Int J Clin Exp Med 2017;10(7):10764-10772
www.ijcem.com /ISSN:1940-5901/IJCEM0020794

Original Article

Platelet count/spleen diameter ratio in the differentiation of alcoholic liver disease from alcoholic liver disease plus viral hepatitis (B, C or B + C) or viral hepatitis alone

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Received November 30, 2015; Accepted February 29, 2016; Epub July 15, 2017; Published July 30, 2017

Abstract: Aim: Alcoholic liver disease and viral hepatitis are treated differently, making differential diagnosis essential. We aimed to determine whether platelet/spleen ratios can be used for differential diagnosis. Methods: This retrospective study enrolled 180 patients diagnosed with alcoholic (n=56) or viral liver disease (n=68) or combined alcoholic and viral liver disease (n=56) between 2009 and 2012. Patients without liver biopsy or complete data were excluded. Patients' demographic and clinical data were collected, platelet/spleen ratios were determined. Data were compared between groups and associations between platelet/spleen ratios and alcoholic or viral liver disease were determined by univariate and ROC analysis. Results: Platelet/spleen ratios and liver function parameters were significantly different between groups (all *P*-values <0.05). Univariate analysis of platelet/spleen ratios compared between different groups revealed significant differences in platelet/spleen ratios between alcohol vs. combined group and viral vs. combined group but not between alcohol vs. viral group. Optimal cut-offs of platelet/spleen ratio to differentiate alcoholic liver disease and viral liver disease from combined alcoholic and viral liver disease were 2306 and 1650, respectively. Conclusion: Platelet/spleen ratio can only be used to differentiate alcoholic or viral liver disease from coexisting alcoholic and viral liver disease in conjunction with confirmation of viral hepatitis.

Keywords: Alcoholic liver disease, differential diagnosis, platelet count/spleen diameter ratio, viral hepatitis

Introduction

Consumption of alcohol and viral hepatitis act synergistically to promote the development of chronic liver disease and its progression from fibrosis to cirrhosis and hepatocellular carcinoma (HCC) [1]. Alcoholic liver disease alone is responsible for the greatest percentage of deaths associated with alcoholism globally [2]. Hepatitis B virus (HBV) infection is also an important risk factor for developing the late complications of chronic liver disease, cirrhosis and HCC [3]. Taiwan, in particular, has a high prevalence of chronic HBV infection and alcoholic liver disease is also increasing [4, 5]. Therefore, early diagnosis of liver disease in Taiwan is becoming increasingly important to ensure early treatment of liver disease and avoidance of late complications.

Viral hepatitis is diagnosed easily via clinical laboratory tests for hepatitis B virus (HBV), hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), anti-HBe antibodies (anti-HBeAg) and hepatitis C virus (HCV). The diagnosis of alcohol-related liver abnormalities is more difficult, and the available diagnostic methods do not readily distinguish alcoholic liver disease from viral liver disease only or a combination of alcoholic and viral liver disease. Liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and alpha fetoprotein (AFP) levels are diagnostic of liver function abnormalities but elevated levels are not definitive for alcoholic liver disease. Progression in all types of liver disease is evaluated by ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) examinations and upper endoscopy [6]. In patients with

chronic viral hepatitis, viral load (HBV DNA) is a marker of virus replication and predictive of progression to cirrhosis and HCC [3]; however, while alcohol consumption is a risk factor in the progression of viral hepatitis, it was not associated with virus replication in one study of patients with viral liver disease [7]. Liver biopsy is relied upon to accurately evaluate fibrosis in progressive liver disease but this invasive procedure is associated with risk of complications compared to less invasive tests such as liver elastography, which is used to determine the degree of fibrosis [8]. More fibrosis is found in alcoholic liver disease and its histopathologic characteristics differ from those in patients with HCV non-alcoholic hepatitis [9]. Nevertheless, no single test is able to differentiate alcoholic liver disease from viral liver disease or confirm coexisting alcoholic and viral liver disease. The challenge is to find a diagnostic method that is able to identify alcoholic liver disease at admission without relying on patient history to suggest alcoholism or invasive tests such as liver biopsy so that the appropriate treatment can be initiated as early as possible. Treatment regimens for alcohol-related and viral-related chronic liver disease are vastly different. Alcoholic liver disease is treated with alcohol abstinence or drugs to induce it, nutritional therapies and corticosteroids [10], while HBV and HCV viral hepatitis is treated with antiviral therapies, hepatoprotective drugs and sometimes immunosuppression [11, 12].

Upper abdominal ultrasound examination is usually performed for patients with biochemical results suggestive of liver abnormalities and it includes measuring spleen diameter to determine the platelet count/spleen diameter ratio. The platelet/spleen ratio is a non-invasive measure to evaluate risk of esophageal bleeding (varices) in patients with progressive liver disease (cirrhosis with portal hypertension) by linking thrombocytopenia with spleen size [13]. In chronic liver disease without portal hypertension, platelet counts may be diminished because of the shortened mean lifetime of platelets or the toxic effects of alcohol or viruses, and there may be no obvious splenomegaly without portal hypertension but the ratio may still indicate risk of progression. We hypothesized that the platelet/spleen ratio could be a marker of risk of progression in coexisting alcohol and viral liver disease in which alcohol has influenced disease progression and thus may even be able to differentiate alcoholic liver disease.

Considering that the prevalence of hepatitis B viral infection is especially high in Taiwan, the combination of viral liver disease and alcoholic liver disease increases morbidity as the disease phases progress and that differential diagnosis is exceptionally important to starting early and appropriate treatment, this study aimed to determine whether the platelet/spleen ratio is able to differentiate alcoholic liver disease from viral disease only and coexisting alcoholic and viral liver disease.

Methods

Study subjects and design

A convenience sample of 180 adult subjects diagnosed with abnormal liver function due to alcohol-related liver disease or viral hepatitis (positive HBsAg, HBV-DNA positive or anti-HCV positive and HCV RNA positive) or both alcoholic and viral liver disease at Cathay General Hospital/Fu-Jen Catholic University, Taipei, Northern Taiwan and E-DA Hospital/I-SHOU University, Kaohsiung, Southern Taiwan, between 2009 and 2012 were enrolled in this study. Patients with liver disease but without biopsy or without complete pathology data were excluded. Among the included patients, 56 had alcoholic liver disease (alcohol group), 68 had viral hepatitis (viral group), and 56 had alcoholic liver disease combined with viral hepatitis (combined group). Patients' demographic and clinical data were collected from medical records and were reviewed retrospectively.

Ethical considerations

All participants were assured that their anonymity would be protected and that each participant in the study would be identified only by a number. During their hospitalization, all patients provided signed informed consent that their data could be collected and evaluated in future study. The evaluations commenced after approval of the study protocol by the Institutional Review Board of Cathay General Hospital and E-DA Hospital.

Methods

In this retrospective study, subjects' alcohol consumption behavior was evaluated routinely

Table 1. Subjects' demographics and characteristics among groups

Variables	Alcohol (n=56)	Viral (n=68)	Combined (n=56)	*P*-value
Age, yrs	43.5 (37.3, 48.8)	43.0 (35.0, 50.0)	50.0 (39.0, 59.8)†,‡	0.001*
Sex				0.013*
Male	54 (96.4)	54 (79.4)†	51 (91.1)	
Female	2 (3.6)	14 (20.6)	5 (8.9)	
BMI, Kg/m^2	23.6 ± 3.7	24.9 ± 3.5	24.6 ± 3.7	0.861
Hb, g/dl	13.4 (10.5, 15.7)	14.7 (13.2, 15.3)	13.8 (12.2, 15)	0.045*
MCV, fL	98.9 (90.2, 105.8)	90.1 (88.1, 92)†	91.3 (87.7, 95.6)†	<.001*
WBC, uL	6595 (4950, 8600)	6100 (4972.5, 7255)	6055 (4942.5, 7552.5)	0.585
Platelet, *1000/uL	198.8 ± 87.1	179 ± 42.9	151.9 ± 60.9†	0.001*
Spleen size, cm	9 (8.1, 10.8)	9.4 (8.3, 10.6)	9.7 (8.9, 11.2)	0.202
Platelet/spleen ratio	1794.7 (1399.7, 2927.9)	1975 (1438.5, 2335)	1525.8 (1069.3, 2133.3)	0.021*
International normalized ratio (INR)	1.1 (1, 1.2)	1.1 (1, 1.1)	1.1 (1, 1.3)	0.512
Total bilirubin, mg/dL	1.2 (0.6, 2.2)	0.8 (0.6, 1.1)†	0.8 (0.6, 1.8)	0.044*
Albumin, g/dL	3.8 (3.2, 4.1)	4.1 (3.8, 4.4)†	3.7 (3.3, 4.2)‡	<.001*
Globulin, g/dL	2.8 (2.4, 3.4)	2.9 (2.5, 3.3)	3.1 (2.8, 3.6)	0.032*
AST/ALT ratio	1.3 (1, 1.9)	0.6 (0.5, 0.8)†	0.8 (0.5, 1.3)†,‡	<.001*
ALT, IU/L	44.5 (28.5, 76.5)	91 (57.3, 138.5)†	78 (39.3, 187.5)†	<.001*
AST, IU/L/l	61 (38.3, 114.3)	54 (39, 81.8)	71 (37.8, 164)	0.127
Total Protein, mg/dL	6.6 (6, 7)	6.7 (6.2, 7.2)	6.9 (6.3, 7.3)†	0.045*
r-GT, IU/L	383.5 (137.8, 709)	51 (29.3, 142.3)†	101 (55, 290)†,‡	<.001*
Serum ferritin, ng/mL	395 (198, 869.5)	415 (354, 933)	330 (191.8, 787.5)	0.424
AFP, ng/ml	4.9 (3.2, 8.1)	3.8 (2.4, 7.8)	6.0 (4.0, 18.0)‡	0.006*
HBsAg				0.189
Positive	ND	40 (59.7)	40 (71.4)	
Negative	ND	27 (40.3)	16 (28.6)	
HBV DNA, Log10 copies	ND	6.1±1.9 (n=40)	4.9 ± 1.8 (n=38)‡	0.003*

Data were presented as median (IQR: Q1, Q3) for continuous variables without normal distribution; mean ± SD for continuous variables with normal distribution; n (%) for categorical variables. Difference among three groups were compared using Kruskal-Wallis test with a post-hoc pair-wise comparisons, Mann-Whitney U test for continuous variables without normal distribution; One-way ANOVA test with a post-hoc pair-wise comparisons, Bonferroni test for continuous variables with normal distribution; Pearson Chi-square test or Fisher's exact test if any cell number less than 5 for categorical variables. Two sample t-test was performed in HBV DNA copies numbers between viral and combined groups. *P<0.05, indicates significantly different among three groups. †,‡P<0.0167, indicate significantly different as comparing with alcohol group† and viral group‡, separately (N=180).

through interviews with patients and family members regarding the duration, types, and amounts of alcohol per day. Heavy alcoholism was defined as consuming more than 80 g of ethanol each day for at least 5 years. Routine hematology and blood chemistries were performed for all patients, including mean corpuscular volume (MCV), platelet count, total bilirubin, albumin, globulin, aspartame aminotransferase (AST), alanine aminotransferase (ALT), AST/ALT ratio, r-GT, and alpha-fetoprotein (AFP). All patients also had tests for hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and anti-HBe antibodies (anti-HBeAg) (Abbott Laboratories, Chicago, IL, USA) and serum HBV DNA (Cobas Amplicor, Hepatitis B Virus Test; Roche Diagnostics, Branchburg, NJ, USA) with a lower detection limit of 300 copies/mL. All included patients underwent ultrasound and liver biopsy to confirm liver status. Platelet count/spleen diameter ratios (hereafter called "platelet/spleen ratio") were determined for all patients based on platelet counts and spleen measurement taken during ultrasound examination. For analysis purposes, patients were stratified into three groups: an alcohol group with alcoholic liver disease only, a viral group with viral hepatitis only, and a combined group representing those with both alcoholic and viral liver disease. The viral hepatitis only group was included as a control group. To determine possible associations between the platelet/spleen ratios and alcoholic or virus-related liver disease, univariate analysis of platelet/spleen ratios was performed and a series of comparisons were made between 5 different subsets of patient groups (1. alcoholic + combined vs. viral only; 2. alcoholic vs. viral only; 3. alcoholic vs. viral + combined; 4. alcohol vs. combined; and 5. viral only vs. combined). Significant associations between platelet/spleen ratios and specific comparison groups as determined by univariate analysis were analyzed further by receiver operating characteristic (ROC) curve

Table 2. Comparison of the platelet/spleen ratio between groups for different methods

Group		Platelet/spleen ratio	*P*-value
Comparisons 1			
Alcohol + Combined	n=97	1572.9 (1312.0, 2482.9)	0.252
Virus only	n=58	1975 (1438.5, 2335)	
Comparisons 2			
Alcohol	n=42	1794.7 (1399.7, 2927.9)	0.481
Viral	n=58	1975 (1438.5, 2335)	
Comparisons 3			
Alcohol	n=42	1794.7 (1399.7, 2927.9)	0.090
Viral + Combined	n=113	1780 (1361.4, 2237.5)	
Comparisons 4			
Alcohol	n=42	1794.7 (1399.7, 2927.9)	0.020*
Combined	n=55	1525.8 (1069.3, 2133.3)	
Comparisons 5			
Virus	n=58	1975 (1438.5, 2335)	0.018*
Combined	n=55	1525.8 (1069.3, 2133.3)	

Data were summarized as median (IQR) and compared using Mann-Whitney U test. *P<0.05, significantly different between groups.

analysis to identify the best cut-off point for the specific associations and the accuracy, sensitivity, specificity, and predictive value of the platelet/spleen ratio.

Statistical analysis

Statistical analysis was performed with SPSS 17.0 statistics software (SPSS Inc, Chicago, IL, USA). Subjects' demographic and clinical characteristics data are presented as mean ± SD for continuous variables with normal distribution, and n (%) for categorical variables by group. Differences between the three groups were compared using one-way ANOVA test with post-hoc pair-wise comparisons, Bonferroni test for continuous variables with normal distribution; Pearson Chi-square test or Fisher's exact test if any cell number was less than 5 for categorical variables. For continuous data without normal distribution, data were represented as median (IQR: Q1, Q3) by group and compared using Kruskal-Wallis test with post-hoc pair-wise comparisons and Mann-Whitney U test. A two sample t-test was performed in HBV DNA copies numbers between viral hepatitis and combined hepatitis/alcoholic groups. To determine possible associations between the platelet/spleen ratios and alcoholic or virus-related liver disease, univariate analysis was performed and comparisons were made between 5 different subsets of combinations of patients groups (Subset 1. alcoholic + combined vs. viral only; Subset 2. alcoholic vs. viral only; Subset 3. alcoholic vs. viral + combined; Subset 4. alcohol vs. combined; and Subset 5. viral only vs. combined). The platelet/spleen ratios for each subset were also summarized as median (IQR) by group and were compared using Mann-Whitney U test because data were not normally distributed. In addition, to identify the best cut-off point for associations between postoperative platelet/spleen ratios and alcoholic liver disease or viral hepatitis disease, results of univariate analysis that showed significant association ($P<0.05$) between the platelet/spleen ratio and specific subsets of alcoholic liver disease, virus hepatitis or combined viral/alcoholic disease were selected for further analysis using receiver operating characteristic (ROC) curve analysis. The areas under the ROC curve (AUC), 95% CI of AUC were derived from ROC curve analysis with or without adjusting for sex separately. The best cut-off point for postoperative platelet/spleen ratio was determined based on subsequent maximization of Youden's index (= sensitivity + specificity - 1). The corresponding accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated according to the cut-off point determined by Youden's index.

Results

A total of 180 subjects were enrolled into this study, among which 56 had been diagnosed with alcoholic liver disease (alcohol group), 68 were diagnosed with viral hepatitis (viral group), and 56 had alcoholic liver disease combined with viral hepatitis (combined group). Median age was 43.5 years (IQR: 37.3, 48.8) in the alcohol group, 43 years (IQR: 35, 50) in the viral group, and 50 years (IQR: 39.0, 59.8) in the combined group. Ages in the combined group were significantly higher than those in the alcohol and viral groups (both *P*-values <0.0167). Both alcohol and combined groups had more than 90% males while the viral group had almost 80% males, which was lower than the alcohol group. (79.4% *vs*. 96.4%, P<0.0167). All

Table 3. Summary of the observed AUC values with corresponding best cut-off, sensitivity, specificity, PPV, and NPV

Method	AUC (95% CI of AUC)	*P*-value	Cut-off of platelet/spleen ratio†	Accuracy‡	Sen.‡	Spec.‡	PPV‡	NPV‡
Comparisons 4	0.638 (0.524, 0.752)	0.020*	2312	68.0% (66/97)	47.6% (20/42)	83.6% (46/55)	69% (20/9)	67.6 (46/68)
Comparisons 4 (Adjusted)	0.664 (0.554, 0.775)	0.006*	2306	68.0% (66/97)	47.6% (20/42)	83.6% (46/55)	69% (20/9)	67.6 (46/68)
Comparisons 5	0.629 (0.525, 0.732)	0.018*	1618	62.8% (71/113)	69.0% (40/58)	56.4% (31/55)	62.5% (40/64)	63.3% (31/49)
Comparisons 5 (Adjusted)	0.665 (0.565, 0.765)	0.002*	1650	61.9% (70/113)	67.2% (39/58)	56.4% (31/55)	61.9% (39/63)	62.0% (31/50)

Method 4: Alcohol vs. combined group; Method 4 (Adjusted): Alcohol vs. combined group with adjusting sex; Method 5: Virus vs. combined group; Method 5 (Adjusted): Virus vs. combined group with adjusting sex. Abbreviations: AUC, area under the receiver operating characteristic (ROC) curves; CI, confidence intervals; Sen., sensitivity; Spec., specificity; PPV, positive predictive value; NPV, negative predictive value. *P<0.05, indicates significance of the AUC. †The cut-off was derived based on the maximization of Yuden index according to the derived ROC curve. ‡The diagnostic results were calculated accordingly to the cut-off of platelet/spleen ratio.

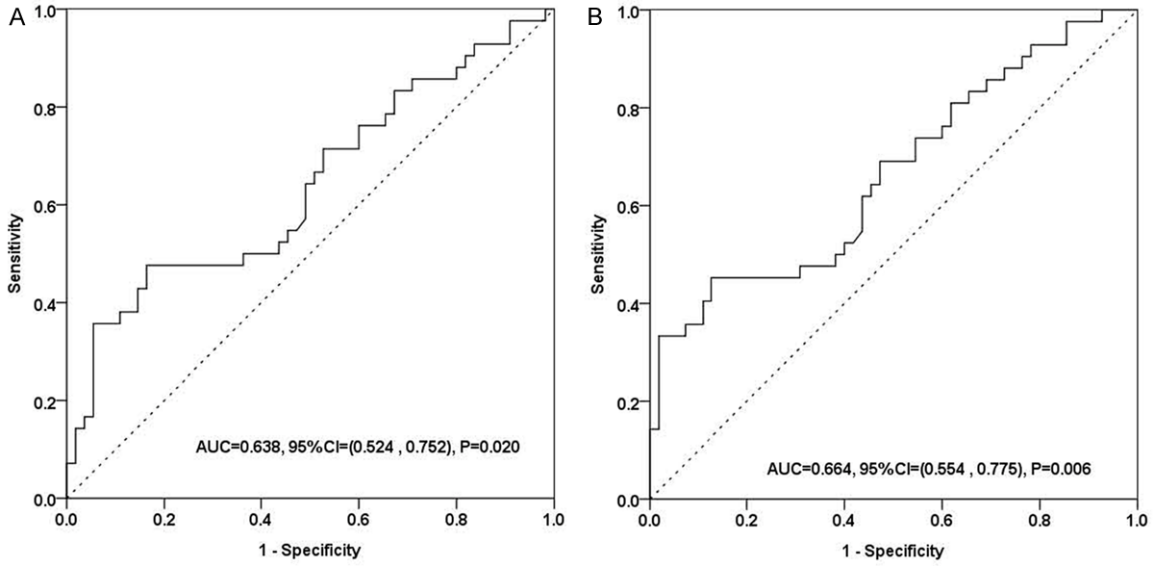

Figure 1. The receiver operating characteristic (ROC) curves of identifying alcoholic liver disease as comparing combined group in method 4 (A), and for adjusting sex (B), respectively.

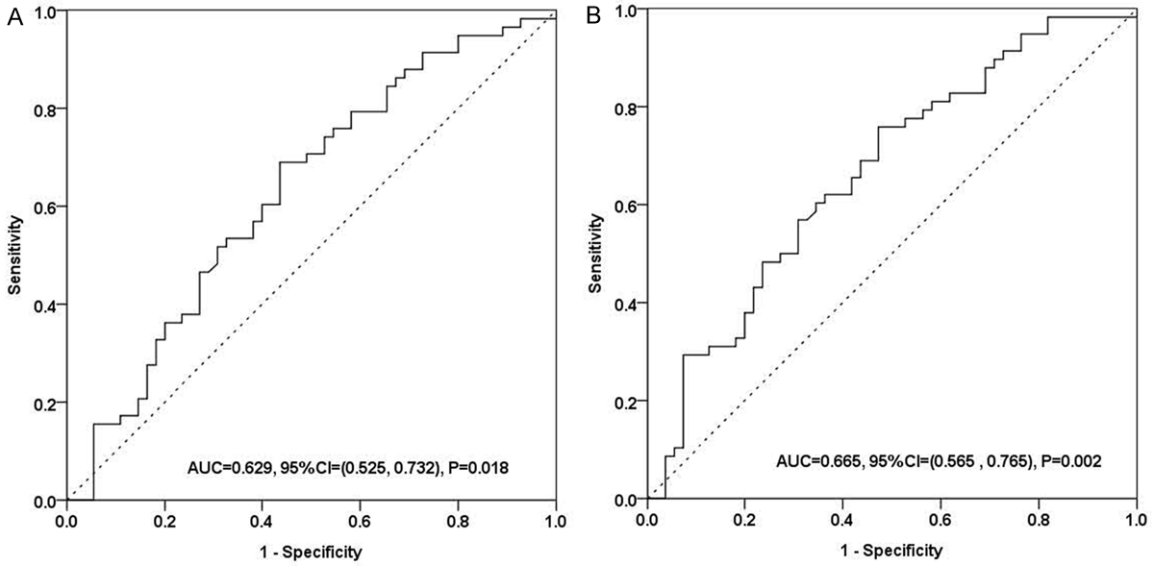

Figure 2. The receiver operating characteristic (ROC) curves of identifying virus hepatitis disease as comparing combined group in method 5 (A), and for adjusting sex (B), respectively.

subjects' demographic and clinical characteristics are summarized in **Table 1**. The dispersion of MCV, platelet, platelet count/spleen diameter ratio, total bilirubin, albumin, globulin, AST/ALT ratio, ALT, r-GT, and AFP were significantly different between the three groups (all *P*-values <0.05). For viral hepatitis markers, the combined group had lower HBV DNA copy numbers than the viral group (P=0.003) (**Table 1**).

Differences are shown between comparisons (1-5) of different combinations of patient groups using the platelet/spleen ratio as a marker for identifying alcoholic liver disease. **Table 2** represents the univariate analysis of platelet/spleen ratios and comparison of results between different groups. No significant differences were found between groups in Comparisons 1, 2, and 3. Significant differences are shown between groups in Comparisons 4 and 5 compared to the platelet/spleen ratios between the other groups. In Comparison 4, the alcohol group had a higher platelet/spleen ratio than the combined group for all subjects (P=0.020).

In Comparison 5, all subjects in the viral hepatitis group had a higher platelet/spleen ratio than those of the combined group subjects (P=0.018) (**Table 2**).

Table 3; **Figures 1** and **2** represent the AUC values determined for corresponding best cut-off of platelet/spleen ratios, accuracy, sensitivity, specificity, PPV and NPV from Comparisons 4 and 5. The optimal cut-off of platelet/spleen ratio was derived as 2306 to differentiate alcoholic liver disease from the combined alcoholic and viral liver disease after adjusting for sex. The determinations for accuracy, sensitivity, specificity, PPV, and NPV were 68%, 47.6%, 83.6%, 69%, and 67.6%, respectively. The optimal cut-off of platelet/spleen ratio was derived as 1650 to differentiate viral liver disease from combined alcoholic and viral liver disease and after adjusting for sex. The determinations for accuracy, sensitivity, specificity, PPV, and NPV were 61.9%, 67.2%, 56.4%, 61.9%, and 62.0%, respectively (**Table 3**).

Discussion

Results of the present study revealed significant differences between the three different groups of patients with chronic liver disease (alcohol, viral, and combined groups) in platelet/spleen ratios, total bilirubin, albumin, globulin, liver enzymes and AFP. When univariate analysis of platelet/spleen ratios was applied to compare the groups arranged in various subsets, significant differences were found in platelet/spleen ratios between the alcohol group vs. the combined group and the viral hepatitis vs. the combined group. Optimal cut-offs of platelet/spleen ratio to differentiate alcoholic liver disease and viral liver disease separately from combined alcoholic and viral liver disease were 2306 and 1650, respectively, indicating that the platelet/spleen ratio was able to differentiate alcohol and viral liver disease separately from combined alcohol and viral disease although it could not differentiate alcoholic liver disease from viral liver disease alone without confirmation of viral hepatitis.

The platelet/spleen ratio is primarily applied to predict risk of esophageal varices in cirrhotic patients with portal hypertension. These patients represent about 60% to 80% of all cirrhosis patients, depending on the severity and etiology of the disease [13]. However, whether they have chronic alcoholic liver disease or chronic viral liver disease or any other cirrhotic liver disease, variceal rupture may occur emergently if they have portal hypertension and risk must be monitored. In fact, authors today suggest that all cirrhotic patients should be evaluated for varices beginning at the time cirrhosis is diagnosed [14]. Consequently, screening endoscopy is performed every two to three years to determine risk [15]. The platelet/spleen ratio may also be performed, which provides a non-invasive means to evaluate patients based on ultrasound measurements of the spleen and the platelet count, which are both performed routinely in patients with liver abnormalities. Esophageal varices can also be correctly diagnosed by clinical, biochemical and Doppler ultrasound non-endoscopic criteria in 81% of patients with chronic liver disease and 71% of patients with cirrhosis [16]. If such a high percentage of patients with chronic liver disease are candidates for primary prevention of esophageal varices, then cirrhosis is occurring in enough patients to warrant applying the platelet/spleen ratio as a screening tool. In addition, we reasoned that the platelet/spleen ratio may have expanded utility among chronic liver disease patients in helping to distinguish alcoholic liver disease from viral liver disease and combined alcohol/viral liver disease, based on differences in disease progression among alcoholic patients. However, although the performance of the platelet/spleen ratio did show reasonable accuracy, specificity, sensitivity and predictive values in the present study, the study population may not have included sufficient numbers of patients with thrombocytopenia and splenomegaly stemming from cirrhosis, which may have limited the potential of the platelet/spleen ratio to distinguish alcoholic liver disease from viral hepatitis alone.

Heavy chronic consumption of alcohol, which is defined as more than 80 g per day for 5 years or more, is associated with more severe disease and is reported to influence the progression of disease in patients with chronic viral liver disease [9, 17-19], as well as other forms of liver disease such as iron overload disorders and obesity-related liver disease [18]. Alcoholic liver disease also has three classic stages: simple steatosis, alcoholic hepatitis and chronic hepatitis with fibrosis and cirrhosis, which will be accompanied by histologic changes characteristic of alcohol-related liver disease, including perivenular fibrosis, a significant indepen-

dent risk factor for progression of alcoholic liver injury to fibrosis and cirrhosis [20]. Data suggest that alcohol exerts synergistic effects on liver injury from viral hepatitis through its effects on virus replication [21]. Viral replication has been shown to be enhanced in alcoholics with viral liver disease compared to viral hepatitis patients who did not consume alcohol [22]. Also, alcoholic cirrhotic patients with high viral load (HBV DNA) had a higher incidence of HCC than those with lower viral load, suggesting that increasing levels of HBV DNA lead to the progression of cirrhosis to HCC [17]. Excessive alcohol use is also associated with greater risk of progressing to HCC, [23] and alcoholic cirrhotic patients with HBV infection have significantly higher incidence of HCC than those with HBV infection only or alcohol liver disease only [17].

Evidence-based reports such as these that show the influence of alcohol on the progression of chronic liver disease encouraged us to consider the potential of the platelet/spleen ratio to differentiate alcoholic liver disease from viral hepatitis alone and combined alcohol/viral liver disease. Although alcoholic liver disease was distinguished from combined alcohol/viral liver disease in the present study, but only when viral disease was confirmed, we feel that additional study with a larger patient population and with staging of the liver disease in all patients (also including compensated and decompensated cirrhosis), may still indicate the potential usefulness of the platelet/spleen ratio in differentiating alcoholic liver disease.

Limitations

The present study had limitations; primarily that it was a retrospective study with a relatively small sample from only two institutions in Taiwan, which usually would preclude generalizing results to populations outside of Taiwan. In addition, while we considered issues related to the diagnosis and differentiation of chronic hepatitis among study subjects, we did not evaluate stages of fibrosis, cirrhosis or HCC or the risk of progression in these patients, which may influence the interpretation of results. Prospective cross-sectional studies are needed with a larger sample to confirm results of the present study and to examine the utility of platelet-spleen ratio further in the differential diagnosis of alcoholic vs. viral liver disease.

Conclusions

The platelet/spleen ratio can only be used to differentiate alcoholic liver disease from coexisting alcoholic and viral liver disease in conjunction with confirmation of viral hepatitis. It cannot be used to differentiate alcoholic liver disease from combined alcohol/viral liver disease or viral hepatitis only. A method for differentiating alcoholic liver disease quickly and accurately would be especially useful clinically to determine early and appropriate treatment and help to avoid the late complications of chronic liver disease. Future research to identify such a method is warranted.

Disclosure of conflict of interest

None.

Abbreviations

ALT, Alanine aminotransferase; AFP, Alpha fetoprotein; anti-hbeag, Anti-hbe antibodies; AST, Aspartate aminotransferase; CT, Computed tomography; Hbeag, Hepatitis B e antigen; Hbsag, Hepatitis B surface antigen; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HCC, Hepatocellular carcinoma; MRI, Magnetic resonance imaging; MCV, Mean corpuscular volume; NPV, Negative predictive value; PPV, Positive predictive value.

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References

[1] Gao B. Interaction of alcohol and hepatitis viral proteins: implication in synergistic effect of alcohol drinking and viral hepatitis on liver injury. Alcohol 2002; 26: 69-72.

[2] Jaurigue MM, Cappell MS. Therapy for alcoholic liver disease. World J Gastroenterol 2014; 20: 2143-2158.

[3] Chen CJ, Yang HI, Boeje UH. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. Hepatology 2009; 49: 572-584.

[4] Hu JT, Yang SC, Huang SF, Lin CL, Lin PH, Tseng TL, Yang SS. Current status of alcoholic liver disease in Taiwan. Gastroenterol J Taiwan 2011; 28: 234-241.

[5] Lin CW, Chen YS, Lai CH, Perng DS, Weng HC, Hu JT, Huang YW, Hsu MY, Yang SS. Esophagogastric varices predict mortality in hospitalized patients with alcoholic liver disease in Taiwan. Hepatogastroenterology 2010; 57: 305-308.

[6] Toshikuni N, Izumi A, Nishino K, Inada N, Sakanoue R, Yamato R, Suehiro M, Kawanaka M, Yamada G. Comoparison of outcomes between patients with alcoholic cirrhosis and those with hepatitis C virus-related cirrhosis. J Gastroenterol Hepatol 2009; 24: 1276-1283.

[7] Khan KN, Yatsuhashi H. Effect of alcohol consumption on the progression of hepatitis C virus infection and risk of hepatocellular carcinoma in Japanese patients. Alcohol Alcohol 2000; 35: 286-295.

[8] Zhang D, Li P, Chen M, Liu L, Liu Y, Zhao Y, Wang R. Non-invasive assessment of liver fibrosis in patients with alcoholic liver disease using acoustic radiation force impulse elastography. Abdom Imaging 2015; 40: 723-9.

[9] Nakano M, Maruyama K, Okuyama K, Takahashi H, Yokoyama K, Takagi S, Shiraki H, Ishii H. Characteristics of alcoholics with HCV infection: histopathologic comparison with alcoholics without HCV infection and chronic type C hepatitis. Alcohol Alcohol 1993; 28: 35-40.

[10] Gao B, Bataller R. Alcoholic liver disease: Pathogenesis and new therapies. Gastroenterology 2011; 141: 1572-1585.

[11] Sarrazin C, Berg T, Ross RS, Schirmacher P, Wedemeyer H, Neumann U, Schmidt HH, Spengler U, Wirth S, Kessler HH, Peck-Radosavljevic M, Ferenci P, Vogel W, Moradpour D, Heim M, Cornberg M, Protzer U, Manns MP, Fleig WE, Dollinger MM, Zeuzem S. Prophylaxis, diagnosis and therapy of hepatitis C virus (HCV) infeccction: the German guidelines on the management of HCV infection. Z Gastroenterol 2010; 48: 289-351.

[12] Comberg M, Protzer U, Petersen J, Wedemeyer H, Berg T, Jilg W, Erhardt A, Wirth S, Sarrazin C, Dollinger MM, Schirmacher P, Dathe K, Kopp IB, Zeuzem S, Gerlich WH, Manns MP; AWMF. Prophylaxis, diagnosis and therapy of hepatitis B virus infection: the Gernman guideline. Z Gastroenterol 2011; 49: 871-930.

[13] Giannini E, Botta F, Borro P, Risso D, Romagnoli P, Fasoli A, Mele MR, Testa E, Mansi C, Savarino V, Testa R. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. Gut 2003; 52: 1200-1205.

[14] DeFranchis R. Evolving consensus in portal hypertension. Report of the Baveno IV International Consensus Workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2005; 43: 167-176.

[15] Jensen DM. Endoscopic screening for varices in cirrhosis: findings, implications, and outcomes. Gastroenterology 2002; 122: 1620-1630.

[16] Pilette C, Oberti F, Aubé C, Rousselet MC, Bedossa P, Gallois Y, Rifflet H, Calès P. Non-invasive diagnosis of esophageal varices in chronic liver diseases. J Hepatol 1999; 31: 867-873.

[17] Lin CW, Lin CC, Mo LR, Rousselet MC, Bedossa P, Gallois Y, Rifflet H, Chen YS, Yen YC, Hu JT, Yu ML, Lee PH, Lin JT, Yang SS. Heavy alcohol consumption increases the incidence of hepatocellular carcinoma in hepatitis B virus-related cirrhosis. J Hepatol 2013; 58: 730-735.

[18] Balasubramanian S, Kowdley KV. Effect of alcohol on viral hepatitis and other forms of liver dysfunction. Clin Liver Dis 2005; 9: 83-101.

[19] Scotet V, Merour MC, Mercier AY, Chanu B, Le Faou T, Raguénes O, Le Gac G, Mura C, Nousbaum JB, Férec C. Hereditary hemochromotosis: effect of excessive alcohol consumption on disease expression in patients homozygous for the C282Y mutation. Am J Epidemiol 2003; 158: 129-134.

[20] O'Shea RS, Dasarathy S, McCullough AJ; Practice Guideline Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology: Alcoholic liver disease. Hepatology 2010; 51: 307-328.

[21] Zhang T, Li Y, Lai JP, Douglas SD, Metzger DS, O'Brien CP, Ho WZ. Alcohol potentiates hepatitis C virus replicon expression. Hepatology 2003; 38: 57-65.

[22] Pessione F, Degos F, Marcellin P, Duchatelle V, Njapoum C, Martinot-Peignoux M, Degott C, Valla D, Erlinger S, Rueff B. Effect of alcohol consumption on serum hepatitis C virus RNA and histologic lesions in chronic hepatitis C. Hepatology 1998; 27: 1717-1722.

[23] Morgan TR, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. Gastroentrol 2004; 127: 587-596.