

The role of red cell distribution width as a noninvasive index for predicting liver cell failure and portal hypertension in cirrhotic patients

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The liver distortion that occurs in cirrhosis results in increased resistance to portal blood flow and hence in portal hypertension which is one of the most common and serious complications of liver cirrhosis. Red cell distribution width (RDW) is routinely performed as part of a complete blood cell counts. Elevated RDW values were also shown to be associated with increased risk of mortality in the general population. However, to our knowledge, the role of RDW values predicting LCF and portal hypertension in LC has not been well-defined. The present study was designed to investigate the role of RDW as a noninvasive predicting index for LCF and portal hypertension in cirrhotic patient which will improve the diagnostic efficiency and provide useful information with other serum markers for the detection of LCF in LC. We found significantly good correlation between Child–Pugh and RDW values which can ultimately be used to predict the survival of patients with LC. There was also good correlation between RDW and those receiving β -blockers, so it may be used as an indicator for patient compliance, but there was no significant correlation with the grade of encephalopathy and portal hypertension.

Keywords:

complete blood count (CBC), international normalization ratio (INR), liver cirrhosis (LC), liver cell failure (LCF), liver function test (LFT), model for end stage liver disease (MELD), prothrombin time (PT), portal vein (PV), red blood corpuscles (RBCs), red blood cell distribution width (RDW)

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Introduction

Cirrhosis is an increasing cause of morbidity and mortality in developing countries, it being the 14th most common cause of death worldwide. It results in 1.03 million deaths per year worldwide [1]. Liver biopsy was used in the diagnosis of liver cirrhosis (LC), but the nature of liver biopsy such as invasiveness, cost, poor compliance, and contraindications restricted the widespread utilization particularly in the follow-up [2]. One of the most common and serious complications of LC is portal hypertension. Portal hypertension is a detrimental complication resulting from the obstruction of portal blood flow, such as cirrhosis or portal vein (PV) thrombosis [3,4]. In LC, increased intrahepatic vascular resistance to the portal flow elevates portal pressure and leads to portal hypertension. Once portal hypertension develops, it influences extrahepatic vascular beds in the splanchnic and systemic circulations, causing collateral vessel formation and arterial vasodilation. This helps to increase the blood flow into the PV. Consequently, esophageal varices or ascites develops.

Red cell distribution width (RDW) is an automated measure of the heterogeneity of red blood cell (RBC)

sizes (e.g. anisocytosis) and routinely performed as part of a complete blood cell counts [5–7]. RDW is used in the differential diagnosis of anemia [8]. Recently, a series of studies have demonstrated that RDW can serve as a novel, independent predictor of prognosis in patients with cardiovascular diseases (e.g. heart failure [9–11], stable coronary diseases [12], acute myocardial infarction [13], strokes [14], and pulmonary hypertension [15]). Elevated RDW values were also shown to be associated with increased risk of mortality in the general population [16–18]. However, to our knowledge, the role of RDW values predicting liver cell failure (LCF) and portal hypertension in LC has not been well defined. The present study was designed to investigate the role of RDW as a noninvasive index for predicting LCF and portal hypertension in cirrhotic patients which will improve the diagnostic efficiency.

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Patients and methods

A total of 147 patients were enrolled in the study. Of them, 108 were men and 39 were women diagnosed as LC in Assiut University Hospital and El-Rajhi Hospital. LC was diagnosed based on the history, physical examination, biochemical (liver function test, coagulation profile), and ultrasound (US) findings of cirrhosis.

Inclusion criteria

The patients were diagnosed to be cirrhotic based on history (previously diagnosed to be cirrhotic, presence of esophageal varices diagnosed with previous upper endoscopy, history of previous hepatic encephalopathy), physical examination (ascites, lower limb edema, jaundice, etc.), hypoalbuminemia, prolonged prothrombin time and decrease in prothrombin concentration, serological testing for HBsAg and HCVAb and cirrhosis findings in abdominal US. Complete blood count including RDW was done for all of them. Medical history was taken from all of them especially receiving β -blocker or not.

Exclusion criteria

Evidence of iron deficiency anemia and patients suffering from hematemesis for less than 1 month.

Data collection

All patients were subjected to complete blood count including RDW, liver function test, prothrombin time and concentration, international normalized ratio (INR) and abdominal US. The PV diameter was measured using US and the patients were classified according to whether they had PV dilatation and not. PV diameter was used as an indicator for portal hypertension [19]. They were divided into three groups according to Child's score (A, B, C) which is used as an indicator for liver cell function. Also they were classified according to whether they were receiving β -blockers or not.

Statistical analysis

All the data analysis was performed using performed using SPSS version software (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean value \pm SD, and categorical data were reported as percentages. Any value of *P* less than 0.05 was considered statistically significant.

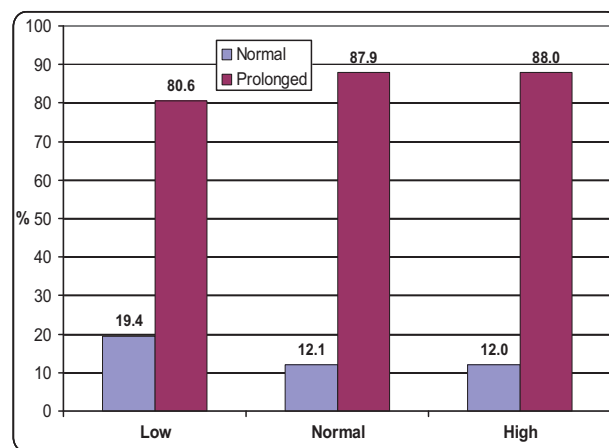
Results

A total of 147 patients were enrolled in the study. Of them, 108 were men and 39 were women. Regarding age, 58 patients were between 50 and 60 years; 53

patients were 60–70 years; 13 patients were between 40 and 50 years; 10 patients were between 70 and 80 years. Five patients were between 80 and 90 years. Four patients were between 30 and 40 years. Another four patients were between 10 and 20 years; 31 of them had low RDW, 25 high, and 91 had normal RDW with mean \pm SD (range): 13.19 \pm 1.82 (9.8–19.4).

Prothrombin time (PT) was prolonged in 127 patients and was normal in 20 patients with mean \pm SD (range): 18.63 \pm 4.84 (11.7–45.8). INR increased in 122 patients and was normal in 25 patients with mean \pm SD (range) of 1.55 \pm 0.40 (0.99–3.92). Total bilirubin (TB) increased in 122 patients and was normal in 25 patients with mean \pm SD of 101.51 \pm 123.29 and median (range) of 50.7 (2.1–712.4). A total of 135 patients had hypoalbuminemia, and 12 patients had normal albumin level with mean \pm SD (range) of 25.26 \pm 6.56 (13.9–45.2). Eighteen patients had mild ascites, 41 patients had moderate, and 35 patients had marked ascites, and 53 patients had no ascites. The PV was dilated in 39 patients and not dilated in 64 patients; 23

Figure 1



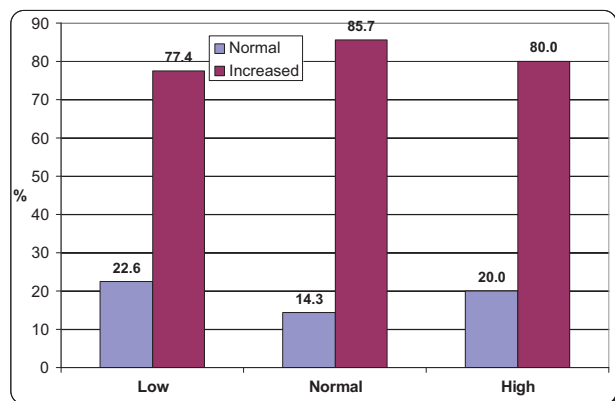
Prothrombin time.

Table 1 Correlation of red cell distribution width with coagulation profile, liver function, and Child's score

	RDW	
	r Value	P value
PT	0.200	0.015*
INR	0.189	0.022*
TB	0.210	0.011*
ALB	-0.173	0.036*
Child's score	0.221	0.007*

ALB, albumin; INR, international normalized ratio; PT, prothrombin time; PV, portal vein; RDW, red cell distribution width; TB, total bilirubin.

Figure 2



International normalized ratio.

patients had grade I, 15 patients had grade II, 11 patients had grade III, and eight patients had grade IV hepatic encephalopathy, but 90 patients were not suffering from encephalopathy.

Seven patients were receiving β -blockers, but 140 were not. Patients were classified according to Child–Pugh score. Eleven patients were of Child A; 56 were of Child B; and 80 were of Child C with mean \pm SD (range) of 9.74 \pm 2.07 (5.0–14.0). RDW was low in 19.4% of patients with normal PT; it was normal in 12.1%; and was high in 12% of them, but was low in 80.6% of patients with prolonged PT. RDW was normal in 87.9% and high in 88% of them (Fig. 1). There were significant correlation between RDW and the prolongation of PT ($P=0.015$) (Table 1). RDW was low in 22.6% who had normal INR, normal in 14.4% and high in 20% of them, but was low in 77.4% of patients with increased INR, normal in 85.7%, and high in 80% of them (Fig. 2). There were significant correlation between RDW and INR ($P=0.022$) (Table 1).

RDW was low in 25.8% of patients with normal TB level, normal in 17.6%, and high in 4% of them, but was low in 74.2% of patients who had increased TB level, normal in 82.4%, and high in 96% of them (Fig. 3). There were significant correlation between RDW and TB ($P=0.011$) (Table 1). RDW was low in 77.4% of patients with hypoalbuminemia, normal in 96.7%, and high in 92% of them. In patients with normal albumin level, 22.6% had low RDW, 3.3% had normal, and 8% had high RDW (Fig. 4). There were significant correlation between RDW and albumin level ($P=0.036$) (Table 1).

RDW was low in 48.4% in patients who had no ascites, normal in 35.2%, and high in 24%. In

patients who had mild ascites, 12.9% had low, 11% had normal, and 16% had high RDW. In cases with moderate ascites, 22.6% had low, 29.7% had normal, and 28% had high RDW. In cases with marked ascites, 16.1% had low, 22% had normal, but 32% had high RDW, so there were significant correlation between RDW and degree of ascites ($P=0.590$) (Fig. 5).

Ascites

RDW was low in 26.1% of patients with PV dilatation, normal in 44.3% and high in 31.6%. But in patients who did not have PV dilatation, 73.9% had low, 55.7% had normal and 68.4% had high RDW, so there were no significant correlation between RDW and PV dilatation ($P=0.255$) (Fig. 6).

RDW was low in 77.4% in patients who had no hepatic encephalopathy, normal in 57.1%, and high in 56%. In patients with grade I encephalopathy, 12.9% had low, 16.5% had normal, and 16% had high RDW. In patients with grade II encephalopathy, 3.2% had low, 13.2% had normal, and 8% had high RDW. In patients with grade III encephalopathy, 6.5% had low, 5.5% had normal, and 16% had high RDW. In patients with grade IV encephalopathy, 0% had low, 7.7% had normal, and 4% had high RDW, so there were no significant correlation between RDW and the degree of hepatic encephalopathy, but there were significant correlation between low RDW and patients with no encephalopathy ($P=0.276$) (Fig. 7).

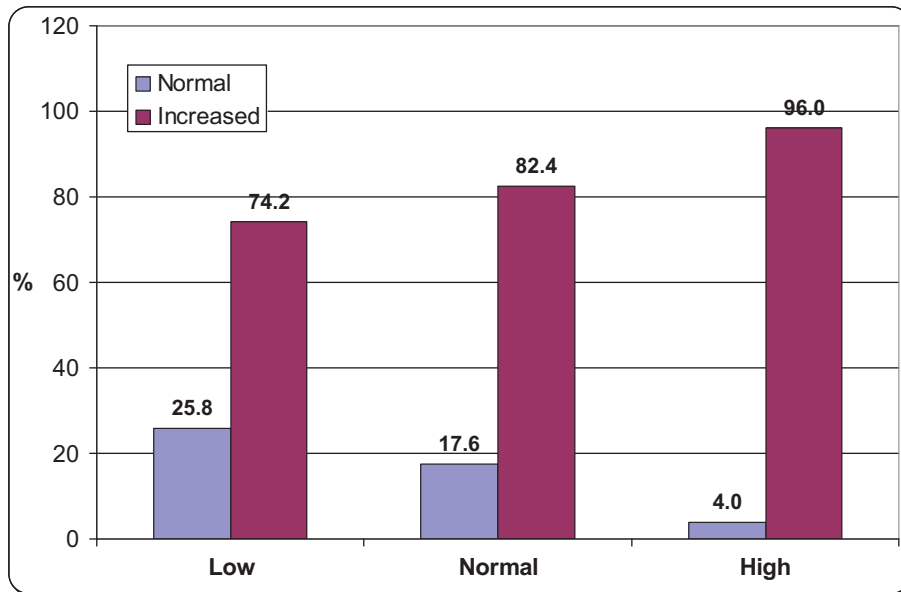
RDW was low in 3.2% of patients who was receiving β -blockers, normal in 6.6%, and high in 0%. But was low in 96.8%, normal in 93.4%, and high in 100% of patients who did not receive β -blockers, so there were significant correlation between RDW and patients who receive β -blockers ($P=0.353$) (Fig. 8).

RDW was low in 19.4% of patients with Child A, normal in 4.4% and high in 4%. In Child B, 38.7% had low, 41.8% had normal, and 24% had high RDW. In Child C, 41.9% had low, 53.8% had normal, and 72% had high RDW (Fig. 9). There were significant correlation between RDW and the grade of Child's score ($P=0.007$) (Table 1).

Discussion

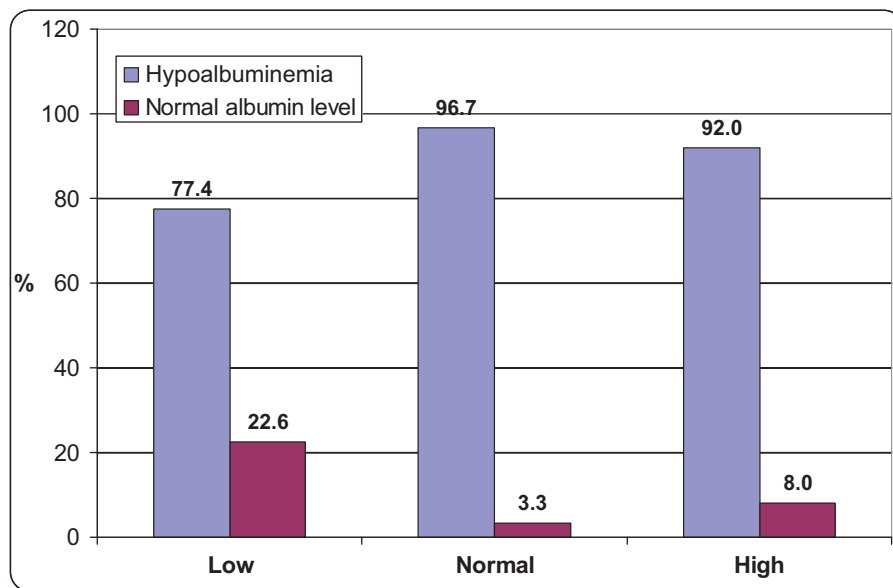
In the current study we found the mean age was between 40 and 70 and RDW tends to be normal in 61% of patients. About 36% had no ascites and 61% had no encephalopathy that may be due to good

Figure 3



Total bilirubin.

Figure 4

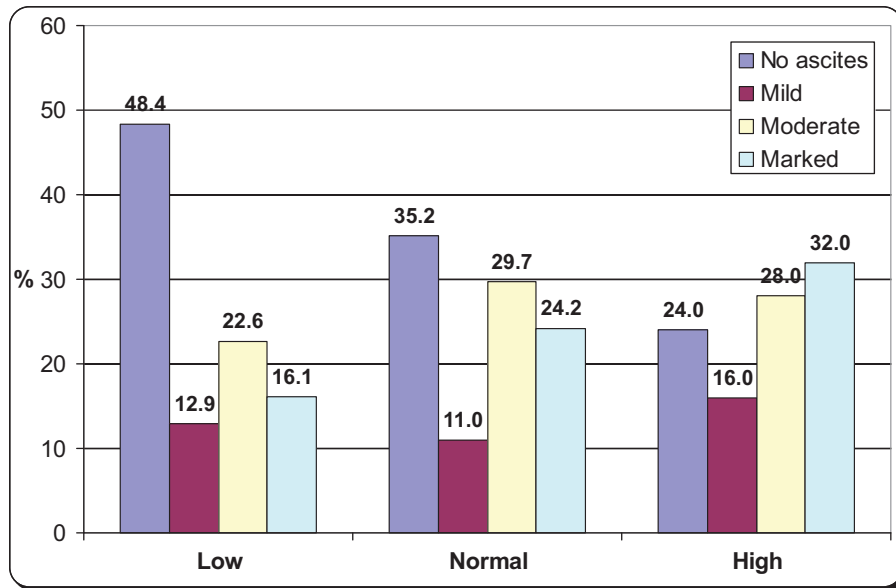


Albumin.

compliance for medical treatment and regular follow-up, but about 95% did not receive β -blockers, which was missed in most of the prescriptions. We found that RDW values in most of the cirrhotic patients were positively correlated with PT, INR, TB, hypoalbuminemia, and amount of ascites. RDW reflects the variability in circulating RBC size. It is based on the width of the RBC volume distribution curve, with larger values indicating greater variability [20]. The liver is the largest organ in the body and is responsible for filtering harmful chemical substances; accumulation of toxins may affect the size of RBCs and

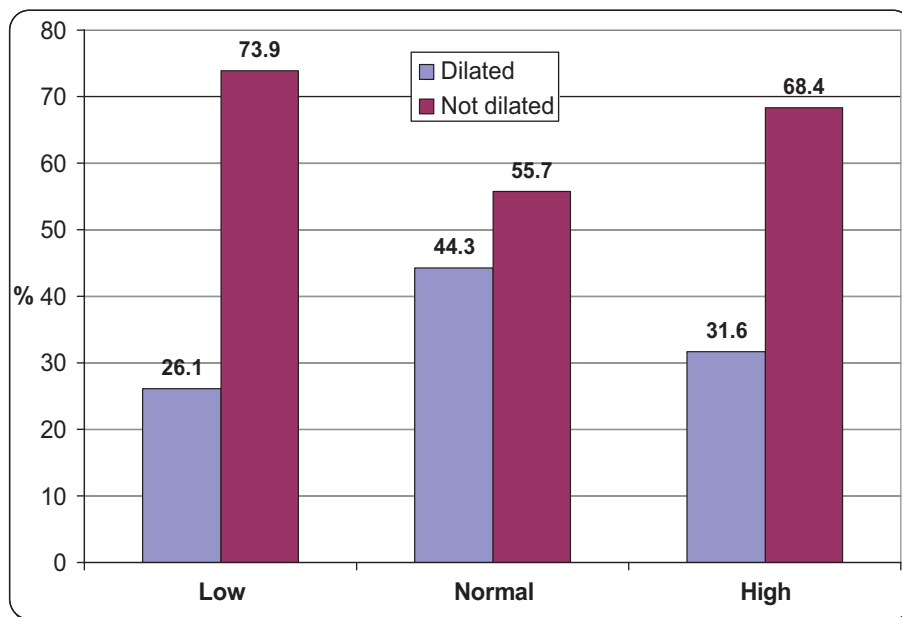
therefore the RDW values. Thus, we speculate that this is an important factor that influences disease progression, and may present an important predictor index for LCF. Recently, several studies have investigated the association between RDW and the severity of chronic liver diseases including nonalcoholic fatty liver disease, alcoholic cirrhosis, and primary biliary cirrhosis [21–26]. However, Milic *et al.* [26] found that a statistically significant increase in RDW relevant to the disease severity was not observed in neither in groups of patients with alcoholic cirrhosis nor with nonalcoholic cirrhosis.

Figure 5



Ascites.

Figure 6

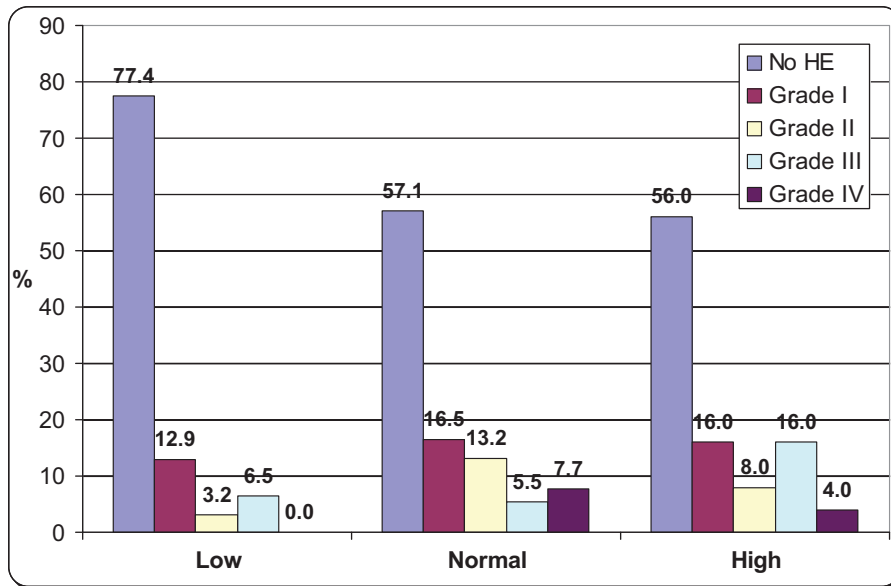


Portal vein.

Lou *et al.* [27] reported the association between RDW values and HBV-infected patients of different disease states and they found that the RDW values were increased in patients with hepatitis B significantly and associated with its severity. However, patients with HBV-related LC were not included in their study. In the present study, we investigated the association between RDW values and LCF and portal hypertension in LC despite its cause. A recent study has shown that RDW is correlated with hepatocellular carcinoma [26]. Liver fibrosis is

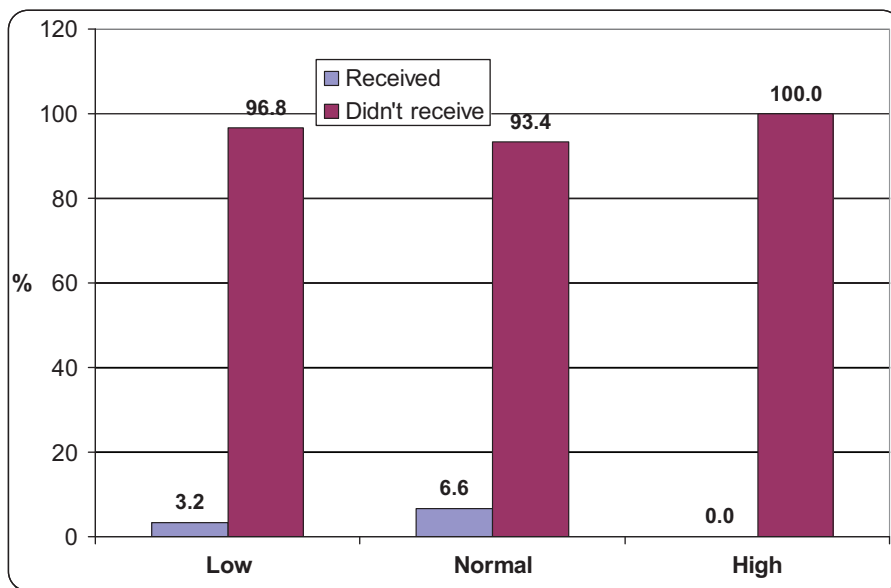
characterized by a continuous wound-healing response and chronic inflammation. Recently, in a large unselected cohort of patients, RDW showed a strong and graded association with inflammatory markers, which was independent of ferritin, age, sex, and other hematological variables [28]. Inflammation might contribute to increased RDW values not only by impairing iron metabolism but also by inhibiting the production of response to erythropoietin or by shortening RBC survival [29,30]. A number of studies have shown that proinflammatory cytokines

Figure 7



Hepatic encephalopathy.

Figure 8



Receiving β -blocker.

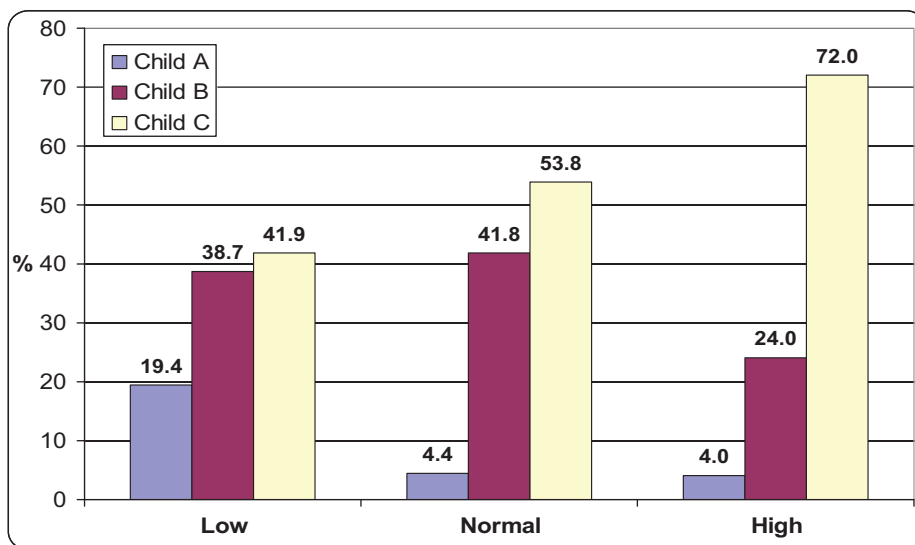
suppress erythropoietin gene expression, inhibit proliferation of erythroid progenitor cells, downregulate erythropoietin receptor expression, and reduce erythrocyte life span [31].

During the inflammation response, many kinds of inflammatory cytokines may suppress erythrocyte maturation and allow larger, newer reticulocytes to enter the circulation, thus resulting in increased RDW values [32,33]. Red cell distribution is typically elevated in conditions of increased red cell destruction and bone marrow depression [34,35].

Anemia is a common complication in patients with advanced liver diseases [36,37]. When portal hypertension occurs in patients with chronic liver diseases, the spleen frequently enlarges and thus reduces the numbers of RBCs in the blood [38,39]. These may be another mechanism that causes increased RDW values in patients with LC.

The study also indicated an increasing correlation of RDW values with worsening of Child–Pugh score. Thus, the RDW values may be associated with the survival of patients suffering from cirrhosis. The

Figure 9



Childs score.

Child–Pugh score was originally developed as an indicator of perioperative mortality in patients with LC and is most widely used to classify liver impairment and predict the survival of patients suffering from cirrhosis [24]. The study indicated an increasing correlation of RDW values with worsening of Child–Pugh score; hence mortality in patients with LC. Hu and colleagues observed that RDW levels are positively related to Child–Pugh and model for end-stage liver disease scores among patients with HBV-related LC [21,24]. Also we found that RDW is significantly low in patients with no hepatic encephalopathy, but no significant correlation with the grade of encephalopathy which merits further investigation. Increased resistance to portal blood flow due to alteration of the hepatic architecture leads to dilatation of PV, splenomegaly, and formation of esophageal and gastric varices, variceal hemorrhage, ascites, hypersplenism, encephalopathy, etc. In cirrhosis, increased intrahepatic vascular resistance is thought to be located mainly in the hepatic sinusoids. Recent studies have demonstrated that in addition to the increased resistance caused by the morphologic change of chronic liver diseases, a dynamic component of increased resistance (resulting from the active contraction of vascular smooth muscle cells, myofibroblasts, and hepatic stellate cells) is also present. Portal hypertension leads to the dilatation of PV, splenomegaly, and formation of portal systemic collaterals at different sites. In our study patients with LCF had no significant RDW values with PV dilatation. It is still more or less normal, but was significantly low in cirrhotic patients who did not have PV dilatation which must be investigated in a

wider study. Also we found that RDW is highly significantly high in patients who had not received β -blockers; so it may be used as an indicator for patient compliance. β -Blockers, which include propranolol, nadolol, and timolol, are used to provide primary and secondary prophylaxis. β -Blockers lower the cardiac output (via blockade of β_1 adrenoreceptors) and cause splanchnic vasoconstriction (via blockade of vasodilatory adrenoreceptors of the splanchnic circulation), reducing portal and collateral blood flow. Nonselective β -adrenergic blockers have been shown to reduce the risk of first variceal bleeding (from 24 to 15% after a median follow-up of 2 years) and mortality (from 27 to 23%) [40], which show the importance of using RDW as an indicator for patient compliance. Some limitations of this study warrant consideration. First, we did not investigate the causes of elevated RDW values, such as folate and vitamin B12 deficiency, which could confound the association between RDW values and adverse outcome. Second, this was a single-center study. Therefore, our findings need to be confirmed in multicenter and prospectively designed studies. RDW values were not dynamically observed, and thus whether RDW values elevated stepwise when patient's condition progressively deteriorated or whether it improved when the patient received antiviral treatment. Also the prognostic value of RDW in patients with different causes of LC merits further investigation. Despite these limitations, we found significantly elevated RDW values in patients with LCF. RDW is an independent predictor of noninvasive index of LCF in LC which was the aim of our study. Because RDW values are easily attainable

at no additional cost to the routine complete blood cell counts and is highly reproducible, it may serve as an important biomarker. A good correlation between worsening of Child–Pugh and RDW values was also found. A strong correlation between high RDW and patient did not receive β -blocker, so it may be used as an indicator for compliance. There was no significant correlation between RDW and PV diameter and so portal hypertension. Also there was no significant correlation between RDW and grade of hepatic encephalopathy.

Conclusion and recommendation

In conclusion, our study shows that RDW could provide useful information with other serum markers for the detection of LCF in LC. We found significantly good correlation between Child–Pugh and RDW values which can ultimately be used to predict the survival of patients with LC. There was also good correlation between RDW and those receiving β -blockers, so it may be used as an indicator for patient compliance, but there was no significant correlation with the grade of encephalopathy and portal hypertension.

Our study should be further assessed by prospective studies with larger patient populations involving multiple centers. Investigating the causes of elevated RDW values such as folate and vitamin B12 deficiency is recommended. The role of RDW if the condition of the patient is progressively deteriorated or even if improved when the patient received antiviral treatment should be also further evaluated in another study. Also the prognostic value of RDW in patients with different causes of LC merits further evaluation. Searching for another biochemical index for predicting portal hypertension is recommended.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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