Original Article

A Comparison of Mean Platelet Volume between Viral Hepatitis and Non-Viral Hepatitis in Liver Cirrhosis

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Background: A high level of mean platelet volume (MPV) is associated with platelet activation, which occurs in chronic inflammatory disease. Several studies have demonstrated that a high MPV is associated with chronic viral hepatitis and hepatic fibrosis. However, the role of MPV in patients with cirrhosis is unclear.

Objective: To evaluate the MPV in patients with cirrhosis, and to compare the MPV between viral hepatitis and non-viral hepatitis groups. Moreover, the correlation of MPV and factors was also explored.

Materials and Methods: The medical records of 420 cirrhosis outpatients from 2010 to 2017 at Her Royal Highness (HRH) Princess Maha Chakri Sirindhorn Medical center were reviewed and analyzed as a retrospective study. The MPV was expressed as mean±SD. The correlation between MPV values and cirrhosis parameters including mortality outcomes were evaluated.

Results: According to retrospective data, the mean age was 56.23 (SD 12.77). Two-hundred and ninety-two patients were males (69.5%), and one-hundred and twenty-eight patients were females (30.5%). Child-Pugh scores A, B, and C were found in 286 (68.1%), 132 (31.4%), and 2 (0.5%) cases, respectively. There was a significant difference of MPV between the group of viral hepatitis and non-viral hepatitis cirrhosis (10.79±1.05 vs. 10.54±1.00; 95% CI, 0.06 to 0.45), respectively. The median time of follow-up in this study was 40.06 months (range, 0.07 to 121.41). The mortality rate was 18.3%. Elevated MPV was found inversely correlated with albumin and platelet counts, and positive correlation with levels of prothrombin time, and INR in all causes of cirrhosis especially chronic viral hepatitis. However, there was no correlation of MPV and long-term mortality outcomes in all causes of cirrhosis (r=-0.066, 95% CI -0.165 to 0.035) and viral hepatitis causes (r=-0.035, 95% CI -0.158 to 0.095).

Conclusion: The difference of MPV between viral hepatitis and non-viral hepatitis groups causing liver cirrhosis was identified in our study. The MPV was not correlated with long-term mortality outcomes in cirrhotic patients.

Keywords: Platelet volume; Liver cirrhosis; Viral hepatitis; Mortality

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Cirrhosis is a chronic disease associated with hepatocyte dysfunction causing virus, alcohol, drug, autoimmune as well as non-alcoholic fatty liver disease. From recent data of the United States[1,2], the people who were diagnosed with cirrhosis are found about 2.8 million, and they died 1.3 million in 2015. In addition, there are shown cirrhotic causes from alcohol (348,000 cases), hepatitis B (371,000 cases), and hepatitis C (326,000 cases)[2].

Mean platelet volume (MPV) evaluates the mean size of platelets and considers the production and stimulation from bone marrow[3]. MPV is a key role in the activation of platelet especially chronic inflammation[4]. Some studies reported the involvement of MPV in liver diseases such as steatosis, hepatitis, and cirrhosis[5-7]. Moreover, several studies reported the association of MPV in fibrosis and inflammatory process in chronic viral hepatitis particularly chronic viral hepatitis B[3,8,9]. Chronic viral hepatitis B with a high level of MPV was correlated to acute on top chronic liver failure[10,11]. The MPV was a possible biomarker related to acute chronic hepatitis hepatic failure within 4 weeks in patients with chronic hepatitis B cirrhosis in a previous study[10]. A cirrhotic patient with ascites was also found with an increased level of MPV. Thus, the MPV is an important role that indicates the inflammatory process of the liver[9,12]. Moreover, MPV could predict the degree of fibrosis in chronic hepatitis C over chronic hepatitis B[13].

Contrastly in a study[14], MPV level was not found significantly between viral hepatitis and non-viral hepatitis groups. They revealed that a significant relationship was not found between MPV and degree of cirrhosis including the prognosis of disease due to small sample size, a variety of etiologies (e.g., viral hepatitis, alcohol, cholestasis, etc), and Child-Turcotte-Pugh score (CTP). There were scant reports of the association between MPV and mortality outcomes in viral hepatitis cirrhosis.

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In the present study, we aimed to evaluate the MPV between viral hepatitis and non-viral hepatitis groups. Moreover, we investigated the relationship between MPV with viral hepatitis-related mortality outcomes and evaluated the role of the MPV to be a prognostic marker.

Materials and Methods

Study participants

Patients who were diagnosed with cirrhosis and completed data were included in the present study. Inclusion criteria included stable cirrhosis, and those aged more than 18 years. Patients who coexisted with other causes of thrombocytopenia (drug, infection, cancer, allergy, chemical agents, HIV, immune, bone marrow), previous bleeding within 4 weeks, received antiretroviral agents including interferon injection, alcohol drinking with 4 weeks, prior infection within 4 weeks, surgery within 4 weeks, and receiving of blood including blood products within 4 weeks were excluded from the study (data was shown in Figure 1). Data including age, gender, underlying disease, causes of cirrhosis, complete blood count (CBC), albumin, creatinine, glomerular filtration rate (GFR), CTP score, and causes of death were collected and considered. MPV was measured from CBC at the first time of diagnosis of liver cirrhosis.

Study design

The study was a retrospective and descriptive study. The medical records of 420 cirrhosis outpatients from 2010 to 2017 at Her Royal Highness (HRH) Princess Maha Chakri Sirindhorn Medical center (MSMC) were reviewed and analyzed.

The study was done according to the declaration of Helsinki and ICH-GCP and was approved by the Institution Review Board, Srinakharinwirot University (SWU EC-316/2560).

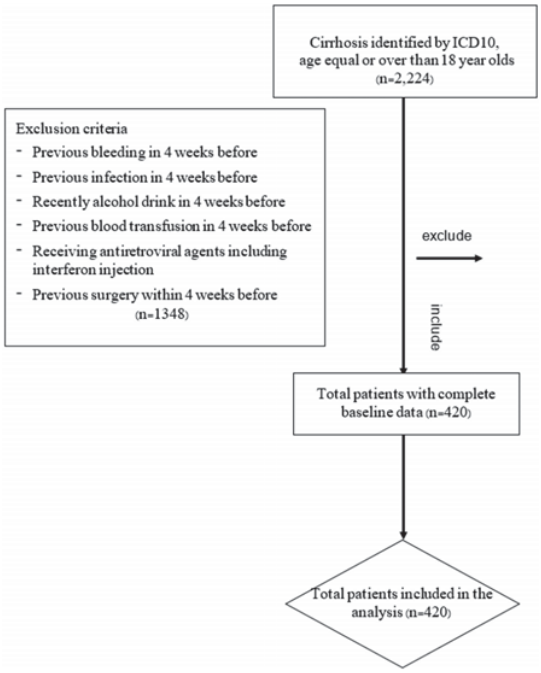

Figure 1. Diagram of inclusion criteria for the study population.

Definition

Cirrhosis is defined by pathology[15] or imaging such as ultrasonography, computer tomography, magnetic resonance imaging[16], and fibroscan[17].

Cirrhosis from viral hepatitis B is defined as HBsAg positive and/or detected HBV viral load[18]. Cirrhosis resulting from viral hepatitis C is defined as an anti-HCV positive and/or detected HCV viral load[19].

Alcohol drinking in alcoholic cirrhosis is defined as received alcohol 20 grams in males, and 60 grams in females[20].

Mortality referred to death from any causes. The time to follow study was defined as the time of diagnosis of liver cirrhosis to death or end of the study. Time to death was defined as the time of diagnosis of liver cirrhosis to death.

CBC analyses

CBC analyzer using SYSMEX XN-3000, coefficients of variation (95% reliability) of mean platelet volume (MPV) was equal or less than 4.0%. CBC results were recorded at the time of diagnosis of cirrhosis.

Sample calculation

The sample size was calculated based on primary research objectives. The two-way hypothesis of two independent groups of variables was evaluated. The MPV in viral hepatitis (9.10 fL) and non-viral hepatitis (8.90 fL)[14] were calculated for sample size using STATA version 14. Thus the sample size was approximately 209 participants in each group.

Measurement

The primary endpoint was evaluated the MPV between viral hepatitis and non-viral hepatitis. Secondary endpoints have identified the correlation of MPV and factors including mortality outcomes, particularly in the viral hepatitis group. Viral hepatitis group was defined when met criteria of hepatitis B[18] and/or hepatitis C[19]. Cirrhosis patient which resulting from the alcoholic, non-alcoholic steatohepatitis, autoimmune hepatitis, and cholestasis with or without viral hepatitis was classified to non-viral hepatitis group.

Statistical analysis

The results of the present study were analyzed as descriptive statistics including percentages, and mean±standard deviation (SD). The Chi-square test was used to compare groups on the categorical measures. The student's t-test and Mann-Whitney U-test were used to compare groups

in a normally normal and nonparametric variable on the continuous measures, respectively. One-way Anova test and Kruskal Wallis tests were used to calculate the difference between quantitative variables in more than two groups in normally normal and nonparametric variables, respectively. Spearman's correlation tests were used for correlating nonparametric variables. All data were analyzed using SPSS software, version 20, and p-values less than 0.05 indicated statistically significant.

Results

Demographic and clinical characteristics

A total of 2,224 patients were diagnosed with cirrhosis followed by ICD-10. Four-hundred and twenty medical records that completed clinical data were included in the analysis (Figure 1). The mean age was 56.23 (SD 12.77). Two-hundred and ninety-two patients (69.5%) were male, and 128 (30.5%) patients were female. CTP A, B, and C were found in 286 (68.1%), 132 (31.4%), and 2 (0.5%), respectively. The etiology of cirrhosis was alcohol (35.7%), hepatitis B (34%), hepatitis C (10%), alcohol combined with hepatitis B (7.4%), non-alcoholic steatohepatitis (5%), alcohol combined with hepatitis C (4.8%), cholestasis (1.2%), hepatitis B combined with hepatitis C (1%), and autoimmune hepatitis (1%). The most diagnostic tool for cirrhosis was ultrasonography (86.9%). Only 29.3% of patients were found chronic liver stigmata from physical examinations. The median time of follow-up in this study was 40.06 months (range, 0.07 to 121.41). Seventy-seven of 420 participants (18.3%) died, and 13 patients died had etiology of cirrhosis from viral hepatitis. The median time of death was 17.52 months (range, 0.12 to 102.6). Liver disease-related death was found in 98%.

Clinical characteristic between viral hepatitis and non-viral hepatitis cirrhosis patients

Patients with viral hepatitis (n=189) and non-viral hepatitis (n=231) were included in the analysis. The baselines characteristic between viral hepatitis and non-viral hepatitis were significantly different in gender, age, heart disease, and CTP as shown in Table 1. The greater level of hemoglobin (Hb), hematocrit (Hct), white blood cell count (WBC), platelet count, MPV, and albumin were found in the viral hepatitis group. Contrastly, the lower level of mean corpuscular volume (MCV), WBC, neutrophil count, monocyte count, prothrombin time (PT), the international normalized ratio (INR) were found in the viral hepatitis group. There was a significant difference in MPV among the groups of viral hepatitis and non-viral hepatitis cirrhosis (Table 2).

All participants with viral hepatitis were categorized into 3 groups by MPV; 1) group A: MPV less than 10 fL, 2) Group B: MPV 10 to 12 fL, and 3) group C: MPV over than 12 fL. Clinical and laboratory results were shown in Table 3. When compared between the groups. The Factors such as sex, gender, Hct were not statistically significant differences. A lower level of Hb and albumin was found in groups B and C. Moreover, the rising level of PT and INR were found in groups B and C. But when analyzed between groups B and C. The level of Hb, albumin, PT, INR levels was quite equally. Except for the lower level of platelet count was found in group B.

Correlation between MPV and clinical parameters of cirrhosis patients

The MPV was found positive correlation with PT (r=0.162, 95% CI 0.062 to 0.250, p=0.001), and INR (r=0.167, 95% CI 0.073 to 0.261, p=0.001). Moreover, the MPV was inversely correlated with platelet count (r=-0.409, 95% CI -0.484 to -0.326) (Table 4 and Figure 2). The mortality, age, CTP, and albumin were not correlated with the MPV. When Subgroup in viral hepatitis, we found the MPV negative correlation with platelet count (r=-0.465, 95% CI -0.574 to -0.346), and albumin (r=-0.158, 95% CI -0.298 to -0.021). The MPV was found positive correlation with PT (r=0.246, 95% CI 0.112 to 0.371), and INR (r=0.285, 95% CI 0.151 to 0.404), respectively (Table 5 and Figure 3).

Discussion

Our study showed men were affected by cirrhosis more than women. The common causes of cirrhosis in Thai people were alcohol and viral hepatitis as the same result in the United States[2]. Physical examination detected cirrhosis in 29.3% of patients which is more than a systematic review done by de Bruyn G[21], reason due to alcoholic cirrhosis with or without hepatitis was found in most of the population in our study. Almost all patients were CTP A, and B resulting in the non-worsening of cirrhosis parameters.

A high level of the MPV was found in the viral hepatitis group which is related to a previous study[6]. The high MPV values in a patient with an inactive state of chronic hepatitis B were reported by Turhan O, et al[6]. Moreover, Hu Y, et al[22] reported the association of elevated MPV in hepatitis B with a degree of disease and related complications such as cirrhosis and thrombocytopenia.

Our study found the rising of MPV correlated with the progression of thrombocytopenia which is similar to the study of Hu Y, et al[22]. But the contrast with the study done by Giannini EG, et al[14]. Viral hepatitis B induced the immune system to control the replication of the virus resulting in chronic inflammation and liver parenchymal damage. The inflammatory cytokine such as interleukin-6 is activated and the young platelet is moved from bone marrow to peripheral blood[22]. So, elevated MPV indicates the state of platelet activations from inflammatory response or infection[22]. The large size of the platelet contains multiple granules that affect hemostatic efficiency[23]. Moreover, hypersplenism in an advanced stage of the liver disease leads to platelet sequestration and destruction.

Schlichting P, et al[24] reported the various causes of mortality in cirrhosis patients such as infection (24%), liver failure (22%), cardiovascular system (14%), and gastrointestinal bleeding (7%) that differ in degree of platelet activation. But the duration of each illness is not equal, for example, an acute state of cardiovascular disease results in

Table 1. Baseline characteristics of cirrhosis patients caused from viral hepatitis and non-viral hepatitis (n=420)

Characteristics	Viral hepatitis (n=189)	Non-viral hepatitis (n=231)	p-value
Age, mean±SD	54.32±12.04	57.80±13.17	0.018*
Gender			<0.001**
Male	112 (59.3)	180 (77.9)	
Female	77 (40.7)	51 (22.1)	
Hypertension			0.310**
Yes	63 (33.3)	88 (38.1)	
No	126 (66.7)	143 (61.9)	
Dyslipidemia			0.250**
Yes	42 (22.2)	41 (17.7)	
No	147 (77.8)	190 (82.3)	
Heart disease			0.031**
Yes	5 (2.6)	17 (7.4)	
No	184 (97.4)	214 (92.6)	
Gout			0.070**
Yes	0 (0)	4 (1.7)	
No	189 (100)	227 (98.3)	
Chronic kidney disease			0.590**
Yes	14 (7.4)	14 (6.1)	
No	175 (92.6)	217 (93.9)	
Diabetic mellitus			0.950**
Yes	29 (15.3)	36 (15.6)	
No	160 (84.7)	195 (84.4)	
Child-turcotte-pugh			<0.001**
A	158 (83.6)	128 (55.4)	
B	30 (15.9)	102 (44.2)	
C	1 (0.5)	1(0.4)	

* Mann-Whitney U-test, ** Chi-square test

high mortality while it will not change in MPV levels. Recently study demonstrated that the elevated MPV is associated with hepatitis B including related to liver fibrosis[25], poor short-term outcomes in hepatitis B virus-related acute on chronic liver failure patients[11] which indicate the progression of the disease. The correlation between MPV and long-term mortality outcomes was not demonstrated in our study.

There were some limitations in our study. First, the study design was a retrospective study and non-randomized patients. Participants which etiology from the alcoholic, non-alcoholic steatohepatitis, autoimmune hepatitis, and cholestasis with or without viral hepatitis were categorized to non-viral hepatitis group. Secondary, small population in CTP group C, and analyzed all causes of viral hepatitis, no monitor MPV during the progression of liver failure, and no measurement of cytokine levels.

Our study showed the elevated MPV was predominant in the viral hepatitis group. Although the previous study showed the association of MPV and short-term outcomes in liver failure-related hepatitis B[11]. But in our study MPV was not associated with long-term mortality. So, the MPV could not be appropriated to predict the progression of disease in long-term outcomes but could be a prognostic marker in the short-term outcome of liver failure.

Conclusions

A high level of MPV was found in the viral hepatitis group. The mean of MPV was not correlated with long-term mortality outcomes in our study. Elevated MPV indicates the progression of disease in the short-term outcome of liver failure.

What is already known on this topic?

The high level of MPV was associated with chronic

Table 2. Baseline laboratory characteristics of cirrhosis resulting from viral hepatitis and non-viral hepatitis causes (n=420)

Laboratory characteristics	Viral hepatitis (n=189)	Non-viral hepatitis (n=231)	p-value
Hemoglobin (g/dL)	12.48±2.00	11.57±2.08	<0.001*
Hematocrit (%)	37.25±5.77	33.97±6.08	<0.001**
Mean corpuscular volume (fL)	84.06±10.37	86.05±9.56	0.041**
White blood cell ($x10^9$/L)	6.13±1.90	6.55±1.99	0.052*
Neutrophil (%)	56.00±11.25	60.41±12.48	<0.001*
Lymphocyte (%)	32.57±10.36	27.16±10.56	<0.001*
Monocyte (%)	7.25±2.23	7.83±2.53	0.026*
Basophil (%)	0.45±0.41	0.47±0.42	0.510*
Eosinophil (%)	3.63±3.68	4.11±4.46	0.670*
Platelet counts ($x10^9$/L)	175.56±78.32	155.51±97.79	<0.001*
Mean platelet volume (fL)	10.79±1.05	10.54±1.00	0.011*
Albumin (g/dL)	3.82±0.63	3.40±0.67	<0.001*
Prothrombin time (sec)	13.68±2.19	14.98±2.75	<0.001*
International normalize ratio	1.15±0.18	1.27±0.22	<0.001*
Creatinine (mg/dL)	0.98±0.71	0.97±1.04	0.708*
Glomerular filtration rate (CKD-EPI)	87.29±25.11	87.12±21.15	0.533*

Data were expressed as the number of patients (%), mean±SD
* Mann-Whitney U-test, ** Student's t-test

Table 3. Clinical and laboratory characteristics of the viral hepatitis patients among 3 groups of mean MPV

Characteristics	Group A (MPV <10.0 fL) n=50	Group B (MPV 10.0 to 12.0 fL) n=108	Group C (MPV >12.0 fL) n=31	p-value
MPV (fl)	9.51±0.42	10.93±0.55	12.38±0.41	<0.001*
Age (year)	55.69±13.67	54.03±12.39	54.42±11.02	0.840*
Gender (male/female)	32/18	60/48	20/11	0.49*
Hemoglobin (g/dL)	13.20±1.89	12.17±1.92	12.38±2.04	0.010**
Hematocrit (%)	38.93±5.58	36.60±5.58	36.82±6.31	0.050**
Albumin (g/dL)	4.03±0.50	3.76±0.75	3.71±0.73	0.013*
Prothrombin time (sec)	12.65±1.40	14.06±2.36	14.03±2.14	<0.001*
International normalize ratio	1.06±0.11	1.18±0.20	1.18±1.92	<0.001*
Creatinine (mg/dL)	0.91±0.44	0.95±0.49	1.20±1.38	0.690*
Platelet counts ($x10^9$/L)	227.28±64.08	167.06±77.49	121.77±51.05	<0.001*

Data were expressed as the number of patients (%), mean±SD
* One-way ANOVA test, ** Kruskal Wallis test

viral hepatitis and hepatic fibrosis.

What this study adds?

The level of MPV was correlated with platelet, PT, and INR in cirrhosis particularly viral hepatitis. But there was not found the relationship between MPV and long-term mortality outcomes.

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Table 4. Correlation of MPV and cirrhosis parameters in all patients (n=420)

Factors	r	95% CI	p-value
Age	-0.081	-0.174 to 0.015	0.096
CTP	0.014	-0.087 to 0.110	0.774
PT	0.162	0.062 to 0.250	0.001
INR	0.167	0.073 to 0.261	0.001
Platelet count	-0.409	-0.484 to -0.326	<0.001
Mortality (death)	-0.066	-0.165 to 0.035	0.179

Potential conflicts of interest

The authors declare no conflict of interest.

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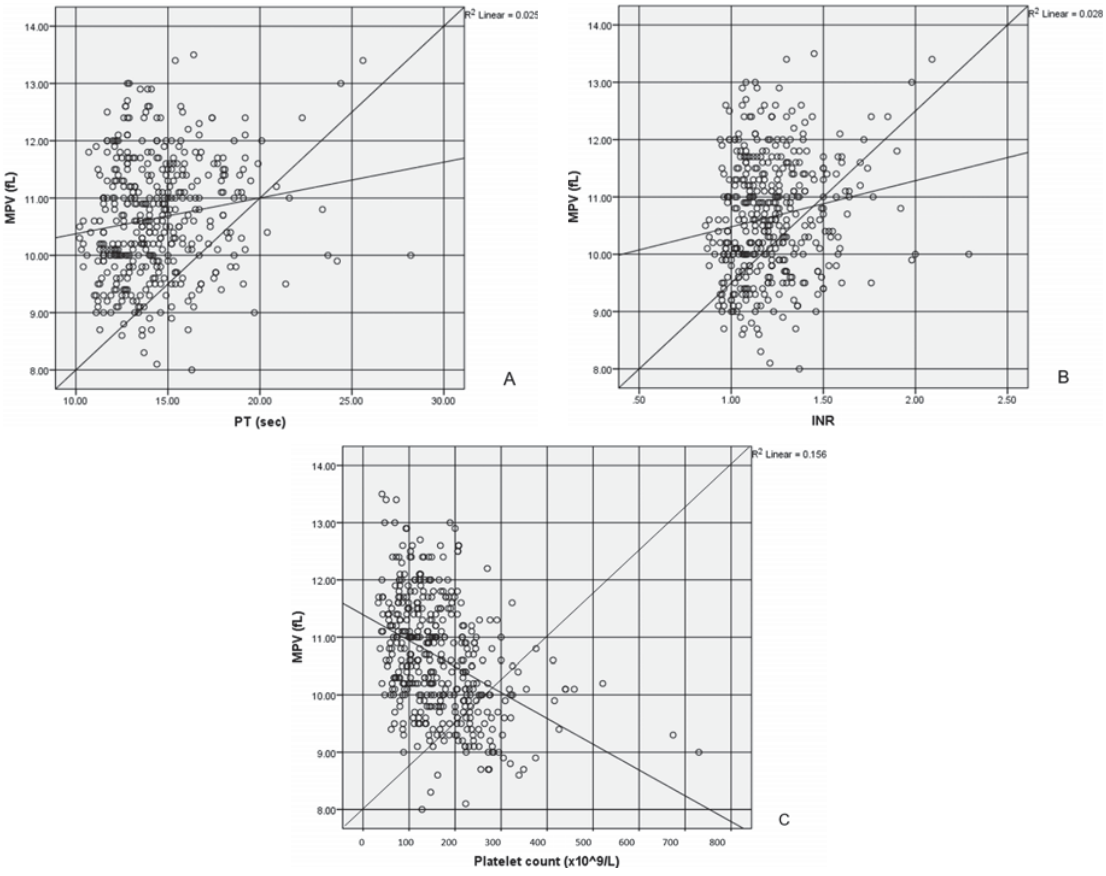

Figure 2. A) Correlation analysis indicate significant positive correlation between mean platelet volume (MPV) and Prothrombin time (PT), r=0.162, p=0.001; B) Correlation analysis indicate significant correlation between MPV and INR, r=0.167, p=0.001; C) Correlation analysis indicate significant negative correlation between MPV and platelet count, r=-0.409, p<0.001 (analyses in all causes of cirrhosis).

Table 5. Correlations of MPV and cirrhosis parameters in viral hepatitis group (n=189)

Factors	r	95% CI	p-value
Age	-0.013	-0.151 to 0.113	0.864
Child-Turcotte-Pugh score	0.11	-0.029 to 0.237	0.132
Prothrombin time	0.246	0.112 to 0.371	0.001
International normalized ratio	0.285	0.151 to 0.404	<0.001
Platelet count	-0.465	-0.574 to -0.346	<0.001
Albumin	-0.158	-0.298 to -0.021	0.030
Mortality (death)	-0.035	-0.158 to 0.095	0.630

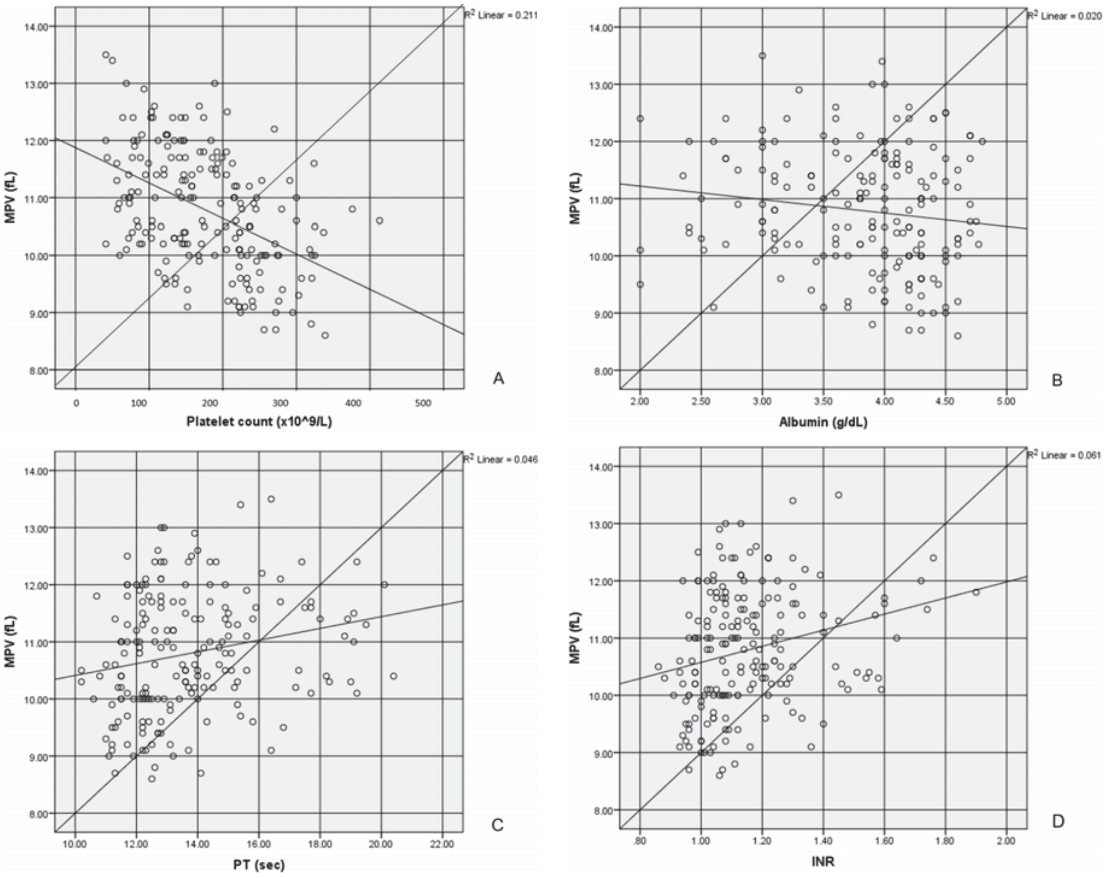

Figure 3. A) Correlation analysis indicate significant negative correlation between mean platelet volume (MPV) and platelet count, r=-0.465, p<0.001; B) Correlation analysis indicate significant negative correlation between MPV and albumin, r=-0.158, p=0.03; C) Correlation analysis indicate significant positive correlation between MPV and PT, r=0.246, p=0.001; D) Correlation analysis indicate significant positive correlation between MPV and INR, r=0.285, p<0.001 (subgroup analyses in viral hepatitis cirrhosis).

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