

May red cell distribution width (RDW)/mean platelet volume (MPV) ratio be a diagnostic parameter in extrahepatic cholestasis due to biliary stones?

RDW / MPV ratio and extrahepatic cholestasis

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Abstract

Aim: Establishing the diagnosis of extrahepatic cholestasis is highly challenging in emergency department conditions. It is necessary to find a fast and inexpensive marker that will be diagnostic at the first stage. Therefore, in this study, we aimed to investigate the diagnostic values of RDW/MPV ratio and PMI values in EHC.

Material and Methods: The diagnosis of extrahepatic cholestasis was established in all patients using biochemical tests, abdominal ultrasound and MRCP. Patients' WBC, Neutrophils (Neu), Lymphocytes (Lym), Monocytes (Mon), Red Blood Cell (RBC), Mean Corpuscular Volume (MCV), RDW, Platelet (PLT) and MPV values were evaluated. RDW/MPV, Lym/Mon, Neu/Mon and PLTxMPV (PMI) values were calculated.

Results: One hundred eighty patients who presented to our emergency department with abdominal pain were included as the patient group, and 106 patients who applied to our emergency department with dyspeptic complaints were included as the control group. Lymphocyte and monocyte counts were statistically significant between the two groups ($p=0.02$, $p=0.05$; respectively). RDW/MPV ratio was 1.54 ± 0.33 in the patient group and 1.34 ± 0.25 in the control group, and it was statistically significantly higher in the patient group ($p=0.02$). Serum ALT, AST, total and direct bilirubin and CRP values were significantly higher in the patient group ($p<0.001$). The mean hospitalization duration was 13.7 ± 6.3 days.

Discussion: We believe that RDW/MPV parameter to be studied in patients presenting to emergency departments with abdominal pain and jaundice can be helpful for the diagnosis of extrahepatic cholestasis due to biliary tract stones.

Keywords

Extrahepatic cholestasis; Biliary stones; Platelet mass; Red cells; Platelet volume

DOI: 10.4328/ACAM.20434 Received: 2020-12-08 Accepted: 2021-01-15 Published Online: 2021-01-26 Printed: 2021-07-01 Ann Clin Anal Med 2021;12(7):726-730

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Introduction

Cholestasis is defined as the impairment of bile flow from hepatocytes into canaliculus and duodenum by mechanical obstruction, drugs, infection, autoimmune, metabolic, or genetic disorders [1,2]. The secretion of bile normally depends on the function of a number of membrane transport systems in hepatocytes and bile-duct epithelial cells (cholangiocytes), and on the structural and functional integrity of the bile-secretory apparatus [2,3]. Cholestasis is classified into two groups according to the localization of the obstruction as intrahepatic and extrahepatic, and it results from hepatocellular disease (intrahepatic) or abnormalities of biliary duct (extrahepatic) [1,4]. Extrahepatic cholestasis (EHC) is defined as the inability of a normal amount of inflow to the bile due to lesions or obstacles at the levels of choledoch or main hepatic duct. The main reasons of EHC include common biliary tract (CBD) stones, cholangiocarcinoma, ampullary carcinoma, pancreatic diseases (pancreatic head carcinoma, pseudotumoral chronic pancreatitis, pancreatic head pseudocysts), congenital malformations (cysts, Caroli disease), duodenal diverticula, ascariasis and hemobilia [5]. The diagnosis of EHC is established with physical examination, and the biochemical imbalance is supported by clinical symptoms and signs. These symptoms and signs include jaundice in the sclerae and skin, abdominal pain, nausea, pale stool and dark orange urine. As the clinical picture of cholestasis progresses, several complications may occur, such as cholangitis, sepsis, multiple organ failure, coagulopathy and renal failure, as well as cirrhosis may also be developed due to prolonged cholestasis. Cholestatic damage of the liver leads to hepatocellular necrosis and apoptosis, proliferation and stellate cell activation occur in the epithelial cells of the biliary tract, resulting in liver fibrosis [7,8].

Diagnosis of EHC is established through laboratory tests, hepatobiliary ultrasonography (US), computed tomography (CT), magnetic resonance cholangiography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) [6].

In the emergency department, complete blood count, total bilirubin, direct bilirubin, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) that are helpful in showing liver damage, are primarily used for the diagnosis of cholestasis [9]. As far as is known, complete blood count parameters including hemoglobin, hematocrit, white blood cells (WBC) and platelets (PLT) are stated to be usually normal in cholestasis except for cholangitis attack [10].

In an emergency department, establishing the diagnosis of extrahepatic cholestasis is highly challenging. It is necessary to find a fast and inexpensive marker that will be diagnostic at the first stage. Within this context, complete blood count parameters have not been adequately reviewed in the literature. On the other hand, recently there have been many studies showing that levels of some parameters in complete blood change in different illness states in addition to biological functions [11-13].

It has been demonstrated that red cell distribution width (RDW), which is among complete blood count parameters and shows the change in red blood volume, may be a prognostic marker reflecting inflammatory status. The RDW level has been

found to be associated with morbidity and mortality in the elderly [14,15]. RDW has been found to be significantly lower in patients with pregnancy-induced intrahepatic cholestasis that resembles EHC, but no correlation has been found between RDW and disease severity [11]. Platelets have been shown to be involved in the inflammation process besides their known hemostatic functions [16]. The mean platelet volume (MPV) is the best parameter showing platelet size and studies have reported changes in MPV value in diseases that progress with chronic inflammation including rheumatoid arthritis and ulcerative colitis [17]. The platelet mass index (PMI), which is formulated with "platelet count multiplied by MPV", is a good marker of PLT functions and provides important information about the plaque-forming capacity. In addition, some studies have demonstrated that PMI is a better inflammatory marker than MPV [18,19].

Fewer tests that could be indicators of EHC will both save time and reduce costs. Therefore, the objective of this study was to investigate diagnostic benefit of RDW, MPV, PMI, Lymphocytes/Monocytes (Lym/Mon) ratio and Neutrophils/Lymphocyte ratio (Neu/Lym=NLR), which are studied in almost all patients presenting to emergency departments, in patients with biliary tract stones induced extrahepatic cholestasis.

Material and Methods

Study Design

This study was conducted in the emergency and/or general surgery services of the Health Sciences University Mehmet Akif Inan Health Application and Research Center between January 2017 and June 2020 after receiving the approval from the Ethics committee. Patients with extreme obesity, hematologic disorders, those who were receiving chemotherapy, aspirin or drugs affecting platelet function, pregnant women, patients with a history of previous surgery for biliary tracts, those with chronic hepatic disease, advanced chronic obstructive pulmonary disease due to prominent pulmonary emphysema and patients with abnormal kidney function were excluded from the study. The patient group consisted of patients aged over 18 years who presented to the emergency department with complaints such as abdominal pain, nausea and jaundice, and who were diagnosed with extrahepatic cholestasis on physical examination, laboratory and imaging investigations and ERCP following hospitalization. The control group included patients aged over 18 years who presented to the emergency department with dyspeptic complaints, did not require hospitalization after investigations and treatments administered and who had no any diagnosed chronic disease/a history of receiving drugs. Complete blood count, biochemical parameters and imaging data studied at the time of presentation were retrospectively evaluated in both groups.

In order to evaluate the clinical status of patients, symptoms of obstructive cholestasis including jaundice, itching, the color of urine and stool were evaluated. Patients' demographic data such as gender, age and complete blood count including WBC, Neu, Lym, Mon, red blood cell (RBC), Mean corpuscular volume (MCV), RDW, PLT, MPV were analyzed with an automated hematology analyzer (Sysmex Corporation Automated Analyzer XN-10, Chuo-ku, Kobe, Japan). RDW/MPV, Lym/Mon, Neu/Mon

and PMI were calculated. C-reactive protein (CRP), ALT, AST, total and direct bilirubin, albumin, GGT, amylase, lipase and electrolytes were analyzed and recorded. The diagnosis of extrahepatic cholestasis was established in all patients using biochemical tests, abdominal ultrasound, MRCP. The diagnosis was confirmed with biochemical and imaging investigations in patients with extrahepatic cholestasis. Diagnostic and therapeutic ERCP was performed in all patients.

Ethical Considerations

All patients included in the study were informed in detail about the objectives of the study and gave verbal and written consent. Before the beginning of the study, the necessary ethics approval was received from the local ethics committee of our hospital on 15.06.2020 (Decision number: HRU/20.11.01). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Statistical Analysis

Data obtained in this study were statistically analyzed using the SPSS version 22.0 (Statistical Package for Social Sciences. IBM Inc., Chicago, IL, USA) statistical package software. The normality of the data was analyzed with the Kolmogorov-Smirnov test. In a comparison of the variables between the groups, Student's t-test was used for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Numerical variables are expressed with mean±standard deviation, while categorical variables are expressed as frequency and percentage (%). $P < 0.05$ values were considered statistically significant.

Results

The study included 180 patients diagnosed with extrahepatic cholestasis and 106 controls who presented to our emergency and/or general surgery departments with dyspeptic complaints. Among the patients, 57 (31.7%) were male and 123 (68.3%) were female; whereas among the control subjects, 35 (33.1%) were male and 71 (66.9%) were female. The mean age was 57.8 ± 18.0 years in the patient group and 54.1 ± 14.2 years in the control group. There was no statistically significant difference between the patient and control groups in terms of gender and age ($p > 0.05$).

When blood analysis was compared between the patient and control group, the mean WBC value was found as 10.142 ± 5.1 in the patient group and 9.7 ± 3.1 in the control group ($p = 0.47$). Neutrophil count was 7.7 ± 5.0 in the patient group and 5.5 ± 2.7 in the control group ($p = 0.37$). Lymphocyte count was 1.7 ± 0.71 in the patient group and 2.7 ± 1.13 in the control group ($p = 0.05$). Lymphocyte count was approximately statistically significant between the two groups. Monocyte count was 0.6 ± 0.3 in the patient group and 0.7 ± 0.22 in the control group. Monocyte count was statistically significantly lower in the patient group compared to the control group ($p = 0.02$). The mean RBC value was 4.60 ± 0.67 in the patient group and 4.90 ± 0.65 in the control group ($p = 0.06$). The mean MCV value was 87.0 ± 8.69 in the patient group and 82.70 ± 6.15 in the control group ($p = 0.65$). The mean RDW value was 13.12 ± 1.67 in the patient group and 13.32 ± 1.58 in the controls ($p = 0.12$). The mean PLT was 261.64 ± 99.27 in the patient group and 275.19 ± 71.34 in the control group ($p = 0.07$). The mean MPV value was 8.84 ± 1.84

in the patient and 10.13 ± 1.26 in the control group ($p = 0.14$). The RDW/MPV ratio was calculated as 1.54 ± 0.33 in the patient group and 1.34 ± 0.25 in the control group. The RDW/MPV ratio was statistically significantly higher in the patient group compared to the control group ($p = 0.02$). The Lym/Mon ratio was 3.82 ± 2.64 in the patient group and 4.24 ± 1.76 in the control group ($p = 0.20$). The Neu/Lym ratio was 6.81 ± 9.08 in the patient group and 2.73 ± 3.00 in the control group ($p = 0.68$). PLT×MPV, which reflects PMI, was 2261.40 ± 890.53 in the patient group and 2763.80 ± 723.64 in the control group ($p = 0.66$). Serum ALT, AST, total and direct bilirubin, and CRP values were significantly higher in the patient group ($p = 0.0$). The mean hospitalization duration was 13.7 ± 6.3 days. Laboratory findings of the Patient and Control Groups are given in Table 1.

Table 1. Laboratory findings of the patient and control groups

Parameter	Patients		Controls		p
	mean	± SD	mean	± SD	
WBC	10.14	5.06	9.07	3.09	0.47
Neutrophils	7.65	5.00	5.51	2.71	0.37
Lymphocytes	1.67	0.71	2.65	1.13	0.05
Monocytes	0.57	0.30	0.66	0.22	0.02
RBC	4.61	0.67	4.88	0.65	0.06
MCV	86.96	8.68	82.69	6.15	0.65
RDW	13.12	1.67	13.32	1.58	0.12
PLT	261.63	99.27	275.19	71.34	0.07
MPV	8.84	1.84	10.13	1.26	0.14
RDW/MPV	1.54	0.33	1.34	0.25	0.02
LYM/MON	3.82	2.64	4.24	1.76	0.20
NEUT/LYM	6.81	9.08	2.73	3.00	0.68
PLT/MPV	2261.39	890.53	2763.76	723.64	0.66
ALT	198.64	176.33	16.26	6.72	<0.01
AST	177.04	204.97	18.79	6.30	<0.01
Total Bilirubin	3.88	4.00	0.38	0.19	<0.01
Direct Bilirubin	3.17	4.00	0.12	0.06	<0.01
Albumin	38.40	5.95	44.40	2.95	<0.01
GGT	466.82	444.00	20.07	15.00	<0.01
Calcium	9.03	0.74	9.37	0.50	<0.01
CRP	53.86	77.05	7.22	13.31	<0.01

WBC: white blood cells; RBC: red blood cells; MCV: mean corpuscular volume; RDW: red cells distribution width; PLT: platelets; MPV: mean platelet volume; ALT: alanine transaminase; AST: aspartate transferase GGT: gamma-glutamyl transferase; CRP: C-reactive protein.

Discussion

Obstructive biliary stones are the leading benign cause in the etiology of extrahepatic cholestasis (EHC) (80%). The incidence of EHC with both benign and malignant causes increases with age. In this study, all patients had EHC related to biliary stones, and the mean age of the patients was 57.8 ± 18.0 years, consistently with the literature [20]. The clinical condition of the patients is the first and most important parameter indicating the disease. The primary clinical symptoms of extrahepatic cholestasis are abdominal pain, jaundice of the skin and sclerae, dark urine, uncolored stool and itching. In adult extrahepatic (mechanical) obstruction, 40% of patients present with jaundice as the primary symptom [20]. In the current study, the patients were those who presented to the emergency department and the complaints of presentations were mostly mild-to-moderate

abdominal pain (55%) and vomiting (25%).

Elevation in AST, ALT, total and direct bilirubin and GGT is seen as a result of the damage in the liver due to cholestasis. AST and ALT usually increase by 2-4 times compared to normal values, while GGT increases by 2-4 times, and ALP by up to 10 times of the normal values [21]. When the level of total bilirubin exceeds 2.5 mg/L, icterus is clinically seen and secondary biliary cirrhosis begins to develop at the bilirubin levels higher than 2-6 mg/L [10,21]. In our study, the total bilirubin value in the patient group was 3.88. In a study by Trifan et al., the mean total bilirubin value varied between 2.8 and 14.1 mg/dL before therapeutic ERCP, while this value returned to normal in the majority of the patients after endoscopic therapy [22]. In our study, all patients were referred to the gastroenterology and general surgery departments and were treated with endoscopic retrograde cholangiopancreatography (ERCP) method or surgical intervention.

As expected, in our study, AST, ALT, GGT, ALP, total and direct bilirubin levels were significantly higher in the patient group compared to the control group ($p < 0.001$). However, these parameters may be related to the other diseases of the biliary duct, liver and pancreas. Therefore, the diagnosis of extrahepatic cholestasis can not be based only on clinical symptoms and signs. A marker indicating extrahepatic cholestasis has not yet been identified. There are various studies in the literature investigating complete blood count parameters in intrahepatic cholestasis, but we could find only one study examining complete blood count parameters in extrahepatic cholestasis [23]. Guducu et al. measured the levels of MPV and serum biliary acid as markers of fetal status in pregnant women with intrahepatic cholestasis, and could not find a correlation between MPV and any biochemical parameter [24]. Again, Yayla et al. studied WBC, MPV and Platelet/Lymphocyte ratio (PLR) as inflammatory markers in gestational intrahepatic cholestasis and found these parameters higher compared to the controls, while RDW was found to be significantly lower. In addition, they found that MPV was increased with disease severity [11]. Eroglu et al. found higher MPV values in the same patient group, while Neu/Lym ratio was also higher, and MPV predicted gestational intrahepatic cholestasis with 65% sensitivity and 59% specificity [25].

In order to evaluate extrahepatic cholestasis in a first-line health center with a complete blood count, Morsy et al. studied RDW, MPV, platelet distribution width (PDW), Platecrit (PCT), Neu/Lym ratio and PLR between patients with extrahepatic cholestasis of different etiologies, and could not find significant difference between the groups except for MPV and PDW that were significantly higher in the distal malignant group. The authors concluded that among complete blood count parameters RDW, MPV, PDW, PCT, Neu/Lym ratio and PLR were not helpful in understanding the etiology of extrahepatic cholestasis [23]. In our study, no significant differences were found between the patient and control groups in terms of WBC, neutrophils, RBC, MCV, RDW, PLT, MPV, Lym/Mon ratio, Neu/Lym ratio and PMI, suggesting that these complete blood count parameters can not be useful in the diagnosis of extrahepatic cholestasis. In addition, PMI that is a good marker of PLT function was not significantly different compared to the control group,

suggesting that platelet function of these patients might be not impaired during the first presentation and thus, there was no need for prophylactic antiplatelets. In our study, Lym, Mon and RDW/MPV values were significantly higher in the patient group compared to the control group. This result suggested that Lym and Mon functions might be more effective in the development of the clinical picture of cholestasis and associated formation of hepatic fibrosis.

The RDW/MPV parameter has never been studied in the literature so far, making us think that it may be useful for the diagnosis of EHC. However, since there is no study in the literature on this issue, we could not compare our results with other studies.

Study Limitations

This study has some limitations. First, the number of patients in the study was relatively small and the study was designed as a retrospective study. Secondly, the study was conducted in a single center. However, being the first study on this issue in the literature makes our strength aspect. We believe that our result will be guiding for future studies.

Conclusion

According to our results, we found that the RDW/MPV parameter was significantly higher in patients with extrahepatic cholestasis due to biliary stones. We consider that routine evaluation of this parameter in patients presenting to emergency departments with abdominal pain and jaundice can be helpful for the diagnosis of extrahepatic cholestasis due to biliary stones. This study is the first in the literature on this issue. However, our results should be supported by further multicenter studies containing a larger number of patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:

Eyup Sabri Seyhanli, Huseyin Avni Demir. May red cell distribution width (RDW)/ mean platelet volume (MPV) ratio be a diagnostic parameter in extrahepatic cholestasis due to biliary stones? *Ann Clin Anal Med* 2021;12(7):726-730