Original Article

Red Cell Distribution Width: A Surrogate Biomarker to Predict Tumor Burden in Carcinoma Gallbladder

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Abstract

Aim: To assess the role of red cell distribution width as a marker to predict tumor burden in gallbladder cancer (GBC). **Methods:** One hundred and twenty-eight patients with newly diagnosed GBC were included in the study. Peripheral blood samples were obtained, and red cell distribution width (RDW) was assessed. Tumor markers and other biochemical parameters were also recorded. **Statistical Analysis:** Quantitative variables were summarized using mean and standard deviation or median and interquartile range based on the normality of the distribution. The association of RDW with stage of tumor was analyzed using Chi-square test. All statistical tests were interpreted for significance using a cutoff value of $P < 0.05$. **Results:** RDW showed a positive correlation with total bilirubin, total leukocyte count, and erythrocyte sedimentation rate ($P < 0.002$), but not with platelet count ($P < 0.643$). RDW showed a significant correlation with tumor markers CA 19-9 ($P < 0.003$), carcinoembryonic antigen ($P < 0.003$), and CA 125 ($P < 0.002$). In Stage IVB, there were significantly more patients with high RDW (78%) than normal RDW (21.8%). However, the results were not statistically significant ($P < 0.073$). **Conclusion:** In the present study, we have utilized RDW for correlation with tumor markers in carcinoma gallbladder and as a predictor of stage. We demonstrated higher levels of RDW with advanced stages of GBC. Overall, the study suggested that RDW may be utilized as a surrogate biomarker to predict tumor burden and disease in patients with GBC.

Keywords: *Gallbladder, red cell width, tumor markers*

Introduction

Gallbladder cancer (GBC) is one of the most common and aggressive malignant neoplasms of the biliary tract. Clinical manifestation of GBC is nonspecific, leading to late diagnosis and poor 5-year survival.[1] Currently, the diagnosis and staging of GBC mainly depends on noninvasive imaging such as computed tomography (CT) scan and invasive examination such as laparoscopy and biopsy. However, there is no ideal single tumor marker for the diagnosis and prognosis of GBC. Tumor markers such as carcinoembryonic antigen (CEA), CA 125, CA 242, and CA 19-9 have been used individually and in combination for the diagnosis and assessment of tumor burden of GBC with inconsistent result.[2] Therefore, inexpensive and convenient markers which could be used in predicting tumor burden of GBC are desirable. Red cell distribution width (RDW) is an index of the heterogeneity in the size of circulating erythrocytes.[3] It may be utilized to quantify the amount of anisocytosis in peripheral blood sample. RDW index reflects decreased erythropoiesis and abnormal life span of red blood cells. RDW is a measure of size variability in circulating red blood cells and is routinely reported as a part of complete blood count analysis. Main clinical utility of RDW is in

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the differential diagnosis of anemia.[4] It is also correlated to inflammation, undernutrition, impaired renal function, and inadequate production of erythropoietin.[5,6] High RDW levels are associated with increased mortality in patients with cardiovascular disease,[7] brain vascular disease,[8] strokes,[9] septicemia, chronic obstructive pulmonary disease, and hepatitis. Several studies have demonstrated that higher RDW values have been associated with patients of solid tumors as compared to healthy individuals.[10] There is an increasing evidence that RDW may play a role in diagnosis or as a prognostic marker in cancers such as renal cell, gastric, lung, mesothelioma, ovarian, esophageal, multiple myeloma, hepatocellular, endometrial, and breast cancer.[11] Furthermore, it can be used to differentiate between benign and malignant tumors.[12]

There is no specific study correlating RDW with GBC as a predictor of stage. Hence, this study was envisaged to determine the association of RDW with hematological parameters and tumor markers and assess its role as a surrogate marker to predict the burden of disease in GBC which is very prevalent in Indo-Gangetic belt.

Methods

Study design and population

In this prospective observational study, 128 newly diagnosed patients with GBC were enrolled from December 2017 to February 2019. This study was performed in accordance with the ethical guidelines and was approved by the institutional ethics committee. Informed consent was obtained from all included participants. Exclusion criteria of the study included previously treated malignancy, pregnancy, kidney transplantation, hematological disorders, severe anemia, infectious or inflammatory disease, iron supplementation therapy, recent deep venous thrombosis (past 6 months), recent blood transfusion (past 3 months), chronic obstructive pulmonary disease, hepatitis B or C, heart failure, arrhythmia, untreated thyroid disease, and severe liver and/or renal insufficiency. The following parameters were assessed: gender, age, presence of cholelithiasis, lymph node involvement, metastases, stage (according to the 8th ed.ition AJCC), and resectability status. Patients who were resectable on radiological imaging underwent radical cholecystectomy with nodal dissection. Personal habits of smoking or alcohol intake were also recorded.

Analysis of red cell distribution width, carcinoembryonic antigen, CA 19-9, and CA125 levels

Peripheral blood samples were obtained from newly diagnosed patients with GBC. Blood samples of all cases for hemogram were analyzed with Beckman Coulter LH-750/Sysmax XN-1000 coulter as per our laboratory protocol. Normal RDW levels are 11.5–14.5. Serum levels of CEA, CA 19-9, and CA 125 were measured using Advia Centaur XP, Siemens chemiluminescence method. According to the manufacturer's instructions, cutoff value for normal CEA is <5 ng/mL, CA 19-9 is <37 U/mL, and CA 125 is 0–35 U/L.

Statistical analysis

Data were analyzed using IBM SPSS v20.0 (IBM Corporation). Quantitative variables were summarized using mean and standard deviation (SD) or median and interquartile range based on the normality of the distribution. The association of RDW with stage of tumor was analyzed using Chi-square test. All statistical tests were interpreted for significance using a cutoff value of $P < 0.05$.

Results

Patients' characteristics

In the present study, 128 newly diagnosed patients with carcinoma gallbladder were included. Patients' characteristics are mentioned in Table 1. Female-to-male ratio was 4.5:1. Age ranged from 26 to 80 years, with a mean of 55.4 [Table 1]. Almost 46% of patients presented with obstructive jaundice. These patients were optimized by either endoscopic retrograde cholangiopancreaticography stenting or percutaneous biliary drainage. Nearly 93.8% of patients had pain at presentation either due to lymph nodal involvement or gallbladder mass lesion. Loss of weight (68%), loss of appetite (62.8%), and fever (38%) were other common presenting symptoms in our patients. Most of the patients (63.2% and 25%) were of higher stage (IV and III) and the remaining (10.9% and 0.8%) were of lower Stage (II and I), respectively [Figure 1].

Correlation of red cell distribution width levels with biochemical and hematological parameters in gallbladder cancer patients

The various blood parameters included hemoglobin, total bilirubin, direct bilirubin, platelet count, erythrocyte sedimentation rate (ESR), total leukocyte counts (TLCs), and tumor markers (CEA, CA 19-9, and CA 125). RDW varied from 12.4 to 24.4 (mean, 16.82; SD 3.22) [Table 2]. RDW showed a positive correlation with total bilirubin, TLC, and ESR ($P < 0.002$), but not with platelet count ($P < 0.643$). RDW had a negative correlation with hemoglobin levels, but it was also statistically significant ($P < 0.003$). Furthermore, RDW showed a significant correlation with tumor markers such as CA 19-9 ($P < 0.003$), CEA ($P < 0.003$), and CA 125 ($P < 0.002$) [Table 3].

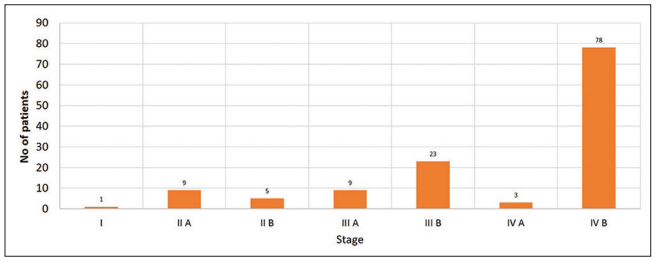

Figure 1: Number of participants in each stage

Table 1: Profile of study participants (*n*=128)

Characteristics	Count	Column, *n* (%)
Sex		
Male	23	18.0
Female	105	82.0
Jaundice		
No	69	53.9
Yes	59	46.1
Pain		
No	8	6.2
Yes	120	93.8
Fever		
No	77	60.2
Yes	51	39.8
Loss of weight		
No	48	37.5
Yes	80	62.5
Loss of appetite		
No	41	32.0
Yes	87	68.0
Smoking		
No	111	86.7
Yes	17	13.3
Alcohol		
No	122	95.3
Yes	6	4.7
Family history of malignancy		
No	128	100.0
Yes	0	0.0
Drug		
No	128	100.0
Yes	0	0.0
DM		
No	119	93.0
Yes	9	7.0
HTN		
No	123	96.1
Yes	5	3.9

HTN=Hypertension, DM=Diabetes mellitus

Correlation of red cell distribution width with stage of gallbladder cancer

In Stage I (0%) and II (58%), RDW was in normal range but in Stage III (65%) and IV (79%), it was high. In Stage IVB, there were significantly more patients with high RDW (78%) than normal RDW (21.8%). However, the results were not statistically significant ($P < 0.073$).

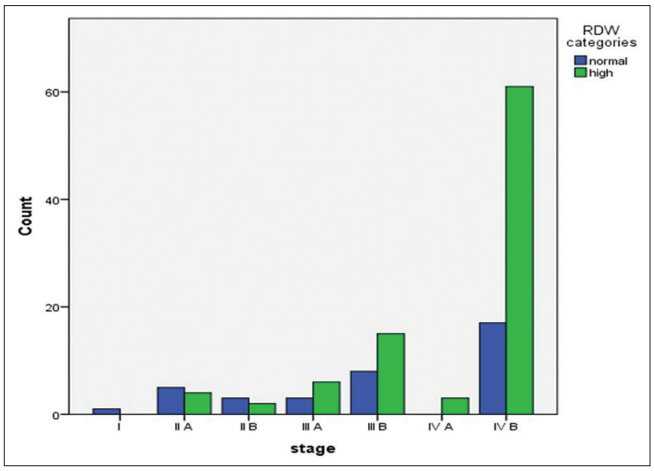

Figure 2: Correlation of red cell distribution width with stage of gallbladder cancer

Table 2: Blood parameters of study participants (*n*=128)

Parameter	Mean	SD	Median	Percentile 75
Bilirubin (total)	7.35	9.32	0.89	15.97
Direct bilirubin	3.87	5.34	0.20	7.57
Hb	10.89	1.88	11.35	12.00
TLC	10,839.4	4041.1	10,300.0	12,200.0
RDW	16.82	3.22	16.25	18.50
ESR	22.0	17.4	15.0	28.5
Platelet	3.13	0.96	3.09	3.80
CA 19-9	2875.21	6309.78	150.50	1169.50
CEA	37.50	93.18	5.21	24.00
CA 125	198.75	344.58	76.40	258.00

SD=Standard deviation, Hb=Hemoglobin, TLC=Total leukocyte count, RDW=Red cell distribution width, ESR=Erythrocyte sedimentation rate, CEA=Carcinoembryonic antigen, CA 19-9= Carbohydrate antigen 19-9, CA 125=Cancer antigen 125

Table 3: Correlation of red cell distribution width with other biochemical and hematological parameters (*n*=128)

Parameter	Correlation coefficient	Significant (two-tailed)
Bilirubin (total)	0.495**	0.001
Direct bilirubin	0.516**	0.002
Hb	−0.627**	0.003
TLC	0.394**	0.001
ESR	0.354**	0.002
Platelet	0.041	0.643
CA 19-9	0.260**	0.003
CEA	0.389**	0.003
CA-125	0.318**	0.002

Hb=Hemoglobin, TLC=Total leukocyte count, ESR=Erythrocyte sedimentation rate, CEA=Carcinoembryonic antigen, **= There was also a positive correlation of RDW with hematological parameters such as hyperbilirubinemia, TLC, and ESR, CA 19-9= Carbohydrate antigen 19-9, CA 125=Cancer antigen 125

In stage IV high RDW predicted more tumour burden [Figure 2].

Discussion

GBC is one of the most malignant tumors in biliary system, with a poor overall survival rate and high degree of malignancy. Patients with GBC are often asymptomatic and symptoms are usually nonspecific. Diagnosis is based on radiological investigations and tumor markers. Laboratory findings lack specificity and are not diagnostic of GBC. In advanced cases, obstruction may cause increased alkaline phosphatase and bilirubin levels. Tumor markers alone or in combination with some extent give an idea of tumor burden in GBC. An ultrasound is a usual initial diagnostic study whenever there is suspicion of gallbladder or biliary tract disease. Findings in ultrasonography gallbladder include thickening of the wall, luminal mass, calcification, or a mass lesion. Abdominal contrast-enhanced CT scans or magnetic resonance imaging can identify intraluminal polyps, gallbladder wall thickening, mass lesions, hepatic involvement, and nodal or other distant spread. In the present study, we have utilized RDW for correlation with tumor markers in carcinoma gallbladder and as a predictor of stage. We demonstrated higher levels of RDW with advanced stages of GBC. However, the results were not statistically significant, but predictive of higher stages with increasing RDW. Furthermore, a positive correlation was seen with serum tumor markers such as CEA, CA 19-9, and CA 125. Therefore, RDWs increasing values with tumor markers may indirectly predict high tumor burden at the first instance, because RDW has been done routinely in initial blood investigations during the diagnostic workup of GBC. There was also a positive correlation with hematological parameters such as hyperbilirubinemia, TLC, and ESR. Reason for this may be underlying inflammatory process. Wang *et al*.'s study revealed a positive association between clinical RCC stage and the levels of RDW.[12] Beyazit *et al*.[11] indicated that elevated RDW could be a useful biomarker to discriminate benign from malignant causes of biliary obstruction, with a sensitivity of 72% and specificity of 69%, using 14.8% as a cutoff value for RDW. RDW is one of the laboratory parameters that is routinely reported in complete blood count test. John *et al.*[13] have predicted the role of RDW in differentiating benign from malignant gallbladder lesions, suggesting raised RDW in GBC. Recent studies have reported that RDW might not only be a prognostic marker[14,15] but also be considered as a potential diagnostic marker in many cancers.[16] The exact mechanisms of correlation between higher values of RDW with cancer are somewhat unclear. One very likely mechanism is inflammation. It has been recognized that cancer progression depends on a complex interaction of the tumor and host inflammatory response.[16] Second, tumor growth can lead to malnutrition, which may cause changes in erythropoiesis. RDW is always available in routine blood tests and does not increase the cost of diagnostic tool; this particular point stands for a major benefit concerning its easy and cost-effective application as a surrogate marker in predictive of disease burden of GBC. Our study had certain limitations such as small sample size, so the results were positive but might not have been able to predict statistical significance.

Conclusion

In present study RDW was utilized for correlation with tumor markers and as a predictor of stage in carcinoma gallbladder. Higher levels of RDW correlated with advanced stages of GBC. Overall, the study suggested that RDW may be utilized as a surrogate biomarker to predict tumor burden and disease in patients with GBC

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Nil.

Conflicts of interest

There are no conflicts of interest.

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