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

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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 correlation coefficient (r) of the pooled correlation was -0.42 (95%CI -0.65 to -0.13; p = 0.005; I² = 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
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
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).

**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...
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 | Q | DF | Significance level | 95% CI for I² |
|-----------|---|----|-------------------|----------------|
| Q         | 177.56 | 9  | p<0.001           | 96.06%         |
| I²        | 94.02–97.40 | 9  |                  |                |

Decreased platelet count or thrombocytopenia is a common manifestation in liver cirrhosis. 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 |

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 splenopetal 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
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.

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### Supplementary

**Table S1: PRISMA 2020 checklist**

| Item | Topic | No. | Location where item is reported |
|------|-------|-----|---------------------------------|
| I. Title | 1 | Identify the report as a systematic review. | N/A |
| II. Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | Page 2 |
| I. Introduction | 3 | Describe the rationale for the review in the context of existing knowledge. | Page 2 |
| II. Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Page 2 |
| III. Methods | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Page 3 |
| V. 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 |
| V. Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Page 3 |
| V. 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 record retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Page 3 |
| V. 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 |
| V. 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. | - |
| V. Data items | 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. | - |
| V. 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 |
| V. 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 |
| V. 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 |
| V. Synthesis methods | 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 |
| V. Synthesis methods | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Page 3 |
| V. Synthesis methods | 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 |
| V. Synthesis methods | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Page 4 |
| V. Synthesis methods | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Page 4 |
| V. 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 |
| V. Certification 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 |
| Study selection | 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 applicable) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Page 5-8. Supplementary files |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Page 5 |
| Results of syntheses | 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 5-8 |
| Results of syntheses | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Page 9 |
| 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 |
| 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 |
| Registration and protocol | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | - |
| Registration and protocol | 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                        | 1   | Identify the report as a systematic review.                         | No        |
| BACKGROUND                   | 2   | Provide an explicit statement of the main objective(s) or question(s) the review addresses. | Yes       |
| METHODS                      | 3   | Specify the inclusion and exclusion criteria for the review.        | Yes       |
| Eligibility criteria         | 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       |
| INCLUDED STUDIES             | 7   | Give the total number of included studies and participants and summarise relevant characteristics of studies. | Yes       |
| 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                   | 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                        | 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     | I² (%) |
|---------------|--------------------------|----------|-------|--------|
|               |                          | Lower Limit | Upper Limit |       |
| Abbasi et al. [28] | -0.44                  | -0.68 | -0.11 | 0.009  | 98.53 |
| 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 |
| Guo 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  | 98.58 |
| Total (random effects) | -0.42                  | -0.65 | -0.13 | 0.005  | 96.06 |

CI: confidence interval.