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# Prognostic Role of Red Cell Distribution Width in Solid Malignancies

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**Abstract:** ***Background: Red blood cell distribution width (RDW), a parameter that has been generallypointed to differentiate the type of anemia for several decades, which was also found to be a prognostic factor in various types of cancer patients, recent studies found. However, the prognostic value of RDW in cancer patients remains controversial. Here, we performed the study to define the role of RDW as prognostic factor in patients with solid malignancies. Methods: Complete blood count (CBC) were measured in 62 patients with solid malignancies. In this cohort study, subjects was gathered from the period of January to December 2017 to define the subjects' mortality. ROC curve was used to distinguish the cut off of RDW and analyses with Pearson's $\chi^2$ test and Cox regression test. Results: An amount of 13 (21%) male and 49 (79%) female patients was included into our study. Subjects' mean age was 49.75±12.3 years old andmean of RDW was 17.09±2.74%. Cervical cancer (19.4%), Nasopharyngeal cancer (17.7%) and Breast cancer (14.5%) were the most types of solid malignancies were recorded. Of 62 patients, 37 (59.7%) patients died during the follow-up. Seen from theROC curve, we found the cut off of RDW was 16.5% with area under the curve 0.94, RR value was 4.24 (p<0.001; 95%CI= 2.07-8.69) and Hazard Ratio was 7.94(p<0.001; 95%CI= 3.24-9.45). Conclusions: RDW may predict the risk of mortality in patients with solid malignancies and patients with higher RDW are more likely to have worse prognosis than those with lower RDW.***

**Keywords:** Red blood cell distribution width, solid malignancies, Prognosis

## 1. Introduction

Canceris characterized by rapid progress and has became a major cause of morbidity and mortality in most regions worldwide. Over the past decades, the incidence of cancers has been increasing worldwide. The absence of diagnostic marker, along with increasing cancer incidence, altogether making impact toward socio-economic matter. Because of this, many study towards biomarkers was carried out to help with prognosis of cancer.[1-3]

Red blood cell distribution width (RDW) is a parameter that usually reported in a complete blood cell count panels that contains RDW-SD (RDW standard deviation) and RDW-CV (RDW coefficient of variation) value, and it reflects the size heterogeneity of red blood cells. Its main clinical application has been limited to the differential diagnosis of anemia. In our study before, we investigated the role of RDW in diagnosis of iron deficiency anemia.[4]

Recently, RDW has been considered as a inflammatory associated marker, and emerging studies suggest its potential factor for predicting overall mortality of various human inflammatory diseases. Many studies have reported the association between high RDW levels and increased mortality in patients with cardiovascular disease,[5] brain vascular disease,[6] strokes,[7] septicemia,[8] chronic obstructive pulmonary disease,[9] and hepatitis B.[10] Elevated RDW values were also shown to be associated with increased risk of mortality in the general population.[11]

It is well known that cancer is both a cause and a result of chronic inflammation. And it has been reported that the RDW level of many patients with malignant tumors, including solid malignancy, has been widely discussed, proving that the RDW is correlated with the diagnosis, staging and prognosis.[12] Therefore, we hope to analyze the relationship between RDW and solid malignancy through the following this study and explore its potency for becoming an effective, nouveau prognostic indicator in patients with solid malignancy.

## 2. Materials and Methods

Our cohort study was consisted of population of patients presenting to Sanglah Hospital (Denpasar, Bali, Indonesia) between January 2017 and December 2017 for the evaluation and management of solid malignancy in internal medicine department. Patients with a histologically confirmed diagnosis of solid malignancy were included. We excluded were patients with inflammatory conditions such as infections or immune disease, cardiovascular disease, cerebrovascular disease, or COPD.

Blood samples were collected from all patients using routine methods at the time we found the eligible patient. This study was conducted in conformity with the Declaration of Helsinki on medical protocol and ethics, and the regional Ethical Review Board of Sanglah Hospital approved the study.Written informed consent was obtained from all participants.

Blood parameters from the CBC including white blood cells (WBCs), platelets (Plts), hemoglobin, mean cell volume (MCV), and RDW were analyzed with an automated hematology analyzer XE-2100 (Sysmex Corp, Kobe, Japan). The normal range of RDW obtained from the CBC in general and in our laboratory was 11.5%–15%. All included patients were followed at 3-month intervals after the last therapy or until death. Overall survival (OS) was defined as

the intervals from the date of diagnosis was declared to the date of disease recurrence, death, or last follow-up.

The data are reported as number (%) and mean±standard deviation. Shapiro–Wilk goodness of t tests used to assessed the normality. We used ROC curve to define the cut-off of RDW and The Pearson's $\chi^2$ test was utilized to calculate the associations between RDW and clinical parameters. Value of $P<0.05$ was considered statistically significant.

## 3. Results

A total of 62 eligible solid malignancies patients were enrolled. Thecharacteristics of the patients are outlined in table 1. The mean age was 49.75±12.3 (range: 19–79) years at the time of diagnosis. We found 13 (21%) male patients and 49 (79%) female patients.

**Table 1:** Characteristics of the patients

| **Variable** | Total Patient (n=62) |
|---|---|
| Age (year) mean±SD | 49.75±12.3 |
| **Gender** | |
| Male (%) | 13(21%) |
| Female (%) | 49(79%) |
| **Type of Malignancies** | |
| Cervical Ca (%) | 12 (19,4%) |
| Nasopharyngeal Ca (%) | 11 (17,7%) |
| Breast Ca (%) | 9 (14,5%) |
| Colon Ca (%) | 8 (12,9%) |
| Ovarium Ca (%) | 8 (12,9%) |
| Lung Ca (%) | 5 (8,06%) |
| Others (%) | 9 (14,5%) |
| **Karnofsky Score** | |
| 50 (%) | 4 (6,5%) |
| 60 (%) | 24 (38,7%) |
| 70 (%) | 30 (48,4%) |
| 80 (%) | 4 (6,5%) |
| **Stadium of Cancer** | |
| I | 1 (1,6%) |
| II | 6 (9,7%) |
| III | 16 (25,8%) |
| IV | 39 (62,9%) |
| **Complete Blood Count** | |
| Hb (g/dL) mean±SD | 7.66±1.49 |
| MCV (fL) mean±SD | 85.94±10.21 |
| MCH (Pg) mean±SD | 27.20±3.90 |
| MCHC (g/dL) mean±SD | 31.58±1.73 |
| RDW-CV (%) mean±SD | 17.08±2.74 |
| WBCs ($10^3$/µl) mean±SD | 12.87±14.17 |
| Plts ($10^3$/µl) mean±SD | 330.55±168.59 |

**Abbreviations:** Ca, cancer; Hb, hemoglobin; MCV, mean cell volume; MCH, mean cell hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW-CV, Red blood cell distribution width coefficient of variation; WBCs, white blood cells; Plts, platelets.

During the follow-up, maximum until 3 month after last therapy (chemotherapy or radiotherapy), we found from 62 patients, 37 (59.7%) patients were died. From the ROC curve (fig. 1), we found that area under the curve was 0.94 (95%CI 0.88-0.99) with cut offof RDW was 16.5%. With this cut off, we made 2 by 2 table (table 2) and found RR value was 4.24 (p<0.001; 95%CI= 2.07-8.69).

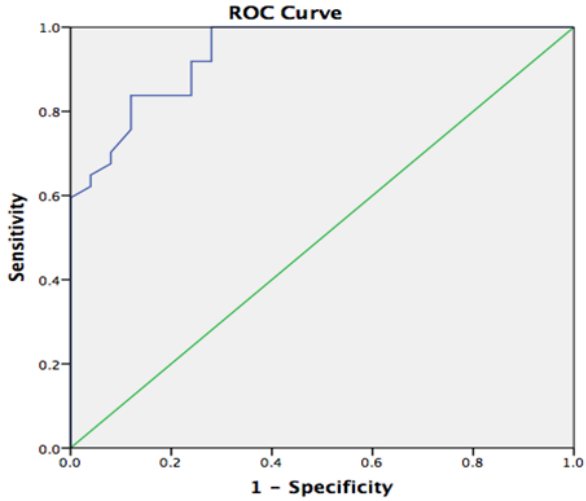


**Figure 1:** ROC Curve

**Table 2:** Two by two table

| Cut off RDW | Patient Condition | | Total |
|---|---|---|---|
| | Died | Alive | |
| RDW > 16.5% | 30 | 3 | 33 |
| RDW ≤ 16.5% | 7 | 22 | 29 |
| **Total** | 37 | 25 | 62 |

From the Cox regression test, we found the Hazard Ratio was 7.94 (p<0.001; 95%CI= 3.24-9.45).

## 4. Discussion

Red cell distribution width (RDW) is a widely available by the vast majority of automated analysts. Reflecting the size heterogeneity of the circuiting erythrocytes, higher RDW values are suggestive of increased variation of red cell volumes (anisocytosis). Until recently, RDW had been a typically overlooked erythrocyte parameter, however, recent studies have clearly demonstrated that RDW is a reliable biomarker of cardiovascular morbidity and mortality, as well as an indicator of active, acute or chronic inflammatory conditions, such as infections and auto-immune diseases, since RDW is an early detector of iron deficiency anemia, impaired iron mobilization, increased oxidative stress status and its elevation has been firmly associated with elevation of other inflammation markers, such as C-reactive protein, Interleukin-6 and Tumor Necrosis Factor-a.[13,14]

Despite the great number of published studies evaluated the clinical significance of RDW as a prognostic factor in patients with impaired cardio metabolic function and active inflammation, extremely limited data exists concerning the capability of RDW as a biomarker of prognostic factor in solid malignancies. Our preliminary results demonstrated that elevated RDW could be helpful in the differential diagnosis of iron deficiency anemia and anemia on chronic disease, being significantly higher in the group of patients with iron deficiency anemia.[15]

In this study, we found a positive correlation between RDW and solid malignancies mortality, with higher RDW associated with increased risk of solid malignancies mortality, showed RDW may be used to predict the mortality of tumor and the risk assessment of tumor patients. Analysis suggested that higher RDW correlated with

increased risk of hospital mortality. Similar trends could also be observed in the model adjusted for a greater number of characteristics, suggesting that RDW may be an effective tumor prognostic factor. Although several previous studies suggested that RDW was associated with mortality in various cancers,[14-18] evidence to solidify the relationship remains uncommon. Moreover, most studies only demonstrated associations between the RDW and a single type of cancer; the relationship between RDW and all-combined cancer mortality remains unclear, and the role of RDW in tumor short-term prognosis is also very vague. Therefore, we evaluated the relationship between RDW and all-solid tumor mortality and proved the effect of RDW in tumor short-term prognosis.[19]

In this study, we found the cut off RDW was 16.5%. This cut off was near similar with the study by Julia Riedl et al. (2014), which is the cut off RDW was 16% to predict the mortality of cancer. In this study, the AUC of ROC was 0.94, which may be considered a high value. The AUC can be thought of as an indicator of overall 'accuracy.' A major practical fault of the AUC as an index of diagnostic performance is that it summarises the entire ROC curve, including regions that are frequently irrelevant to practical applications.[20-21]

Nonetheless, there were several limitations of present study. Firstly, the sample size is relatively small and the findings could be from chance. Secondly, this is an observational study and so still there could be residual confounding factors. Further study is needed to examine the role of the RDW in predicting the clinical outcomes in a large sample size and long-term follow-up.

## 5. Conclusions

In summary, our study revealed a potential RDW value to predict the risk of mortality in patients with solid malignancies and patients with higher RDW are more likely to have poorer prognosis than those with lower RDW. Because CBC can routinely examine RDW values, this relatively inexpensive and easily available parameter may be used as a new marker to aid in the treatment and prognosis of solid malignancies. Better-designed studies in the future should be performed to further confirm the value of monitoring RDW.

## 6. Disclosure

The authors report no conflicts of interest in this work.

## References

[1] Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer 2013; 132: 1133-45. doi: 10.1002/ ijc.27711.
[2] Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer Journal for Clinicians* 2011; vol. 61, no. 4, pp. 212–236.
[3] Zheng RS, Zeng HM, Zhang SW. Estimates of cancer incidence and mortality in China. *Chinese Journal of Cancer* 2017; vol. 36, no. 1, pp. 66–71.
[4] Purnamasidhi CAW, Suega K, Bakta IM. Role of Red Cell Distribution Width (RDW) in the diagnosis of Iron Deficiency Anemia. Indonesia Journal of Biomedical Science (*IJBS*) 2019; Volume 13, Number 1: 12-15
[5] Nishizaki Y, Yamagami S, Suzuki H, Joki Y, Takahashi S, Sesoko M, Yamashita H, et al. Red blood cell dis- tribution width as an effective tool for detecting fa- tal heart failure in super-elderly patients. Intern Med. 2012;51(17):2271-2276.
[6] Karabulut A, Uzunlar B. Correlation between red cell distribution width and coronary ectasia in the acute myocardial infarction. ClinApplThrombHemost. 2012;18(5):551-552.
[7] Yesil A, Senates E, Bayoglu IV, Erdem ED, Demirtunc R, KurdasOvunc AO. Red cell distribution width: a novel marker of activity in in ammatory bowel disease. Gut Liver. 2011;5(4):460-467.
[8] Lee WS, Kim TY. Relation between red blood cell dis-tribution width and in ammatory biomarkers in rheuma- toid arthritis. Arch Pathol Lab Med. 2010;134(4):505- 506.
[9] de Gonzalo-Calvo D, de Luxan-Delgado B, Rodriguez-Gonzalez S, Garcia-Macia M, Suarez FM, Solano JJ, Rodriguez-Colunga MJ, et al. Interleukin 6, soluble tu-mor necrosis factor receptor I and red blood cell distri-bution width as biological markers of functional depen- dence in an elderly population: a translational approach. Cytokine. 2012;58(2):193-198.
[10] Rhodes CJ, Howard LS, Busbridge M, Ashby D, Kondili E, Gibbs JS, Wharton J, et al. Iron de ciency and raised hepcidin in idiopathic pulmonary arterial hypertension: clinical prevalence, outcomes, and mechanistic insights. J Am CollCardiol. 2011;58(3):300-309.
[11] Chiba T, Marusawa H, Ushijima T. In ammation-asso-ciated cancer development in digestive organs: mecha-nisms and roles for genetic and epigenetic modulation. Gastroenterology. 2012;143(3):550-563.
[12] Mladenova D, Kohonen-Corish MR. Review: Mouse models of in ammatory bowel disease--insights into the mechanisms of in ammation-associated colorectal can- cer. In Vivo. 2012;26(4):627-646.
[13] Baicus C, Caraiola S, Rimbas M, Patrascu R, Baicus A. Utility of routine hematological and in ammation parameters for the diagnosis of cancer in involuntary weight loss. J Investig Med. 2011;59(6):951-955.
[14] Beyazit Y, Kekilli M, Ibis M, Kurt M, Sayilir A, Onal IK, Purnak T, et al. Can red cell distribution width help to discriminate benign from malignant biliary obstruc-tion? A retrospective single center analysis. Hepatogas- troenterology. 2012;59(117):1469-1473.
[15] Ozkalemkas F, Ali R, Ozkocaman V, Ozcelik T, Ozan U, Ozturk H, Kurt E, 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.
[16] Spell DW, Jones DV, Jr., Harper WF, David Bessman J. The value of a complete blood count in predicting can- cer of the colon. Cancer Detect Prev.

2004;28(1):37-42.
[17] Speights VO, Johnson MW, Stoltenberg PH, Rappaport ES, Helbert B, Riggs MW. Complete blood count indices in colorectal carcinoma. Arch Pathol Lab Med. 1992;116(3):258-260.
[18] Seitanides B, Giakoumakis G, Tsakona C. Increased red cell volume distribution width in patients with bone marrow metastases. J ClinPathol. 1988;41(11):1246.
[19] Agarwal S. Red cell distribution width, in ammatory markers and cardiorespiratory tness: Results from the National Health and Nutrition Examination Survey. Indian Heart J. 2012;64(4):380-387.
[20] Lee AH, Happereld LC, Bobrow LG, Millis RR. Angiogenesis and in ammation in invasive carcinoma of the breast. J ClinPathol. 1997;50(8):669-673.
[21] Hartman ZC, Yang XY, Glass O, Lei G, Osada T, Dave SS, Morse MA, et al. HER2 overexpression elicits a pro- in ammatory IL-6 autocrine signaling loop that is critical for tumorigenesis. Cancer Res. 2011;71(13):4380-4391.