary value	Sensibility	Specificity	Youden index
RDW	0.691 (0.595, 0.788)	0.049	<0.001	12.750	0.775	0.533	0.308
CA-125	0.779 (0.696, 0.862)	0.042	<0.001	15.650	0.775	0.750	0.525
Combined diagnostic indicator	0.772 (0.690, 0.855)	0.042	<0.001	—	0.800	0.674	0.474

ROC, receiver operating characteristic; AUC, area under the ROC curve; SE, standard error; RDW, red blood cell distribution width; CA-125, cancer antigen 125.



**Figure 1.** Receiver operating characteristic curve of red blood cell distribution width, cancer antigen 125, and the combined diagnostic indicator for prognosis.

in peripheral blood red cells. Infection, anemia, nutritional deficiency, and other factors can lead to an increase in RDW.<sup>14</sup> Several recent studies have confirmed the independent correlation between RDW and cardiovascular disease.<sup>5,15</sup> Similar mechanisms and relationships between COPD and cardiovascular disease have been identified related to inflammation, oxidative stress, and endothelial dysfunction.<sup>16</sup> Inflammatory cytokines also lead to increased RDW by inhibiting erythropoietin-induced erythrocyte maturation. Additionally, high RDW reflects an underlying chronic inflammatory response in the body. Inflammatory response is an important pathogenesis in COPD, which is closely related to disease severity and patient prognosis. AECOPD can enhance the systemic inflammatory response and promote the release of inflammatory cells and inflammatory mediators. In this study, our analysis showed that RDW was an independent risk factor for AECOPD. RDW is significantly associated with prognosis in patients with AECOPD, with higher RDW associated with worse prognosis. This may be owing to the combined effects of high oxidative stress, severe inflammatory response, and activation of the neuroendocrine system.

Serum CA-125 measurement is convenient and inexpensive in clinical practice.<sup>17</sup> Serum CA-125 level is often used in the clinic for the diagnosis and differential diagnosis of ovarian tumors. It has also been reported that serum CA-125 is elevated in other diseases.<sup>18</sup> In the respiratory system, CA-125 is mainly distributed in submucosal cells and goblet epithelial cells. Levels of CA-125 have been shown to be independently influenced by the right heart chambers.<sup>19</sup> It has been reported that CA-125 can be used in the differential diagnosis of heart failure.<sup>20</sup> Another study showed that CA-125 is associated with severity and fluid retention in chronic heart failure.<sup>21</sup> CA-125

is associated with an enlarged right ventricular lumen in right ventricular dysfunction. These findings suggest that increased cardiac pressure may be a mechanism for the upregulated expression of serum CA-125. Uz et al.<sup>22</sup> reported a correlation between CA-125 and pulmonary artery systolic pressure. Some clinical studies have shown that patients with COPD often have different degrees of cardiovascular injury.<sup>23</sup> Several previous studies have reported that CA-125 is associated with prognosis in patients with COPD.<sup>24,25</sup> Similarly, in this study, serum CA-125 was an independent risk factor for AECOPD and had good diagnostic ability in the prognosis of AECOPD.

To further confirm the relationship between RDW, CA-125, and AECOPD prognosis, we used a combined diagnostic indicator, based on the results of multiple logistic regression analysis. RDW, CA-125, and the combination of these two indicators were statistically significant in ROC curve analysis of prognosis ( $P < 0.05$ ). According to cutoff values, patients with RDW greater than 12.75% and CA-125 greater than 15.65 U/mL were predicted to have poor prognosis. We suggest that RDW and CA-125 can be used as prognostic indicators for AECOPD.

There are some limitations of this study. This was a single-center, retrospective study, and some data were missing, such as outpatient medications. Additionally, we underestimated the number of readmissions as we did not include admissions from other hospitals.

## Conclusion

In this study, we found that the RDW value and serum CA-125 level are potential prognostic indicators for AECOPD. These findings can provide a reference for clinicians.


## Declaration of conflicting interest


The authors declare that there is no conflict of interest.

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## ORCID iDs

Fang He  <https://orcid.org/0000-0002-1712-2309>

Ping Zhao  <https://orcid.org/0000-0003-3646-6673>

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