Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Apr 10; 10(F):513-521.
https://doi.org/10.3889/oamjms.2022.9058
eISSN: 1857-9655
Category: *F - Review Articles*
Section: *Meta-analytic Review Article*

Correlation between Platelet Count and Grading of Esophageal Varices in Liver Cirrhosis Patients: A Meta-Analysis

Fahri Ahmad Baihaqi[1]*, Dinda Olinda Delarosa[2]

[1]*Serui General Hospital, Kepulauan Yapen, Papua, Indonesia;* [2]*Dr. Sitanala General Hospital, Tangerang, Banten, Indonesia*

Edited by: Eli Djulejic
Citation: Baihaqi FA, Delarosa DO. Correlation between Platelet Count and Grading of Esophageal Varices in Liver Cirrhosis Patients: A Meta-Analysis. Open Access Maced J Med Sci. 2022 Apr 10; 10(F):513-521. https://doi.org/10.3889/oamjms.2022.9058
Keywords: Cirrhosis; Esophageal varices; Platelet
***Correspondence:** Fahri Ahmad Baihaqi, Serui General Hospital, Serui, Kepulauan Yapen, Papua, 98213, Indonesia. E-mail: fahribaihaqi@gmail.com
Received: 20-Feb-2022
Revised: 25-Mar-2022
Accepted: 31-Mar-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Esophageal varices are a major complication of liver cirrhosis. Esophageal varices bleeding is life-threatening and an urgent medical emergency. Low platelet count and esophageal varices are common findings in liver cirrhosis. Platelet count is suggested as a non-invasive screening tool to predict the grading of esophageal varices in liver cirrhosis patients. Several studies have found a correlation between platelet count and grading of esophageal varices in liver cirrhosis patients. However, the results are conflicting.

AIM: This meta-analysis aimed to evaluate the correlation between platelet count and the grading of esophageal varices in liver cirrhosis patients.

METHODS: A systematic literature search was performed through the database search from PubMed, SCOPUS, Ovid EMBASE, and EuropePMC to obtain all relevant articles with the following search terms: "correlation" and "platelet" or "thrombocytopenia" AND "esophageal varices" and "liver cirrhosis" or "chronic liver disease" that were published within the year of 2000–2021. Articles were collected by using PRISMA flow diagrams. The data were extracted from the eligible study within inclusion and exclusion criteria. The quality of each study was assessed using the Newcastle Ottawa Scale (NOS). A meta-analysis was conducted to determine the overall pooled correlation coefficient (r) and 95% confidence interval (CI).

RESULTS: There were a total of 1008 patients from eight included studies. The meta-analysis showed that the pooled correlation coefficient between platelet count and grading of esophageal varices in liver cirrhosis patients was r = –0.42 (95%CI –0.65 to –0.13; p = 0.005; I^2 = 96.06%).

CONCLUSION: There was a moderate negative correlation between platelet count and grading of esophageal varices. Thus, low platelet count may indicate higher grades of esophageal varices in liver cirrhosis patients.

Introduction

Cirrhosis is defined as an end-stage chronic liver disease caused by a diffuse pathological process that results in impaired normal liver structure and function characterized by the formation of regenerative nodules and fibrous tissue [1]. Cirrhosis has a high mortality rate and has become a significant health problem worldwide. Cirrhosis is the 13th leading cause of death globally [2]. In 2017, the estimated prevalence of cirrhosis was 122.6 million cases and had caused more than 2.2 million deaths globally [3].

Cirrhosis had a variety of complications, such as hepatic encephalopathy, liver failure, and portal hypertension [4]. Portal hypertension can lead to severe consequences as esophageal varices with risk of rupture and bleeding [5]. Esophageal varices can occur due to an increase in portal vascular resistance caused by portal hypertension [6]. Esophageal varices are estimated to present in 60–80% of cirrhosis patients at the time of diagnosis, while about 30% of cirrhosis patients can develop esophageal variceal bleeding [7], [8]. Esophageal varices bleeding is often life-threatening and associated with high mortality rates. Esophageal varices bleeding had mortality rates of 15% for overall 30-day mortality and 20–70% for one-year mortality [9], [10]. The rate of development of esophageal varices raises approximately 5% per year, and evolvement from small to large varices is about 5–10% per year [11].

Therefore, screening and identifying the esophageal varices and their grades as early as possible is essential to prevent and anticipate the complications, thus improving the prognosis of liver cirrhosis patients [12], [13]. Esophageal varices and their grades can be diagnosed based on endoscopic examination, which is the gold standard [14]. Several guidelines recommend screening for the presence and assessing the bleeding risk of esophageal varices in all cirrhotic patients by endoscopy [14], [15]. However, endoscopy has several limitations, such as it being invasive, expensive, and not readily available in all health centers [16].

To overcome these limitations, as an alternative to endoscopy, a non-invasive screening tool is suggested to predict the presence of esophageal varices and their grades, especially in a resource-limited health

center [1]. Several parameters can be used, including platelet count [17]. Thrombocytopenia (defined as platelet count <150,000/uL) occurs in 64–76% of liver cirrhosis patients with portal hypertension [18].

Portal hypertension is associated with thrombocytopenia and esophageal varices in liver cirrhosis patients [19]. Thus, many studies have investigated the correlation between platelet count and esophageal varices. However, the result seemed inconsistent, and some studies showed a negative correlation between platelet count and grading of esophageal varices [20], [21], while other studies showed a positive correlation [10]. The differences in these results potentially lead to being inconsistent conclusions. Therefore, a meta-analysis is needed as a combined research result that will be used to infer the parameters assessed in the study. This meta-analysis aimed to evaluate the correlation between platelet count and the grading of esophageal varices in liver cirrhosis patients.

Methods

Study design

This study is registered on PROSPERO (CRD42021293263). This meta-analysis study was conducted and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary file: Table S1-2).

Eligibility criteria

Studies were included if they met the following inclusion criteria: The predictor was low platelet count and outcomes of interest was esophageal varices, evaluate the correlation between platelet count and grading of esophageal varices in liver cirrhosis patients who underwent endoscopic examination, outcome reported as correlation coefficient, and articles published only in English. In addition, the exclusion criteria were articles other than original research (e.g., editorials, case reports, review articles, theses, books, or letters to editors) and articles that did not report a correlation coefficient.

Search strategy

A systematic literature search was performed on October 9, 2021, for all published articles, including preprints from PubMed, SCOPUS, Ovid EMBASE, and EuropePMC with the following search terms: “Correlation” AND “Platelet” OR “Thrombocytopenia” AND “Esophageal Varices” AND “Liver Cirrhosis” OR “Chronic Liver Disease” that was published within the year of 2000–2021. To obtain additional articles, manually searching from references of the relevant studies was also performed.

Selection of studies

All articles retrieved from the literature searches were exported to EndNote X9.3.3 bibliographic and reference manager (Clarivate Analytics LLC, Philadelphia, PA, USA, RRID: SCR_014001). All articles were checked for duplication, and after duplicated studies were excluded, authors independently screened the titles and abstracts of the selected articles to choose potentially articles. Once the potential articles were found, authors independently read the full text of each selected article and screened for their full text against the eligibility criteria. If an article did not meet one or more inclusion criteria, it was excluded from our study. Any disagreements were resolved through discussion until a common consensus was reached.

Quality assessment

The quality of each study was assessed with the Newcastle Ottawa Scale (NOS) by two reviewers. This tool evaluates the quality of studies based on three items: Selecting participants and measuring exposure, comparability, and the adequacy of results and follow-up. Each item has subitems on which a star-based score was assigned. The scale awards up to 9 stars per study.

Studies with scores ≥7 were considered to have a low risk of bias, scores of 4–6 as having a high risk of bias, and scores <4 as a very high risk of bias [22]. Studies with total scores of 4 or less were excluded due to a very high risk of bias. The discrepancy in the assessment score was resolved by discussion to reach an agreement.

Data extraction

Microsoft Excel Office 2019 (Microsoft Corporation, Redmond, WA, USA, SCR_016137) was used to tabulate the extracted data. The data extracted included: Authors name, publication year, publication type, study location, study design, number of samples, mean (SD) or median (IQR) platelet count, grading of esophageal varices, and correlation coefficient of each included study.

Data analysis

For studies that reported correlation coefficient, the overall correlation coefficient (r) was calculated with MedCalc® Statistical Software version 20.011 (MedCalc Software Ltd, Ostend, Belgium, RRID: SCR_015044). The fixed or random-effect model was used based on

the heterogeneity test, and statistical heterogeneity was determined using I-squared (I^2). A value >50% indicates a statistically significant heterogeneity. We used a random-effects model if I^2 was greater than 50% in this study. Otherwise, fixed-effects models were used if I^2 was less than or equal to 50%. The result of the analysis was presented in a forest plot.

Subgroup analysis was performed based on grades of esophageal varices (EV grade I, EV grade II, and EV grade III) to determine the association between platelet count among different grades of esophageal varices and to explore causes of heterogeneity among studies. For studies that reported the means and standard deviation, pooled standardized mean difference (SMD) and the 95% confidence interval (95%CI) were calculated using the inverse variance method. Data were reported as medians, and interquartile was converted into means and standard deviation using the method by Hozo *et al*. [23].

Sensitivity analysis was performed using the leave-one-out method, where one study is omitted at a time, and the result of omitting each of the studies is evaluated and presented in summary tables. The sensitivity analysis was conducted to assess each study's effect on the pooled effect size to find if the overall estimate depended on the effect size from a single study and identify any source of heterogeneity [24].

Publication bias was assessed quantitatively using Begg's and Egger's tests. Publication bias is present if Begg's and Egger's test produces a $p < 0.1$ [25]. It was suggested that a minimum of ten studies were needed in meta-analysis to use funnel plots due to the low power of the tests when there are fewer studies [26].

Results

Search results

A total of 134 articles were identified from databases and other sources searching. After removing duplicate and screened identified articles, 14 articles were retained. After the full-text articles were reviewed, according to the eligibility criteria, eight articles met the inclusion criteria and were selected for the meta-analysis. The details of the search result were outlined in the PRISMA flow diagram (Figure 1).

Study characteristics

The characteristics of the included studies are shown in Table 1. This meta-analysis included eight articles comprising 1008 patients. Among these studies, one study was conducted in China [12], two studies were conducted in Egypt [20], [21], one study was conducted in India [26], three studies were conducted in Pakistan [10], [19], [27], [28], and one study was conducted in Singapore [28]. Three studies were prospective observational [12], [20], [21] and five were cross-sectional [10], [19], [27], [28], [29]. The NOS

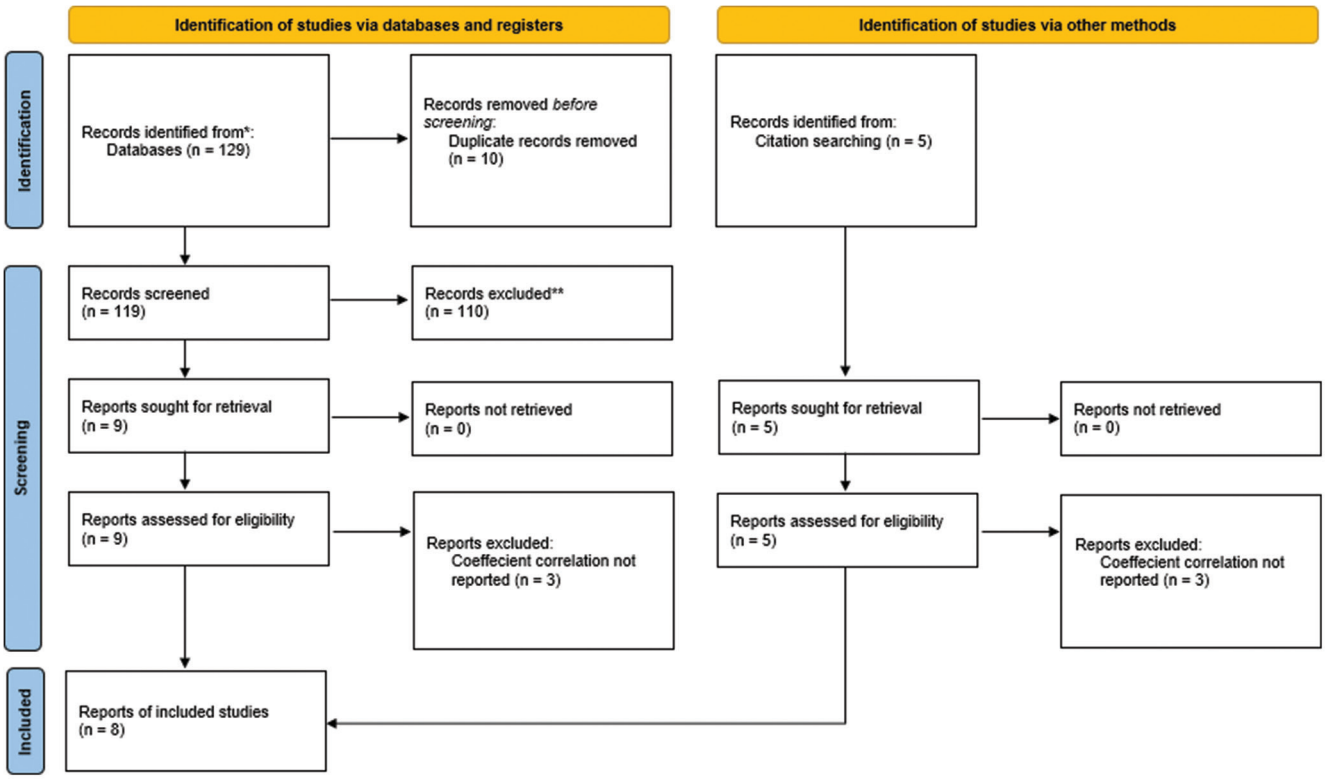

Figure 1: PRISMA flow diagram

Table 1: Characteristics of studies

Author	Year	Location	Study design	Sample (N)	Platelet (*10^9/ul) Mean ± SD/Median (IQR)					NOS score
					No EV	EV grade I	EV grade II	EV grade III	EV grade IV	
Abbasi *et al.* [28]	2010	Pakistan	RO	102	NR	NR	NR	NR	NR	7
Abd-Elsalam *et al.* [20]	2016	Egypt	PO	110	NR	NR	NR	NR	NR	8
Afsar *et al.* [19]	2021	Pakistan	RO	110	NR	213,6 ± 86,8	119,5 ± 68,9	58,4 ± 34,4	21 ± 16,6	7
Divya *et al.* [27]	2020	India	RO	77	NR	130 (104-182)	115 (99-161)	90 (42-153)	NR	7
El-Din Nouh *et al.* [21]	2018	Egypt	PO	210	152,1 ± 17,1	100,5 ± 19,8	65,2 ± 13,0	60,3 ± 14,1	NR	8
Gue *et al.* [29]	2004	Singapore	RO	200	NR	NR	NR	NR	NR	7
Javed *et al.* [10]	2021	Pakistan	RO	105	NR	149 ± 22	122 ± 26	100 ± 23	98 ± 22	7
Liu *et al.* [12]	2020	China	PO	94	122 (94-159,5)	93,5 (62,5-134,2)	79 (48,5-109,5)	65 (46,7-102,7)	NR	7

EV: Esophageal varices, IQR: Interquartile range; NOS: Newcastle-ottawa scale, NR: Not reported, PO: Prospective observational, RO: Retrospective observational, SD: Standard deviation.

scores ranged between 7 and 8. It was identified that all of the included studies had a low risk of bias.

Platelet count and grading of esophageal varices

From eight studies consisting of 1008 patients, seven studies reported a negative correlation between platelet count and grading of esophageal varices in liver cirrhosis patients [12], [19], [20], [21], [27], [28], [29], while one study reported a positive correlation coefficient [10]. A meta-analysis was done on eight eligible studies, the result of the forest plot showed that there is a significant moderate negative correlation between platelet count and grading of esophageal varices in liver cirrhosis patients, with a pooled correlation coefficient (r) of –0.42 (95%CI –0.65 to –0.13; p = 0.005) (Figure 2). A random-effect model was used to determine that the total pooled effect (Table 2) due significant heterogeneity was found (I^2 = 96.06%; p ≤ 0.001) (Table 3).

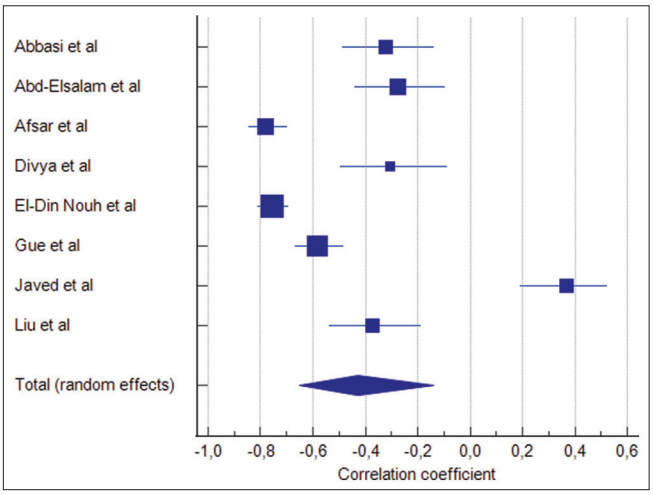

Figure 2: Forest plot of correlation coefficient between platelets count and grading of esophageal varices

As the included studies for meta-analysis are less than ten studies, therefore in this meta-analysis, the publication bias was not assessed with funnel plot but with Begg's and Egger's test instead. This method provides a more objective way of identifying publication bias than the highly subjective funnel plots [30]. Calculated Begg's test (p = 0.256) and Egger's test (p = 0.133) showed no publication bias (Table 4). The sensitivity analysis showed that the overall pooled effect and heterogeneity had no significant change after omitting each study (Supplementary file: Table S3).

Subgroup analysis of the association between platelet count and grades of esophageal varices

Patients were divided into three subgroups based on their esophageal varices grades (EV grade I, EV grade II, and EV grade III) and the association between platelet count among different grades of esophageal varices was compared (Table 5). In terms of platelet count, the subgroup analysis showed a significant difference in SMD among different grades of esophageal varices. In addition, subgroup analysis showed that patients with the highest esophageal varices grades (EV grade III) had the lowest platelet count than other esophageal varices grades, with an SMD of –4.58 (95% CI -6.75 to –2.41; p < 0.001). However, significant heterogeneity was found in these studies.

Discussion

Our meta-analysis aimed to evaluate the overall pooled correlation coefficient between platelet count and grading of esophageal varices in liver cirrhosis patients. Our meta-analysis showed a significant moderate negative correlation between platelet count and grading of esophageal varices in liver cirrhosis patients. Subgroup analysis based on grades of esophageal varices also showed that the lower platelet counts are associated with grades of esophageal varices. Our findings provide evidence that as the platelet count decreased, the grading of esophageal varices increased, suggesting that the platelet count can serve as a non-invasive indicator to predict the grading of esophageal varices in the liver cirrhosis patients. Platelet count is an ideal parameter since platelet count is simple, easy, and inexpensive to perform.

Irreversible fibrosis in the liver caused by chronic liver inflammation was defined as liver cirrhosis which is complicated by portal hypertension [31]. Esophageal varices were a condition in which

Table 2: The correlation coefficient of platelet count and esophageal varices in the included study

Author	Sample (N)	Correlation coefficient	CI (95%)		z	p	Weight (%)
			Lower Limit	Upper Limit			Random
Abbasi *et al*. [28]	102	–0.32	–0.48	–0.13			12.44
Abd-Elsalam *et al*. [20]	110	–0.27	–0.44	–0.09			12.48
Afsar *et al*. [19]	110	–0.78	–0.84	–0.69			12.48
Divya *et al*. [27]	77	–0.30	–0.49	–0.08			12.24
El-Din Nouh *et al*. [21]	210	–0.75	–0.80	–0.69			12.76
Gue *et al*. [29]	200	–0.58	–0.66	–0.48			12.74
Javed *et al*. [10]	105	0.37	0.19	0.52			12.46
Liu *et al*. [12]	94	–0.37	–0.53	–0.18			12.39
Total (random effects)	1008	–0.42	–0.65	–0.13	–2.81	0.005	100.00

CI; confidence interval.

there are abnormally dilated collateral veins within the esophagus wall and a common complication of portal hypertension [20]. Esophageal varices bleeding is associated with mortality and morbidity in liver cirrhosis patients [32].

Table 3: The result of heterogeneity test

Variables	Result
Q	177.56
DF	7
Significance level	p<0.001
I^2	96.06%
95% CI for I^2	94.02–97.40

CI: confidence interval

Decreased platelet count or thrombocytopenia is a common manifestation in liver cirrhosis patients. It was estimated that 84% of liver cirrhosis patients had a low platelet count [33]. Consensus also recommends that screening endoscopy be exempted in liver cirrhosis patients with platelet count >150.000/ul [15]. Although platelet count can be influenced by other causes, such as comorbidities [20], the platelet count is significantly inversely correlated with esophageal varices and has been confirmed as a valuable parameter to predict the presence and grading of esophageal varices [34], [35].

Table 4: The result of publication bias

Publication bias	p
Begg's test	0.256
Egger's test	0.133

The mechanism of thrombocytopenia in liver cirrhosis patients is multifactorial; there are three primary mechanisms: Decreased platelet production, increased platelet destruction, and platelet sequestration [31]. Decreased platelet production caused by a decrease of thrombopoietin (TPO). TPO is secreted from healthy hepatocytes and functions as the regulator of platelet production, mainly to stimulate thrombopoiesis. There was platelet deficiency in chronic liver disease such as liver cirrhosis due to decreased amount of TPO [36]. Other etiologies are caused by bone marrow suppression by infection and the adverse effect of medication [31]. Increased platelet destruction was caused by rapid degradation of platelet mediated by platelet-associated IgG, shear stress, and sepsis [32], [37]. Sequestration process, which is a sequela of portal hypertension, results in an enlarged spleen, which causes a redistribution of blood flow and platelet from circulation to spleen and lead to pooling of platelets and splenic sequestration of platelets [31], [37].

Precise mechanisms regarding the association between low platelet counts to the presence of esophageal varices remain unclear, and its pathogenesis remains to be clarified, although portal hypertension is thought to play a central role. Portal hypertension is often the initial and primary consequence of liver cirrhosis and is responsible for thrombocytopenia and esophageal varices [38]. Specifically, portal hypertension increases splenic arterial blood flow and diminishes splenic venous flow into the portal vein lead to congestive splenomegaly, which is a condition when intrasplenic blood flow congested and spleen enlargement, resulting in increased flow through the splenoportal axis that leads to thrombocytopenia and esophageal varices [38], [39].

Low platelet count and esophageal varices tend to correlate with the degree of portal hypertension [40]. Thus, the greater degree of portal hypertension is associated with a greater risk of developing complications such as thrombocytopenia and esophageal varices [38]. Hence, the association of platelet count to the presence of varices is probably a reflection of the degree of portal hypertension [41].

Our meta-analysis showed noticeable heterogeneity in all of the included studies. Therefore, we conducted a sensitivity analysis and subgroup analysis to investigate the source of heterogeneity. However, it could not identify the source of heterogeneity. The result of the overall pooled correlation coefficient was not significantly changed after conducting sensitivity analysis. Our meta-analysis did not investigate heterogeneity by meta-regression due to the small number of included studies. Studies suggest a minimum of ten studies were needed for meta-regression [26].

The heterogeneity in this meta-analysis may be caused by differences in the characteristics of the sample from each study, including age, gender, etiology of liver cirrhosis, the severity of liver disease, and comorbidities. In addition, the sensitivity and subgroup analysis results were consistent with the overall results, indicating that the result of this study was robust.

To the best of our knowledge, this is the first meta-analysis to assess the correlation between platelet count and grading of esophageal varices in liver cirrhosis patients. This meta-analysis suggests that platelet count can be used as a reliable screening method for predicting the grading of esophageal varices in liver cirrhosis patients. This method may help clinicians in healthcare

Table 5: Subgroup analysis of the association between platelet count and grades of esophageal varices

	Subgroup	Number of studies	Pooled SMD (95% CI)	p-value	Heterogeneity test	
					p-value	I^2
Grades of esophageal varices	Esophageal varices grade I	2	–2.19 (–3.39, –0.99)	< 0.001	< 0.001	90%
	Esophageal varices grade II	2	–4.20 (–6.72, –1.67)	< 0.001	< 0.001	94%
	Esophageal varices grade III	2	–4.58 (–6.75, –2.41)	< 0.001	< 0.001	90%

CI: confidence interval.

facilities with limited medical resources where endoscopy is not readily available to give appropriate primary prophylactic therapy and identify high-risk patients that need a referral to the tertiary hospital for endoscopic examination [21], [42]. In health-care facilities where endoscopy is readily-available this parameter can help clinicians to select patients who need an endoscopy, thereby avoiding unnecessary endoscopy [42].

There were some limitations to this meta-analysis. First, the number of included studies and the sample size were relatively small, which interpretation of our meta-analysis findings might be limited. Second, we noticed significant heterogeneity among the included studies. Third, only English articles were included in this meta-analysis. Thus, there may be differences when including non-English articles.

Conclusion

Based on the result of this study, it can be concluded that there is a moderate negative correlation between platelet count and grading of esophageal varices in liver cirrhosis patients. Thus, low platelet count may indicate higher grades of esophageal varices in liver cirrhosis patients. Therefore, these findings are beneficial and should be considered in the clinical management of liver cirrhosis patients.

References

1. Rye K, Scott R, Mortimore G, Lawson A, Austin A, Freeman J. Towards noninvasive detection of oesophageal varices. Int J Hepatol. 2012;2012:343591. http://doi.org/10.1155/2012/343591
   PMid:22506126
2. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117-71. http://doi.org/10.1016/S0140-6736(14)61682-2
   PMid:25530442
3. GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2020;5(3):245-66. http://doi.org/10.1016/S2468-1253(19)30349-8
   PMid:31981519
4. Shin SU, Lee JM, Yu MH, Yoon JH, Han JK, Choi BI, *et al*. Prediction of esophageal varices in patients with cirrhosis: Usefulness of three-dimensional MR elastography with echo-planar imaging technique. Radiology. 2014;272(1):143-53. http://doi.org/10.1148/radiol.14130916
   PMid:24620910
5. Kraja B, Mone I, Akshija I, Koçollari A, Prifti S, Burazeri G. Predictors of esophageal varices and first variceal bleeding in liver cirrhosis patients. World J Gastroenterol. 2017;23(26):4806-14. http://doi.org/10.3748/wjg.v23.i26.4806
   PMid:28765702
6. Al-Busafi SA, McNabb-Baltar J, Farag A, Hilzenrat N. Clinical manifestations of portal hypertension. Int J Hepatol. 2012;2012:203794. http://doi.org/10.1155/2012/203794
   PMid:23024865
7. Ismail FW, Shah HA, Hamid S, Abbas Z, Abid S, Mumtaz K, *et al*. Noninvasive predictors of large varices in patients hospitalized with gastroesophageal variceal hemorrhage. Hepatol Int. 2008;2(1):124-8. http://doi.org/10.1007/s12072-007-9034-1
   PMid:19669288
8. Nada L, Samira el F, Bahija B, Adil I, Nourdine A. Noninvasive predictors of presence and grade of esophageal varices in viral cirrhotic patients. Pan Afr Med J. 2015;20:145. http://doi.org/10.11604/pamj.2015.20.145.4320
   PMid:27386022
9. Jairath V, Rehal S, Logan R, Kahan B, Hearnshaw S, Stanworth S, *et al*. Acute variceal haemorrhage in the United Kingdom: Patient characteristics, management and outcomes in a nationwide audit. Dig Liver Dis. 2014;46(5):419-26. http://doi.org/10.1016/j.dld.2013.12.010
   PMid:24433997
10. Javed M, Mohammad D, Masood Z, Sheikh G, Iftikhar M, Hamed A. To determine the correlation between mean platelet count and frequency of grading of esophageal varices in patients of liver cirrhosis. Prof Med J. 2021;28(6):833-41. https://doi.org/10.29309/TPMJ/2021.28.06.6258
11. D'Amico G, Morabito A. Noninvasive markers of esophageal varices: Another round, not the last. Hepatology. 2004;39(1):30-4. http://doi.org/10.1002/hep.20018
    PMid:14752818
12. Liu H, Chen P, Jiang B, Li F, Han T. The value of platelet parameters and related scoring system in predicting esophageal varices and collateral veins in patients with liver cirrhosis. J Clin Lab Anal. 2021;35(3):e23694. http://doi.org/10.1002/jcla.23694
    PMid:33389784
13. Supriyanto I, Suyata S, Rasyad SB, Bakry F. Correlation between aspartate aminotransferase to platelet ratio index score and the degree of esophageal varices with liver cirrhosis. Indones J Gastroenterol Hepatol Dig Endosc. 2012;13(3):141-144. https://doi.org/10.24871/1332012141-144
14. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology. 2017;65(1):310-35. http://doi.org/10.1002/hep.28906
    PMid:27786365
15. de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63(3):743-52. http://doi.

org/10.1016/j.jhep.2015.05.022
PMid:26047908

16. Tafarel JR, Tolentino LH, Correa LM, Bonilha DR, Piauilino P, Martins FP, *et al*. Prediction of esophageal varices in hepatic cirrhosis by noninvasive markers. Eur J Gastroenterol Hepatol. 2011;23(9):754-8. http://doi.org/10.1097/MEG.0b013e3283488a88
PMid:21691209
17. Giannini EG, Zaman A, Kreil A, Floreani A, Dulbecco P, Testa E, *et al*. Platelet count/spleen diameter ratio for the noninvasive diagnosis of esophageal varices: Results of a multicenter, prospective, validation study. Am J Gastroenterol. 2006;101(11):2511-9. http://doi.org/10.1111/j.1572-0241.2006.00874.x
PMid:17029607
18. Sheikh MY, Raoufi R, Atla PR, Riaz M, Oberer C, Moffett MJ. Prevalence of cirrhosis in patients with thrombocytopenia who receive bone marrow biopsy. Saudi J Gastroenterol. 2012;18(4):257-62. http://doi.org/10.4103/1319-3767.98431
PMid:22824769
19. Afsar A, Nadeem M, Shah SA, Hussain H, Rani A, Ghaffar S. Platelet count can predict the grade of esophageal varices in cirrhotic patients: A cross-sectional study. F1000Res. 2021;10:101. http://doi.org/10.12688/f1000research.28005.2
PMid:35035881
20. Abd-Elsalam S, Habba E, Elkhalawany W, Tawfeek S, Elbatea H, El-Kalla F, *et al*. Correlation of platelets count with endoscopic findings in a cohort of Egyptian patients with liver cirrhosis. Medicine (Baltimore). 2016;95(23):e3853. http://doi.org/10.1097/MD.0000000000003853
PMid:27281094
21. Nouh MA, Ali KA, Badawy AM, El-Daly AH. Correlation of thrombocytopenia with grading of esophageal varices in chronic liver disease patients. Menoufia Med J. 2018;31(2):588-93. https://doi.org/10.4103/1110-2098.239725
22. Lo C, Mertz D, Loeb M. Newcastle-Ottawa Scale: Comparing reviewers' to authors' assessments. BMC Med Res Methodol. 2014;14:45. https://doi.org/10.1186/1471-2288-14-45
PMid:24690082
23. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13. http://doi.org/10.1186/1471-2288-5-13
PMid:15840177
24. Patsopoulos NA, Evangelou E, Ioannidis JP. Sensitivity of between-study heterogeneity in meta-analysis: Proposed metrics and empirical evaluation. Int J Epidemiol. 2008;37(5):1148-57. http://doi.org/10.1093/ije/dyn065
PMid:18424475
25. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: Power of statistical tests and prevalence in the literature. J Clin Epidemiol. 2000;53(11):1119-29. http://doi.org/10.1016/s0895-4356(00)00242-0
PMid:11106885
26. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, *et al*., editors. Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (Updated February 2021). Chichester (UK): Cochrane; 2021. Available from: https://www.training.cochrane.org/handbook [Last accessed on 2021 Oct 17].
27. Divya S, Nagarajan K, Thirumal P. A study of correlation between platelet count and severity of esophageal varices in patients with chronic liver disease. IOSR J Dent Med Sci. 2020;19(12):38-43. https://doi.org/10.9790/0853-1912013843
28. Abbasi A, Butt N, Bhutto AR, Munir SM. Correlation of thrombocytopenia with grading of esophageal varices in chronic liver disease patients. J Coll Physicians Surg Pak. 2010;20(6):369-72. http://doi.org/06.2010/JCPSP.369372
PMid:20642964
29. Gue CS, Yap CK, Ng HS. The correlation between cytopenia and esophageal varices in patients with liver cirrhosis. Med J Malaysia 2004;59(5):604-8.
30. Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Stat Med. 2001;20(4):641-54. http://doi.org/10.1002/sim.698
PMid:11223905
31. Hasan I, Jasirwan C, Loho I, Nababan S, Zulkifly S, Handayu A. Non-invasive predictors of moderate large esophageal varices in compensated cirrhotic patients. J Gastroenterol Hepatol Res. 2021;10(2):3478-82. https://doi.org/10.17554/j.issn.2224-3992.2021.10.1000
32. Sarangapani A, Shanmugam C, Kalyanasundaram M, Rangachari B, Thangavelu P, Subbarayan JK. Noninvasive prediction of large esophageal varices in chronic liver disease patients. Saudi J Gastroenterol. 2010;16(1):38-42. http://doi.org/10.4103/1319-3767.58767
PMid:20065573
33. Sigal SH, Sherman Z, Jesudian A. Clinical Implications of Thrombocytopenia for the Cirrhotic Patient. Hepat Med. 2020;12:49-60. http://doi.org/10.2147/HMER.S244596
PMid:32341665
34. Kumar P, Singh K, Joshi A, Thakur P, Mahto SK, Kumar B, *et al*. Evaluation of non-invasive marker of esophageal varices in cirrhosis of liver. J Family Med Prim Care. 2020;9(2):992-6. http://doi.org/10.4103/jfmpc.jfmpc_854_19
PMid:32318456
35. Priyadarshi B, Khan I, Kumar V, Verma A, Midha T, Madhuri S, *et al*. Study the association between platelets count and grades of oesophageal varies in patients of cirrhosis of liver with portal hypertension. Int J Adv Med. 2020;7(4):603. https://doi.org/10.18203/2349-3933.ijam20201108
36. Miller JB, Figueroa EJ, Haug RM, Shah NL. Thrombocytopenia in Chronic Liver Disease and the Role of Thrombopoietin Agonists. Gastroenterol Hepatol (N Y). 2019;15(6):326-32.
37. Mitchell O, Feldman DM, Diakow M, Sigal SH. The pathophysiology of thrombocytopenia in chronic liver disease. Hepat Med. 2016;8:39-50. http://doi.org/10.2147/HMER.S74612
PMid:27186144
38. Saab S, Bernstein D, Hassanein T, Kugelmas M, Kwo P. Treatment options for thrombocytopenia in patients with chronic liver disease undergoing a scheduled procedure. J Clin Gastroenterol. 2020;54(6):503-11. http://doi.org/10.1097/MCG.0000000000001338
PMid:32195771
39. Hasan SM, Dmitriew M, Leonard J. Variceal bleed and portal hypertensive gastropathy in a noncirrhotic patient with isolated splenomegaly. Case Reports Hepatol. 2020;2020:8893713. http://doi.org/10.1155/2020/8893713
PMid:33381333
40. Brown RS Jr. Current management of thrombocytopenia in chronic liver disease. Gastroenterol Hepatol (N Y). 2019;15(3):155-7.
PMid:31061657
41. Zaman A, Becker T, Lapidus J, Benner K. Risk factors for the presence of varices in cirrhotic patients without a history of variceal hemorrhage. Arch Intern Med. 2001;161(21):2564-70. http://doi.org/10.1001/archinte.161.21.2564
PMid:11718587
42. Esmat S, Rashid L. A comparative study between three noninvasive predictors of oesophageal varices in post hepatitis C virus liver cirrhosis in Egypt. Acta Gastroenterol Belg 2011;74(4):497-502.
PMid:22319958

Supplementary

Table S1: PRISMA 2020 checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	N/A
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 2
Objectives	4	Provide an explicit statement of the objective (s) or question (s) the review addresses.	Page 2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	-
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	-
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4
Effect measures	12	Specify for each outcome the effect measure (s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Page 3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used.	Page 3-4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 5
Study characteristics	17	Cite each included study and present its characteristics.	Page 5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 6-8. Supplementary files
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 6-8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 6, Supplementary files
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 8
	23b	Discuss any limitations of the evidence included in the review.	Page 9
	23c	Discuss any limitations of the review processes used.	Page 9
	23d	Discuss implications of the results for practice, policy, and future research.	Page 9-10
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title page
Competing interests	26	Declare any competing interests of review authors.	Title page
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

Table S2: PRISMA Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	No
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective (s) or question (s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No

Table S3: The result of sensitivity analysis

Omitted study	Correlation coefficient	CI (95%)		p	I^2 (%)
		Lower Limit	Upper Limit		
Abbasi *et al*. [28]	−0.44	−0.68	−0.11	0.009	96.53
Abd−Elsalam *et al*. [20]	−0.44	−0.68	−0.12	0.008	96.46
Afsar *et al*. [19]	−0.35	−0.60	−0.04	0.027	95.89
Divya *et al*. [27]	−0.44	−0.68	−0.12	0.008	96.54
El−Din Nouh *et al*. [21]	−0.36	−0.60	−0.05	0.021	95.21
Gue *et al*. [29]	−0.40	−0.66	−0.04	0.028	96.54
Javed *et al*. [10]	−0.52	−0.67	−0.32	<0.001	92.45
Liu *et al*. [12]	−0.43	−0.67	−0.10	0.011	96.58
Total (random effects)	−0.42	−0.65	−0.13	0.005	96.06
Registration	12	Provide the register name and registration number.			No

CI: confidence interval.