

## Original Research Article

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# Association between red cell distribution width and tumour stage in patients with resected cancer of the head of the pancreas

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## ABSTRACT

**Background:** Predicting the clinical outcome in pancreatic cancer is often challenging due to the lack of reliable and cost effective prognostic parameters. Red Cell Distribution Width (RDW), an index of the variability in the size of the circulating RBCs has been reported to have prognostic significance in some malignancies. There is a scarcity of literature supporting its relevance in pancreatic cancer. Objective was to study the association between RDW and tumor stage in patients with pancreatic cancer attending a tertiary care hospital in South India and to correlate RDW and survival after surgery for pancreatic cancer.

**Methods:** Retrospective analysis of prospectively collected digital medical records of 254 pancreatic cancer patients, who had undergone surgery at a tertiary centre between 2002 and 2015. This was supplemented with data obtained from telephone conversations with the patients and/or their next of kin.

**Results:** Higher RDW values were associated with advanced tumor stages 84.2% of patients with stage 3 cancer and 92.3% with stage 4 cancer had high RDW values. High values were significantly associated with lower survival. The mean duration of survival for people with normal values was 83 months while that for patients with higher values was significantly lower at 72 months.

**Conclusions:** There appears to be a significant association between RDW and tumor stage in pancreatic cancer. RDW also correlates with the duration of survival in pancreatic cancer patients. Thus, it may be useful in predicting the clinical outcome in pancreatic cancer.

**Keywords:** CA head of pancreas, RDW, Tumour staging

## INTRODUCTION

Pancreatic cancer is a malignant neoplasm of the pancreatic tissue. Although infrequent, it is one of the most rapidly lethal cancers, with a 5 year survival rate of less than 7 per cent, causing more than 331,000 deaths per year.<sup>1,2</sup> Predicting the clinical outcome of pancreatic cancer is often very challenging. Although CA 19-9

levels have increasingly been used as a diagnostic as well as prognostic tool for pancreatic cancer, some studies show no correlation.<sup>3,4</sup> The American Society of Clinical Oncology does not recommend using CA19-9 as a standalone diagnostic and prognostic tool for pancreatic cancer.<sup>5</sup> In such a scenario, identification of additional parameters that are reliable, reproducible and cost effective could be helpful in predicting disease outcome

in pancreatic cancer patients. Red Cell Distribution Width (RDW) is an index of the variability in the size of the circulating red blood corpuscles. RDW values are widely available to clinicians as a part of routine haemograms, but it is rarely used except to distinguish different types of anemia. Recently high RDW values have been linked to several cardiovascular diseases, sepsis, COPD and hepatitis.<sup>6,7</sup> Reports indicating that an increase in RDW values correlate with tumor stage and prognosis in lung cancers (Koma et al) and tumor stage and grade in renal cell carcinoma (Wang et al) have garnered considerable attention.<sup>8,9</sup> There is however, a paucity of literature focusing on RDW in the setting of pancreatic cancer. The present study attempts to gain insight into the prognostic value of RDW in pancreatic cancer by looking at its association with tumor stage as well as the impact on survival.

## METHODS

This retrospective study was conducted at Amrita Institute of Medical Sciences and Research Centre, Cochin after obtaining the institutional ethical committee clearance. Data of consecutive patients who had undergone potentially curative resectional surgery for cancer of the head of the pancreas at this tertiary referral center between January 2002 and January 2015 were included in the study. Patients with missing data were excluded from the analysis. Data regarding the patient's demographics, tumour stage, RDW value (as recorded on of Sysmex Xn-2000) and treatment details were obtained from the digital records as was the follow up. All Patients (or their next of kin) were then contacted by telephone and complete details of follow up obtained, after informing them, the nature of the current study and their consent to participate was sought. A total of 254 patients were operated in the study period - 135 of them (53%) patients had not followed up and could not be contacted by telephone either. All data was entered into a Microsoft Excel spreadsheet. The patients were divided into two categories - those with high RDW values (more than the Sysmex-Xn upper limit of the normal range of 14.8) and those with low or normal RDW values (less than or equal to 14.8). Patients were also grouped based on their tumor stage (AJCC version 8). The data was then analyzed using SPSS version 20 to look for any association between RDW and tumor stage, variation in RDW values with age and gender and the impact of RDW on survival using Kaplan Meir survival analysis.

## RESULTS

The age of study participants ranged from 36 to 88 (median 64.5). Males were found to be predominant (64.96%). Out of the 254 cases, most (60.2%) of them were diagnosed with stage 2 cancer. The details of which are provided in Table 1,2.

Out of the 254 patients, 177 (69.8%) of them had high RDW values (more than 14.8). It was observed that, as

the tumor stage advanced, the number of individuals in the high RDW category showed a progressive increase from 48.2% of stage one to 99.3% of stage 4. Details of which are provided in Table 3.

**Table 1: Distribution of patients based on their demographic characteristics and red cell distribution width.**

Category	Frequency	%
<b>Sex</b>		
Males	165	64.96
Females	89	35.04
<b>Age group (years)</b>		
30-39	2	0.78
40-49	21	8.26
50-59	73	28.74
60-69	81	31.88
70-79	62	24.40
80+	15	5.90
<b>Current status</b>		
Alive	38	14.96
Dead	81	31.88
Lost to follow up	135	53.14
<b>Red cell distribution width</b>		
<14.8	77	30.31
>14.8	177	69.68
<b>Total</b>	<b>254</b>	<b>100</b>

**Table 2: Distribution of patients based on their tumor stages.**

Tumour stage	Number	%
<b>Stage 1</b>	56	22
<b>Stage 2</b>	153	60.2
<b>Stage 3</b>	19	7.5
<b>Stage 4</b>	26	10.2
<b>Total</b>	<b>254</b>	<b>100</b>

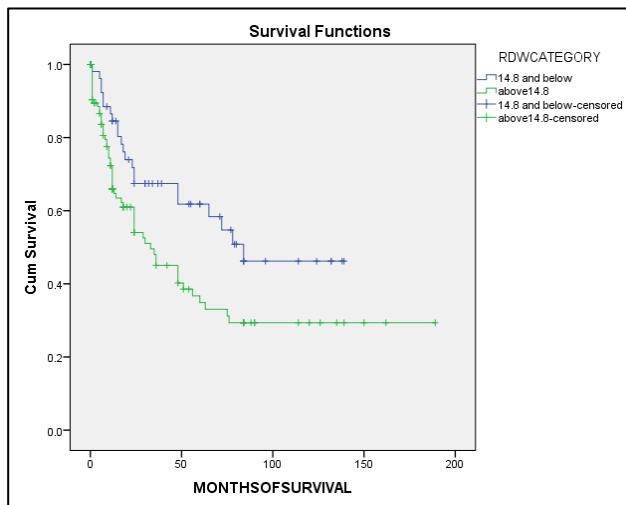
**Table 3: Distribution of participants based on tumour stage and RDW category.**

Tumour stage	Low RDW (%)	High RDW (%)
<b>Stage 1 (56)</b>	29 (51.8)	27 (48.2)
<b>Stage 2 (153)</b>	43 (28.2)	110 (71.8)
<b>Stage 3 (19)</b>	3 (15.8)	16 (84.2)
<b>Stage 4 (26)</b>	2 (0.7)	24 (99.3)
<b>Total</b>	<b>77</b>	<b>177</b>

The mean RDW value was found to progressively increase from stage 1 to stage 4. Stage 1 had a mean of 14.9, stage 2 had a mean of 16.1, stage 3 had a mean of 17.5 and stage 4 had a mean of 18.7. RDW values were independent of age and gender. The mean duration of survival for people with low RDW values (less than or equal to 14.8) was 83 months while those with RDW

values above 14.8 had lower mean duration of survival, 72 months. This is depicted in the Kaplan Meir survival analysis curve in Figure 1.

This difference was statistically significant (log rank test,  $p=0.015$ ).



**Figure 1: Kaplan Meir survival analysis curve for pancreatic cancer patients with respect to their RDW values.**

## DISCUSSION

Red cell distribution width (RDW) is an index of the variability in the size of the circulating red blood corpuscles and is reported in all routine haemograms. Though it is easily available, it would appear to be under-utilized except occasionally to differentiate types of anemias. Very few studies exist on its use as a marker of prognosis or outcome in various diseases, despite literature suggesting variations of RDW in sepsis, COPD, hepatitis and cancer stage. In the current study, RDW values clearly correlated positively with the stage of pancreatic cancer, with a higher RDW value correlating with a more advanced tumour stage. This finding concurs with the results of previous studies correlating RDW to tumour stage in other cancers. The only other study (on search of indexed literature) by Yilmaz et al was concordant for RDW values in pancreatic cancer.<sup>10</sup> The precise mechanism of the association between RDW and tumour stage is unknown.

Several factors affecting RDW values such as RBC circulation half-life and membrane deformability could be affected by inflammation which is recognized as a hallmark of tumour development.<sup>11</sup> Research studies point towards a possible correlation between RDW and C-reactive protein (CRP) values.<sup>12</sup> Neote et al detected several receptors for inflammatory factors on the RBC surface and hypothesized that RBCs are involved in the inflammatory process.<sup>13</sup> Forhecz et al found that inflammatory factors potentially affect iron metabolism,

RBC life span and the release of immature red blood cells into circulation causing an increase in the RDW.<sup>14</sup> Inflammatory factors have also been hypothesized to suppress the action of erythropoietin on erythroid stem cells and prevent the antiapoptotic effect of erythropoietin on maturing RBCs.<sup>14</sup>

The current study also showed that the mean duration of survival for patients with low RDW values (less than or equal to 14.8) was significantly higher than those with high RDW values (above 14.8). This result is also in agreement with several previously published studies in other cancers. Podhorecka et al showed that elevated RDW was associated with shorter survival time in patients with chronic lymphocytic leukemia.<sup>15</sup> A meta-analysis by Ai et al indicated that increased pretreatment RDW predicted poorer overall survival, progress-free survival and event-free survival in patient suffering from hematological malignancies.<sup>16</sup> The reason for this association too remains unknown. A possible explanation is that RDW has correlates with several circulating cytokines such as IL-6, tumor necrosis factor-alpha and hepcidin that could affect the biological behavior of tumor cells.<sup>17,18</sup>

While the finding of the current study that RDW was independent of gender is in agreement with studies such as that by Hoffman et al, the latter found a correlation with age this discrepancy could be from their study in healthy individuals whilst ours was only in malignancy.<sup>19</sup> It is likely that in individuals with malignancies, there could be increased signaling along the IGFs/ mTOR pathway. Persistent IGF-1/mTOR signaling activates erythropoietin resulting in heterogeneity of RBC size due to high turnover rates.<sup>20,21</sup> So the RDW becomes affected by the metabolically driven (growth factor - IGF-1/mTOR) signaling rather than chronological aging.

The present study showed that RDW has a strong association with tumour stage and survival rate, it may be difficult to extrapolate fully, as half of our study subjects (53%) were lost to follow up and this lack of long term survival data may have led to attrition bias. However, in view of the limitations of the present study, larger-scale prospective studies would be required to confirm these results.

## CONCLUSION

There is a significant association between RDW and tumour stage in pancreatic cancer patients. RDW also appears to correlate with duration of survival in these patients. It is a simple and easily available parameter, obtained at no additional cost incurred to the patient and hence may be of use in predicting the clinical outcome in pancreatic cancer patients.

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