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Analysis of Red Cell Distribution Width and Carcinoembryonic Antigen As Predictor of Severity Colorectal Cancer

Eka Widia Pusfitasyari[1], Uleng Bahrun[1,2], Mansyur Arif[1,2,3]

[1]Department of Clinical Pathology, Faculty of Medicine, Hasanuddin University/Dr. Wahidin Sudirohusodo, Makassar, Indonesia. E-mail: ekawidiap1@gmail.com
[2]Hasanuddin University Hospital, Makassar, Indonesia
[3]Dr. Tadjuddin Chalid Hospital, Makassar, Indonesia

ABSTRACT

The incidence of CRC is 16.5 cases in 100,000 population with 6.7% mortality of all malignancies. RDW-CV values and CEA levels were used as predictors of severity in various malignancies. This study aimed to analyze the RDW-CV and CEA levels as predictors of CRC severity. A Retrospective study using medical record data of 245 CRC patients at Dr. Wahidin Sudirohusodo Hospital. Samples were grouped based on stage (metastatic and non-metastatic), tumor location (right colon, left colon, and rectum), type of care (outpatient and inpatient), and outcome (improved and died). The distribution of RDW-CV and CEA data was tested using the Kolmogorov-Smirnov test, comparison of stage, outcome, and type of care using the Mann-Whitney test, correlation with Spearman's correlation test, comparison by location using the Kruskal-Wallis test and ROC curve to determine the cut-off. The median age of subjects was 53.7±12.4 years. RDW-CV values and CEA levels were higher in the metastatic stage than non-metastatic (p=0.005 vs. p=0.000). There was a significant relationship between the incidence of metastases with RDW-CV (p=0.005) and CEA (p=0.000) in CRC. ROC curve analysis shows the optimal cut-off value for RDW-CV as a metastatic prediction is 14.35% (sensitivity 60.4%; specificity=50%), and CEA was 3.24 ng/mL (sensitivity 70.3%; specificity=52.1%). RDW-CV value was highest in the right colon compared to the left colon and rectum (p=0.009). RDW-CV values and CEA levels were higher in patients with mortality than those who recovered (p=0.016 vs. p=0.055). This study shows a significant relationship between RDW-CV and CEA with the metastatic stage of CRC, and based on the outcome, RDW-CV was higher in the mortality group.

Keywords: RDW-CV, CEA, colorectal cancer severity

INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy following lung and breast cancer and is the leading cause of death in male and female patients in the United States. In Indonesia, CRC ranks fourth in malignancy, with 16.5 cases per 100,000 adult population and a mortality rate of 6.7% of all cancer cases. Colorectal cancer is a malignancy originating from the large intestine, consisting of the colon (the longest part of the large intestine) and/or the rectum (the last small part of the large intestine before the anus). The process of CRC carcinogenesis is complex and involves the interaction of genetic and environmental factors. Demographic factors such as old age, male gender, and obesity are reported to dominate the general CRC profile.[1,2]

Carcinoembryonic antigen (CEA) is a complex glycoprotein produced by 90% of CRC, is measured in serum quantitatively, and its increase contributes to the malignant characteristics of the tumor. Carcinoembryonic antigen is a common biomarker used for diagnostic approaches, monitoring therapy response, and prognostics in CRC.[3]

Red blood cell distribution width (RDW) is an essential part of routine blood tests that are commonly carried out in clinical practice. The RDW value reflects the distribution of red blood cell volume and size. Two RDW indicators are the red cell distribution width-variation coefficient (RDW-CV) and the red cell distribution width-standard deviation (RDW-SD), which can be applied to testing various diseases. The red cell distribution width-variation coefficient is a classic evaluation index for the degree of imbalance of erythrocyte morphology in the blood that reflects the heterogeneity of erythrocyte volume and is usually used to evaluate cardiovascular disease, malignancy, and infectious diseases.[4,5]

Several studies reported that the value of RDW-CV in malignancy is closely related to proinflammatory cytokines. Chronic inflammation due to malignancy causes inadequate erythropoietin production, suppressing erythropoiesis,

malnutrition, increased oxidative stress, and cachexia. Li *et al*. analyzed 168 CRC patients and concluded that there was a significant increase in RDW-CV values and CEA levels in advanced-stage CRC patients. The results of this study lead to the hypothesis that an increase in RDW-CV values is associated with a worse prognosis in CRC, but further research on the RDW-CV value is still needed to determine if it can be used as a new cellular marker for early warning and evaluation of CRC severity.[5–7]

Analyzing RDW-CV values with the tumor marker CEA is expected to be a new blood indicator with a more accurate and comprehensive assessment, helping clinicians manage CRC, as both RDW-CV and CEA are easily examined and are non-invasive.

METHODS

This research was a retrospective study with a cross-sectional method using secondary data from patient medical records at Dr. Wahidin Sudirohusodo Hospital, Makassar, from January 2021 to June 2022. The research population was all data of patients diagnosed with CRC by the Surgery Clinicians of Dr. Wahidin Sudirohusodo Hospital. Inclusion criteria were >18 years old, RDW-CV, CEA results, tumor location information based on histopathological examination, metastases based on X-ray, type of treatment, and patient outcomes. Incomplete medical record data were excluded from this study. The samples were then analyzed using the Kolmogorov-Smirnov test to assess data normality, the Mann-Whitney test, Kruskal-Wallis test, Spearman's correlation test, Receiver Operating Characteristics (ROC) curve to assess the Area Under Curve (AUC) and determine the cut-off value, results were significant test if the value of $p < 0.05$.

The research was carried out after receiving ethical clearance from the Health Research Ethics Commission (KEPK) of the Medical Faculty of Hasanuddin University/Hasanuddin University Hospital (RSUH)-\Dr. Wahidin Sudirohusodo General Hospital Makassar number 419/UN4.6.4.5.31/PP36/2022.

Table 1. Sample characteristics

Sample Characteristics	Total (n=245)	Percentage (%)
Gender		
Female	126	51.4
Male	119	48.6
Age (years old)		
18-35	22	9.0
36-45	45	18.4
46-55	62	25.3
55-65	67	27.3
>65	49	20.0
Stage		
Metastasis	101	41.2
Non-metastasis	144	58.8
Cancer location		
Right colon	24	9.8
Left colon	102	41.6
Rectum	119	48.6
Type of clinic		
Inpatient	30	12.2
Outpatient	215	87.8
Outcome		
Died	6	2.4
Recovered	239	97.6

RESULTS AND DISCUSSIONS

This study was conducted at the Medical Records Installation of Dr. Wahidin Sudirohusodo General Hospital using data from 245 CRC patients.

Table 1 shows that most subjects were females, with the dominant age group being 55-65. Most of them were in non-metastatic stages, with the location of the cancer being at the rectum. Most patients were from the outpatient, and more than 97 percent of patients' conditions have recovered.

The subject's age had a median of 55.00 (SD=12.44), the RDW-CV value had a median of 14.60 (SD=3.52), and the mean CEA level was 5.49 (SD=74.40). The Kolmogorov-Smirnov normality test results show that the distribution of age data, RDW-CV, and CEA were not normally distributed ($p<0.05$).

Table 2. Comparison of RDW-CV and CEA according to stage

Variable	Stage	n	Min	Max	Median	SD	p*
RDW-CV (%)	Metastasis	101	10.8	29.7	15.70	3.93	0.05
	Non-metastasis	144	4.9	24.5	14.35	3.04	
CEA (ng/mL)	Metastasis	101	0.3	200.0	12.10	88.55	0.000
	Non-metastasis	144	0.1	240.0	3.17	54.94	

*Mann-Whitney test

The Mann-Whitney differential test showed that the RDW-CV value was found to be higher in the metastatic group than in the non-metastasis (p=<0.0051), and CEA levels were found to be higher in metastases than in non-metastases (p=<0.0001).

Table 3. Correlation test of RDW-CV and CEA with metastasis

Variable	Statistics	Metastasis
RDW-CV	Correlation coefficient (R)	0.180
	p	0.005
	n	245
CEA	Correlation coefficient (R)	0.279
	p	0.000
	n	245

Spearman's correlation test

The test results showed a significant positive correlation between RDW-CV (p=0.005) and CEA (p=0.000) with metastasis. The greater the RDW-CV value and CEA level, the greater the possibility of metastasis. Based on the value of the correlation coefficient (R), the CEA level (R=0.279) has a closer correlation than the RDW-CV value (R=0.180) to the possibility of metastases.

The AUC value of RDW-CV was 0.605 (p<0.01), and CEA was 0.663 (p<0.001), which indicated that the cut-off values of RDW-CV and CEA can be used to predict CRC metastases. Based on the coordinates of the ROC curve, the optimal cut-off value for RDW-CV was 14.35%, and for CEA was 3.24 ng/dL.

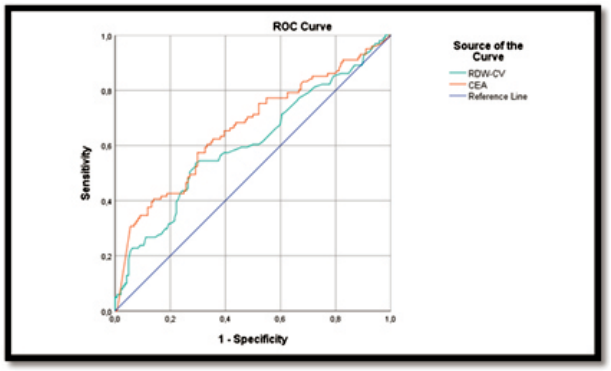

Figure 1. Prognostic value of RDW-CV and CEA towards the stage

Table 4. Area under curve

Variable	Area	Standard Error	p
RDW-CV (%)	0.605	0.037	0.005
CEA (ng/dL)	0.663	0.036	0.000

The prognostic value of the RDW-CW was obtained at a cut-off value of 14.35% with sensitivity 60.4%, specificity 50.0%, Positive Predictive Value (PPV) 5.9%, Negative Predictive Value (NPV) 64.3%, accuracy 54.3%. The CEA prognostic value was obtained at a cut-off of 3.24 ng/dL with a sensitivity of 70.3%, specificity of 52.1%, PPV of 50.7%, NPV of 71.4%, and accuracy of 59.6%. Based on the results of these calculations, the CEA level (59.6%) had a higher accuracy than the RDW-CV (54.3%) in predicting CRC metastases.

Table 6 shows that the mean of RDW-CV was highest in the right colon (17.62%) and lowest in the rectum (15.20%) (p<0.01).

Table 5. Staging calculations of RDW-CV and CEA

Variable	Cut-off Value	Metastasis		Total
		Metastasis	Non-Metastasis	
RDW-CV (%)	≥ 14.35	61	72	133
	<14.35	40	72	112
CEA (ng/mL)	≥ 3.24	71	69	140
	<3.24	30	75	105

Table 6. Comparison of RDW-CV and CEA according to location

Variable	Location	n	Min	Max	Median	SD	p*
RDW-CV (%)	Right colon	24	4.9	29.7	17.75	5.16	0.009
	Left colon	102	10.8	25.2	14.30	3.23	
	Rectum	119	4.9	27.3	14.50	3.24	
CEA (ng/dL)	Right colon	24	0.6	240.0	3.63	71.24	0.584
	Left colon	102	0.1	200.0	4.96	79.00	
	Rectum	119	0.3	200.0	6.08	71.11	

*Kruskal-Wallis test

Table 7. Comparison of RDW-CV and CEA according to the outcome

Variable	Comparison	n	Min	Max	Median	SD	p*
RDW-CV(%)	Died	6	15.3	27.3	17.70	4.42	0.016
	Recovered	239	4.9	29.7	14.60	3.46	
CEA (ng/dL)	Died	6	7.4	200.0	20.97	95.82	0.055
	Recovered	239	0.1	240.0	5.07	73.89	

*Mann-Whitney test

Based on patient outcomes, the RDW-CV value was found to be higher in subjects who died than in subjects who recovered (p<0.05). CEA levels were higher in subjects who died than those who recovered but were not statistically significant (p>0.05). The RDW-CV and CEA cut-off values could not be calculated because too few subjects died (6 people).

This study used a cross-sectional design on 245 samples that met the inclusion and exclusion criteria. Tables 1 and 2 showed the age of the subjects between 23 to 81 years. Most patients were female in the 55-65 age group (27.3%). These results were in line with the findings of a study by Silvia *et al*. at a National Cancer Center. Most CRC patients were females who have entered menopause, where estrogen levels and β-estrogen receptors begin to decrease, which triggers the development of cancer cells. There was consistency in the results of a study conducted by Kim *et al*., which showed that most CRC occurred in female patients who have entered menopause. Siegel *et al*. stated that the incidence of CRC began to increase at the age of 50 years, which is also in line with the findings of this study.[8–10]

The results of the analysis showed that the RDW-CV and CEA values were found to be higher in metastases (p=0.005 vs. p=0.000). The correlation test showed a significant positive correlation between RDW-CV and CEA; the greater the RDW-CV value and CEA level, the greater the possibility of metastases. The correlation coefficient value of CEA levels (R=0.279) correlates more closely than the RDW-CV (R=0.180) to the possibility of metastases. The RDW-CV AUC value was 0.605 (p=<0.005), and the CEA AUC value was 0.663 (p=<0.000), with the optimal cut-off value of RDW-CV 14.35 and CEA 3.24. The RDW-CV prognostic value had a sensitivity of 60.4% and a specificity of 50%. In comparison, the prognostic value of CEA had a sensitivity of 70.3% and a specificity of 52.1%. Still, the accuracy of the CEA level was 59.6%, higher than the accuracy of the RDW-CV 54.3% in predicting metastasis. Gao *et al*. stated that CEA levels in serum and tissues seemed to be increased in CRC, especially advanced-stage CRC; CEA levels increased in 50% of CRC patients with tumor cells that had spread to the lymph nodes and increased in 75% of patients CRC that had metastasized. Yang *et al*., in a study, stated that a significant increase in RDW-CV was found in patients with CRC and further confirmed that the RDW-CV value was closely related to CRC metastases. In line with this study, Li *et al*. also stated that abnormal increases in RDW-CV and CEA values correlated with pathological features of colorectal cancer and showed a tendency for worse malignant tumors.[5,6,11]

Song *et al*. stated that the mechanism underlying the increase in RDW-CV in the outcome of CRC is still unknown. Several studies have revealed potential mechanisms that may be the cause. The RDW-CV value increases in conditions of ineffective erythrocyte production or increased RBC destruction in inflammatory or infectious conditions. The inflammatory process can stimulate erythrocyte proliferation through erythropoietin (EPO) formation, increasing RDW-CV. An increase in RDW-CV can reflect the inflammatory process and oxidative stress degree, providing prognostic information. Tumor growth can cause malnutrition, resulting in erythropoiesis and erythrocyte maturation changes. The condition of patients with CRC can also affect the bone marrow's hematopoietic function, causing a tendency to bleed and reducing iron storage. An increase in RDW-CV can also indicate cytomembrane instability, which can result in multi-organ dysfunction, worsening the patient's condition and prognosis and increasing mortality risk.[12]

Most of the cancer locations in this study were found in the rectum (48.6%). Sutrisna, in his research, stated that the rectum is often the location of most CRCs due to consuming foods that are low in fiber and high in fat, causing the transit time of fecal storage to be longer, resulting in mucosal contact with inflammatory processes and infections over a long time. The median RDW-CV value was highest in the right colon (17.62%). Following research by Cheng *et al*. for tumor location, the RDW-CV value was higher in patients with right-sided CRC than those with left-sided or rectal CRC. There was no significant relationship between CEA levels and tumor location (p>0.05).[7,13]

The RDW-CV and CEA values were also found to be higher in subjects who died compared to subjects who recovered, but a cut-off value could not be determined because there were too few subjects who died.

Limitations in this study were the use of secondary data, limited information from medical records, and the inability to assess other factors that influence the incidence of colorectal cancer, such as lifestyle, obesity, family genetic history, and other factors. An incomplete medical record recording system also caused the exclusion of many samples.

CONCLUSIONS AND SUGGESTIONS

The results of the study show that the RDW-CV and serum CEA levels could be used as predictors related to the severity of CRC, in this case, tumor metastases and poor prognosis for patient survival. The advantages of RDW-CV and CEA examinations are they are easily accessed, cheap, and non-invasive.

Further studies are needed in parallel to determine the increase in RDW-CV and CEA over time as indicators of worsening in assessing the prognostic value of CRC patients.

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