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Authors:
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Association between platelet indices and non-alcoholic fatty liver disease: a systematic review and meta-analysis

Li Li[1], Jianxiu Yu[1], Zhongwei Zhou[2*]

[1] Department of Clinical Laboratory, Binhai County People's Hospital, Binhai, Jiangsu 224500, China

[2] Department of Clinical Laboratory, Yancheng Third People's Hospital (The Yancheng School of Clinical Medicine of Nanjing Medical University, The Sixth Affiliated Hospital of Nantong University, The Affiliated Yancheng Hospital of Southeast University Medical College), Yancheng, Jiangsu 224001, China

[*] **Corresponding author: Zhongwei Zhou**

Department of Clinical Laboratory, Yancheng Third People's Hospital, No. 75 Juchang Road, Tinghu, Yancheng, Jiangsu 224001, China

E-mail: 001zzw@163.com

Abbreviations list:

NAFLD, non-alcoholic fatty liver disease; PC, platelet count; MPV, mean platelet volume; PDW, platelet distribution width; SMD, standardized mean difference; CI, confidence interval; NASH, non-alcoholic steatohepatitis; CLD, common chronic liver disease; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NOS, the Newcastle-Ottawa Quality Assessment Scale.

ABSTRACT

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Background: Platelet indices have the potential for the evaluation of the activity of non-alcoholic fatty liver disease (NAFLD), but their associations are under hard debate. This meta-analysis aims to assess whether platelet count (PC), mean platelet volume (MPV) and platelet distribution width (PDW) are associated with NAFLD and its progression.

Methods: A literature search was conducted using electronic databases to find publications up to July 2022, where the relationship between PC, MPV, PDW and NAFLD was evaluated. Random-effect**s** models were applied to pool effect estimates that were presented as standardized mean differences (SMD) with 95% confidence interval (CI).

Results: Nineteen studies involving 3592 NAFLD patients and 1194 healthy individuals were included. The pooled results showed that NAFLD patients had a lower PC (SMD=−0.66, 95% CI =−1.22 to −0.09, *P*=0.023) but a higher MPV (SMD=0.89, 95% CI=0.26-1.51, *P*=0.005) and PDW (SMD=0.55, 95% CI=0.11-0.99, *P*=0.014) compared to healthy controls. Patients with non-alcoholic steatohepatitis (NASH) exhibited a lower PC (SMD=−0.86, 95% CI=−1.20 to −0.52, *P*<0.001) and a higher MPV (SMD=0.71, 95% CI=0.40-1.02, *P*<0.001) than non-NASH individuals. A meta-regression analysis demonstrated that MPV was significantly positively correlated with aspartate aminotransferase (*P*=0.008), the total cholesterol (*P*=0.003), triglyceride (*P*=0.006) and low-density lipoprotein cholesterol (*P*=0.007), but was significantly negatively correlated with high-density lipoprotein cholesterol (*P*=0.010).

Conclusion: This meta-analysis revealed that NAFLD patients presented a reduced PC but an increased MPV and PDW, and the changes might be associated with NAFLD severity. A higher MPV is associated with lipid metabolic disorders in NAFLD.

Keywords: Platelet count. Mean platelet volume. Platelet distribution width. Non-alcoholic fatty liver disease. Meta-analysis.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a common chronic liver disease (CLD) globally, associated with the growing obesity epidemic today (1,2). The clinicopathological spectrum of NAFLD covers a mild-to-severe range from simple steatosis (SS) to non-alcoholic steatohepatitis (NASH) and then to NASH-related fibrosis or cirrhosis (3). Although the exact mechanisms of NAFLD have not been fully elucidated, it is generally believed that inflammation and fibrosis play significant roles in both the development of NASH and the subsequent development of liver cirrhosis as well as hepatocellular carcinoma (4,5). Up to now, the "gold standard" liver biopsy is still most widely accepted as an effective method of inflammation and fibrosis diagnosis, which is to assess NAFLD activity. However, liver biopsy is an invasive technique, with pains and many potentially serious complications (6,7). Therefore, more simple and effective methods for the measurement of its disease activity are expected.

Recent evidence suggests that platelet activation is one of the central processes tightly associated with the exacerbation of liver inflammation and the severity of fibrosis among patients with CLD such as hepatitis B (8). This progression, in turn, can be thwarted by the inhibition of platelet activation (9), which can be simply characterized by changes in common platelet indices, such as platelet count (PC), mean platelet volume (MPV) and platelet distribution width (PDW). In the recent decade, the association between platelet indices and NAFLD has been assessed in a large body of studies, but inconsistent and even contradictory results have been yielded in these studies. In a recent meta-analysis, the association between MPV and NAFLD was assessed, showing that MPV was elevated in NAFLD patients compared to healthy individuals (10). However, the association between NAFLD and other platelet indices remains controversial. For example, 13,737 subjects with NAFLD were recruited in a cross-sectional study by Okushin et al., in which a positive correlation was found between the PC and NAFLD incidence among male and female populations (11), whereas another prospective cohort study by Liu et al. showed that patients were at an increased risk of NAFLD when PC was reduced (12). Therefore, this meta-analysis was to overview existing literatures on the association between

PC, MPV, PDW and NAFLD. Meanwhile, we updated the prior meta-analysis in which the association between MPV and NAFLD was assessed.

MATERIALS AND METHODS

This systematic review was performed in accordance with the PRISMA reporting checklist, and the protocol had been registered at INPLASY (registration number: INPLASY202220069). Since this study was a systematic review based on published literatures, ethics approval and patients' consent was not required.

Search Strategy and Study Selection

We systematically searched PubMed, EMBASE, Web of Science and China National Knowledge Internet to retrieve relevant studies up to 25 July 2022. Key search terms included: ("NAFLD", "NASH" OR "fatty liver") AND ("platelet count", "platelet number", "mean platelet volume", "MPV", "platelet distribution width" OR "PDW"). All citations from the bibliography of selected articles were reviewed, and those concerning the measurement of NAFLD as well as platelet were manually retrieved.

Studies were included if they met the following criteria: (1) participants aged ≥ 18 years; (2) studies comparing PC, MPV or PDW between NAFLD patients and healthy individuals, or between NASH and non-NASH; (3) full text articles available in English or Chinese language. The following exclusion criteria were set: (1) studies using overlapping samples; (2) those offering incomplete raw data; (3) reviews, case reports, letters, conference abstracts, editorials, and animal or *in vitro* experiments.

Data Extraction

Data extraction was carried out independently by two researchers and checked by a third reviewer. Any disagreement was resolved through discussion. We categorized study information into the following four dimensions. First of all, study characteristics included the first author's name, publication year, study location, study design and the diagnostics of NAFLD. The second category referred to platelet

indices and study population (including the sample size and proportion of the male population in the case as well as control groups). Basic clinical characteristics including age, gender, and body mass index (BMI) were classified to the third category. Lastly, NAFLD-related biochemical measurements were extracted for an association analysis with platelet indices including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), the total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). It is worth mentioning that we did not extract some important parameters related to liver functions or fibrosis, such as serum albumin, total bilirubin and coagulation indices, because they were rarely reported in the studies included.

Quality Assessment

The methodological quality of studies included was assessed using a modified criterion based on the Newcastle-Ottawa Quality Assessment Scale (NOS) (13). Studies were subject to the modified 9-item checklist with three domains: selection, comparability and outcome. We applied the quality category as follows: 7-9 was regarded as high-quality, 3-6 as moderate-quality, and under 3 as low-quality.

Statistical Analysis

All statistical analyses were performed using Stata15.0 (StataCorp LP, College Station, T.X., USA). Standardized mean differences (SMD) and a 95% confidence interval (CI) of platelet indices between pairwise comparisons were calculated for each study. A more conservative random-effects model provides better estimates with a wider CI than a fixed-effects model used for data pooling (14). Statistical heterogeneity between studies was assessed using the standard x^2 test with a significance set at $P < 0.10$, which was quantified using I^2 statistics (15). An I^2 statistic value > 50% indicates substantial heterogeneity. A meta-regression analysis was performed to evaluate the potential sources of heterogeneity. The pre-defined

independent variables included study location (Asia vs. non-Asia), study design (cross-sectional design vs. case-control design), diagnostics of NAFLD (ultrasound vs. liver biopsy), age, the percentage of males, BMI, ALT, AST, ALP, GGT, TC, TG, HDL-C and LDL-C. A sensitivity analysis was performed by omitting one study and pooling the SMD for the others in each turn. Publication biases were determined by the Egger's test.

A *P* value of < 0.05 was considered statistically significant, unless otherwise noted.

RESULTS

Study Selection

As is shown in Figure 1, 1823 citations were retrieved in our database query. After eliminating 887 duplicates, we reviewed titles and abstracts from the remanent 936 articles and discarded 890 irrelevant ones. Subsequently, we read the full text of the 46 articles selected, 27 of which were excluded because of the omission of outcome data, non-use of English or Chinese, or overlapped patients' information. Ultimately, 19 studies were eligible for the meta-analysis (16-34).

Study Characteristics

The 19 studies were published from 2010 to 2021, involving 3592 NAFLD patients (including NASH and non-NASH cases) and 1194 healthy controls. Sixteen studies were cross-sectional, and 3 were case-control. 5 studies were carried out in China, 4 in Turkey, 2 in Japan, 2 in Egypt, 2 in Poland, and the other 4 in India, USA, Serbia, and Iran, respectively. The use of liver biopsy as NAFLD diagnostics was reported in 8 studies. Ultrasound techniques were used in 10 studies, and a combination of both approaches was applied in 1 study. Age, BMI, ALT, AST, ALP, GGT, TC, TG, HDL-C and LDL-C were reported in studies ranging from 7 to 16, with the characteristics detailed in Table 1.

According to the modified NOS checklist, 10 studies were considered high-quality (a score of ≥ 7), and the other 9 were rated as moderate-quality (4 ≤ NOS ≤

6). None of the studies included was graded as low-quality. More information on quality assessment is also provided in Table 1.

Platelet Indices of Patients and Healthy Controls

Results of platelet indices of NAFLD (including NASH and non-NASH) and healthy control subjects are summarized in Table 2. The number of cases and healthy individuals varied from 50 to 873 and from 41 to 217, with the number of male patients and male controls varying from 27 to 690 and from 11 to 119, respectively. Regarding comparisons among platelet indices diverse indices were compared only between NAFLD cases and controls in 13 studies (16-21,23,28-32,34). The comparisons between NASH and non-NASH cases were available in 5 studies without recruiting healthy controls (22,24,25,27,33). Notably, one study provided comprehensive pairwise comparisons of PC, MPV and PDW among NASH cases, non-NASH cases, and healthy controls (26).

Overall Meta-Analysis

We performed meta-analyses to compare platelet indices between NAFLD cases and healthy controls as well as between NASH and non-NASH cases, respectively. Generally, PC was significantly reduced (SMD=−0.66, 95% CI =−1.22 to −0.09, *P*=0.023, Figure 2A), while MPV (SMD=0.89, 95% CI=0.26-1.51, *P*=0.005, Figure 2B) and PDW (SMD=0.55, 95% CI=0.11-0.99, *P*=0.014, Figure 2C) were significantly elevated in NAFLD patients compared to healthy individuals.

In the comparison between patients with and without NASH, the former showed a significantly reduced PC (SMD=−0.86, 95% CI=−1.20 to −0.52, *P*<0.001, Figure 2D) but a significantly increased MPV (SMD=0.71, 95% CI=0.40-1.02, *P*<0.001, Figure 2E) compared with the latter.

Meta-Regression Analysis

We performed a random-effects meta-regression to explain the underlying effect of several independent variables (i.e., study location, study design, diagnostics of NAFLD, age, the percentage of males, BMI, ALT, AST, ALP, GGT, TC, TG, HDL-C, and LDL-C) on the estimated effect size of PC and MPV. The result of the regression analysis showed that PC was not significantly correlated with any of the above variables (all $P>0.05$). MPV was markedly associated with a higher AST ($P=0.008$, Figure 3A), TC ($P=0.003$, Figure 3B), TG ($P=0.006$, Figure 3C) and LDL-C ($P=0.007$, Figure 3D) in NAFLD patients. Additionally, we observed a significant negative association between MPV and HDL-C ($P=0.010$, Figure 3E). Other parameters were not significantly associated with MPV ($P > 0.05$).

Sensitivity Analysis and Publication Bias

Sensitivity analysis indicated that no individual study significantly affected the difference on PC and MPV in the comparison between NAFLD patients and healthy individuals.

There may be a slight publication bias in the pooled estimates of PC ($P = 0.055$ for Egger's test), but the bias was less likely for the estimates of MPV ($P = 0.154$ for Egger's test).

DISCUSSION

This meta-analysis demonstrated that patients with NAFLD had a significantly reduced PC, but a significantly elevated MPV and PDW compared to healthy individuals, and PC reduction as well as MPV elevation might be associated with NAFLD severity. Another important finding of this meta-analysis was that MPV was positively correlated with AST, TC, TG and LDL-C, while negatively correlated with HDL-C for NAFLD patients. As was indicated by our sensitivity analysis, no particular study strongly influenced the results. Generally, our results were relatively stable and reliable.

Low-level inflammation and different degrees of liver injuries were frequently detected in most patients with NAFLD, theoretically acting as primary platelet

activators and resulting in a higher PC (11,35). An opposite result was yielded through our meta-analysis that PC was reduced in NAFLD compared with healthy controls. Furthermore, all the 6 studies of PC comparisons between NASH and non-NASH cases provided the same conclusion, that is, a significant reduction of PC in patients with NASH. Therefore, other NAFLD-related factors leading to PC reduction should be considered, particularly those strongly offsetting the increase of PC via liver inflammation or injuries or both. As NAFLD is a common CLD, which is often comorbid with thrombocytopenia and whose severity has been proven to be associated with the extent of thrombocytopenia (36), the special attention may offer clues for PC reduction in NAFLD. Firstly, splenomegaly and portal hypertension are frequent complications of CLD, and there are a considerable percentage of patients with NAFLD combined with splenomegaly and portal hypertension, which is well known to be linked to the reduction of PC (37,38). Secondly, patients with NAFLD may have a decreased level of thrombopoietin (TPO). As TPO which is produced mainly in the liver is the major modulating factor of platelet production, it could be surmised that the level of TPO decreases in patients with CLD (39). Finally, CLD may contribute to an increase in the immunological destruction of platelets (40). Platelet-associated antibodies significantly increase in patients with CLD, which have been proposed as causative or contributing factors for the reduction of PC (41,42).

Madan et al. conducted a meta-analysis based on 8 studies on the association between MPV and NAFLD and offered a similar finding that MPV was significantly higher in NAFLD patients than that in healthy controls (10). Our upgraded meta-analysis of 13 studies on MPV provided stronger evidence supporting its significance for NAFLD. One of the major strengths of our study was that we explored the association between MPV and the related variables using a meta-regression, and an increased MPV was shown to be associated with AST, TC, TG, LDL-C, and HDL-C in patients with NAFLD. AST and ALT are common biochemical markers reflecting liver injuries, but the level of AST is superior to that of ALT in the diagnostic prediction of fibrosis development in CLD (43,44). TC, TG, HDL-C and LDL-C are the most critical lipid indices (45). Our results suggest that MPV may reflect the extent of fibrosis and lipid metabolic disorders in NAFLD. The higher MPV in patients with NAFLD may be

largely due to platelet activation induced by low-grade inflammation and liver injuries. In addition, an increased insulin resistance, which is another important characteristic of the disease (46), may contribute to a higher MPV, as a positive correlation between MPV and insulin resistance has been confirmed in numerous studies (47,48).

PDW is another parameter reflecting the size of platelets alongside MPV. Recently, the association between PDW and diverse diseases, including metabolic diseases, has gained increasing attention (49). PDW is often used to estimate platelet volume heterogeneity, and the elevated PDW is highly suggestive that platelet volume is heterogeneous (50). There are even reports indicating that PDW may be more sensitive than MPV in reflecting platelet activation (51,52). Our present meta-analysis demonstrated that PDW was significantly elevated in patients with NAFLD compared with healthy controls, which was similar with the pooled results of MPV. This suggests that PDW, like MPV, can be used as an effective index for evaluating platelet activation in patients with NAFLD.

There are several limitations that should be acknowledged. Firstly, statistical heterogeneity was observed in all pooled outcomes. In the meta-regression analysis, we observed a significant correlation between MPV and AST, TC, TG, HDL-C as well as LDL-C, suggesting that these parameters might partly explain the heterogeneity of pooled MPV results. Regrettably, existing information on insulin resistance and inflammatory factors in a few studies included, which may be major contributors to heterogeneity, was insufficient for conducting a meta-regression. Other important parameters related to CLD, such as serum albumin, total bilirubin and coagulation indices, were also rarely reported in the studies included, which called for more detailed studies. Secondly, the sample size was not quite large as a pooled analysis. Particularly, a relatively smaller number of included studies on PDW in comparisons between NAFLD and controls as well as those on PC and MPV in comparisons between NASH and non-NASH might reduce the statistical power and the credibility of the pooled results. In addition, only 1 study (26) provided comprehensive pairwise comparisons of platelet indices among all groups, which was insufficient for a meta-analysis on comparisons between NASH cases and controls as well as between non-

NASH cases and controls. Thirdly, comparisons on PC and MPV across fibrotic grades are currently unavailable due to limited studies. Nonetheless, this topic is worth exploring in depth as liver fibrosis has been suggested to have influences on platelet indices (28). A recent study showed that HCV-infected patients with advance fibrosis had a lower PC as well as a higher MPV and PDW compared with those with mild fibrosis (53). Iida et al. (54) proposed that MPV/PC ratio could be a potential marker to predict liver fibrosis and cirrhosis, because MPV gradually increased and PC gradually decreased during the development of HCV. Fourthly, although no low-quality studies were identified in this meta-analysis, 5 out of the 19 studies had an NOS score of 4, which might limit the strength of the results. Finally, there may be potential publication biases in our meta-analysis, especially the pooled estimates of PC. However, we should be conscious that significant heterogeneity contributes to some degree of publication biases (55).

CONCLUSION

This meta-analysis demonstrated that patients with NAFLD had a reduced PC but an elevated MPV and PDW, and the magnitude of the changes might be correlated with NAFLD progression. Furthermore, a higher MPV in NAFLD patients is strongly suggestive of the presence of lipid metabolic disorders. Therefore, this study suggests that platelet indices, which are easily ignored in the assessment of NAFLD and its progression, should be of concern to clinicians. Further research with a larger sample size is required to confirm these findings, especially the relationship of MPV and PDW with NAFLD progression.

Author Contributions

Design –Zhongwei Zhou; Writing Manuscript –Li Li and Jianxiu Yu; Data Collection –Li Li and Jianxiu Yu; Data Analysis –Li Li and Jianxiu Yu; Literature Search –Li Li and Jianxiu Yu; Edit –Li Li and Zhongwei Zhou.

Conflicts of interest

The authors have no conflict of interest to declare.

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Availability of data

The datasets used and analyzed during this study are available from the corresponding author on reasonable request.

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Table legends:

Table 1. Main characteristics of NAFLD patients included in this meta-analysis.

Table 1. Main characteristics of NAFLD patients included in this meta-analysis.

References	Country	Study design	Diagnostic methods	Age (years)	BMI (kg/m^2)	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	GGT (IU/L)	TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)	Quality score
Kilciler, 2010 (16)	Turkey	Cross-sectional	Liver biopsy	31.7 ± 5.6	26.7 ± 1.9.	89±42.5	41±32	NA	NA	203.9± 41.8	169±88	42.6± 6.97	118.4± 49.1	8
Wang, 2010 (17)	China	Cross-sectional	Ultrasound	49 ± 12	NA	42 ± 54	33 ± 34	NA	NA	184 ± 39	189 ± 115	44 ± 15	105 ± 34	6
Ozhan, 2010 (18)	Turkey	Cross-sectional	Ultrasound	49±12	33±6	42±54	33±34	NA	NA	184±39	189±115	44±15	105±34	8
Das, 2011 (19)	India	Cross-sectional	Ultrasound and biopsy	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	4
Chen, 2012 (20)	China	Cross-sectional	Ultrasound	48.6±7.4	26.7±3.1	31.3±19.4	24.2±1.2	60.4±17.4	44.9±35.4	189.2±34.4	189±185	46.4±10.8	NA	7
Celikbilek, 2013 (21)	Turkey	Cross-sectional	Liver biopsy	40.9±10.2	30.0±4.8	81.5±48.0	50.5± 24.6	76.0± 23.9	45.0±34.6	NA	149± 84.2	40.0±7.3	121.8±31.2	7
Kamada, 2013 (22)	Japan	Cross-sectional	Liver biopsy	54.4±12.8	27.5±5.1	95.8±72.0	62.9±39.3	NA	112±117	200.2±38.7	152. ±678.7	NA	NA	7
Cao, 2013 (23)	China	Cross-sectional	Ultrasound	37.3±10.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	4
Chwist, 2014 (24)	Poland	Cross-sectional	Liver biopsy	NA	NA	NA	51.6± 32.8	NA	NA	NA	NA	NA	NA	4
Goh, 2016 (25)	USA	Cross-sectional	Liver biopsy	48.0±11.6	34.8 ±6.7	77.9±56.9	57.9 ±43.1	NA	NA	NA	NA	NA	NA	7
Abdel, 2016 (26)	Egypt	Cross-sectional	Liver biopsy	47.0±4.8	28.3±2.7	54.0±18.5	47.0±8.9	88.2±19.3	34.0±22.2	NA	NA	NA	NA	8
Hirose, 2016 (27)	Japan	Cross-sectional	Ultrasound	60.9±14.8	261.±4.2	41.3±37.1	NA	281±110	56.1±62.5	187.3±33.7	119±57	NA	NA	5
Milovanovic, 2017 (28)	Serbia	Cross-sectional	Ultrasound	51.8±14.6	29.3 ±4.7	46.1 ±25.8	33.1±19.3	72.3± 23.0	73.6 ± 82.9	223.7± 42.7	213 ± 150	46.4 ± 23.2	139.3± 34.8	8
Saremi, 2017 (29)	Iran	Case-control	Ultrasound	37.6±5.7	27.6±3.5	NA	NA	NA	NA	196.2±37.0	169.6±81.3	44.5±16.3	120.4±374.5	5
Oral, 2019 (30)	Turkey	Case-control	Liver biopsy	34.1±9.1	24.7±3.3	18.5±10.9	17.0±4.6	66.1±20.1	18.2±12.3	178.9±45.1	96.5±43.8	NA	NA	8
Hanafy, 2019 (31)	Egypt	Cross-sectional	Liver biopsy	35.5±4.7	30.7 ±1.7	83.9 ±19.8	76.1 ±18.2	NA	64.9±7.9	273.6 ±10.4	280 ±13.4	33.7 ±4.2	188.3 ±13.6	8
Gu, 2019 (32)	China	Cross-sectional	Ultrasound	NA	27.5±9.8	23.0±3.5	17.2 ±5.0	NA	NA	NA	NA	NA	NA	4
Li, 2020 (33)	China	Cross-sectional	Ultrasound	43.0±8.1	NA	39.6±29.0	35.0±34.1	41.7±5.3	20.8±30.1	NA	NA	NA	NA	5

Michalak, 2021 (34)	Poland	Case-control	Ultrasound	60±15	29.5±4:9	NA	NA	NA	NA	NA	NA	NA	NA	4

NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not accessed.

Table 2. Platelet indices in patients and healthy controls.

References	Group	N (Males)	PC ($\times 10^3$/uL)	MPV (FL)	PDW (FL)
Kilciler, 2010 (16)	NAFLD	60 (60)	NA	8.9 ±1.1	NA
	Controls	54 (54)	NA	8.8 ±0.9	NA
Wang, 2010 (17)	NAFLD	50 (28)	226±78	10.4±1.1	NA
	Controls	50 (24)	261±56	9.1± 1.3	NA
Ozhan, 2010 (18)	NAFLD	70 (28)	226±78	10.43±1.14	NA

	Controls	60 (24)	261±56	9.09±1.25	NA
Das, 2011 (19)	NAFLD	105 (89)	237.9 ± 51.3	8.6±1.14	NA
	Controls	77 (45)	266.8± 59.4	8.5 ±0.97	NA
Chen, 2012 (20)	NAFLD	223 (117)	218.8±55.1	10.07±1.67	NA
	Controls	217 (106)	209.8±52.6	9.89±1.67	NA
Celikbilek, 2013 (21)	NAFLD	54 (27)	240 ± 65	9.70±1.13	NA
	Controls	41 (11)	280 ± 74.8	9.10±0.82	NA
Kamada, 2013 (22)	NASH	107 (57)	191.7±60.1	NA	NA
	Non-NASH	19 (13)	248.8±67.1	NA	NA
Cao, 2013 (23)	NAFLD	56 (39)	NA	12.2±1.24	12.8±1.4
	Controls	50 (35)	NA	10.7±1.0	11.5±1.0
Chwist, 2014 (24)	NASH	27 (NA)	188 ±77	NA	NA
	Non-NASH	43 (NA)	235 ±56	NA	NA
Goh, 2016 (25)	NASH	291 (125)	227.1± 69.7	NA	NA
	Non-NASH	144 (52)	259.1± 78.2	NA	NA
Abdel, 2016 (26)	NAFLD	873 (690)	230.5±51.1	9.1±1.09	15.9±1.4
	NASH	120 (96)	171.9±48.3	10.9±1.8	16.8±1.3
	Non-NASH	753 (594)	171.9±48.3	9.5±1.6	16.5±1.1
	Controls	150 (119)	221.5±69.2	8.3±1.12	15.1±1.6
Hirose, 2016 (27)	NASH	76 (28)	159.0±58.5	NA	NA
	Non-NASH	29 (12)	207.0±54.1	NA	NA

Milovanovic, 2017 (28)	NAFLD	98 (56)	218.4±56.8	9.1±1.3	16.7±0.7
	Controls	60 (32)	255.3±77.9	7.6±1.1	15.9±0.7
Saremi, 2017 (29)	NAFLD	65 (28)	271.2±52.1	10.29±0.95	11.44±1.86
	Controls	65 (37)	262.9±75.8	9.56±1.18	11.08±1.66
Oral, 2019 (30)	NAFLD	225 (138)	234.86±62.56	10.05±0.92	11.83±1.67
	Controls	142 (81)	248.56±63.44	10.09±0.95	12.01±2.01
Hanafy, 2019 (31)	NAFLD	272 (190)	NA	11.6±0.6	NA
	Controls	100 (70)	NA	8.2±0.5	NA
Gu, 2019 (32)	NAFLD	360 (180)	144.5±14.9	NA	NA
	Controls	60 (NA)	247.9±53.0	NA	NA
Li, 2020 (33)	NASH	151 (79)	109±56.3	12.0±6.7	NA
	Non-NASH	102 (64)	171.5±87.4	9.0±3.1	NA
Michalak, 2021 (34)	NAFLD	92 (59)	248±78	7.94±0.95	NA
	Controls	68 (32)	293±62	9.09±0.88	NA

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PC, platelet count; MPV, mean platelet volume; PDW, platelet distribution width; NA, not accessed.

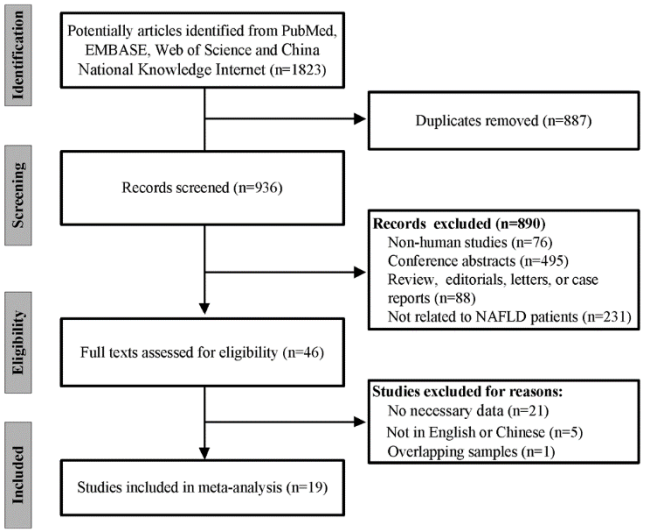

Figure 1. The flow chart of the study selection process.

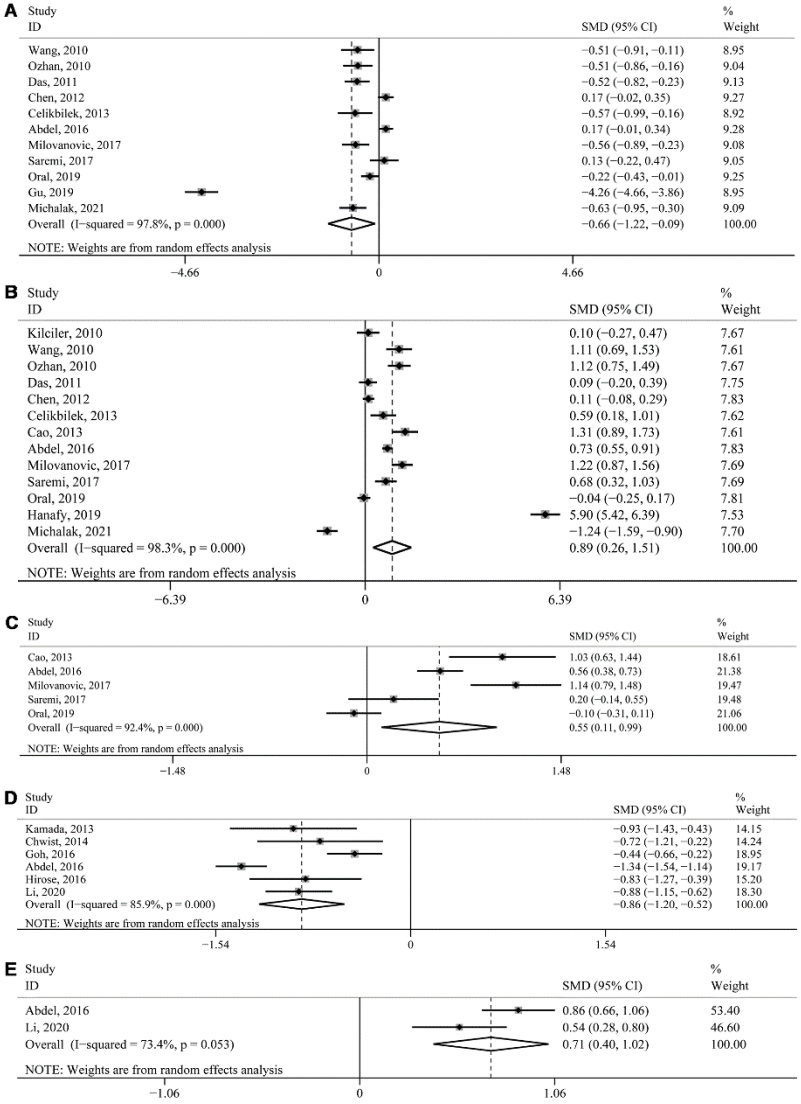
A
Study ID
SMD (95% CI)
% Weight
Wang, 2010 −0.51 (−0.91, −0.11) 8.95
Ozhan, 2010 −0.51 (−0.86, −0.16) 9.04
Das, 2011 −0.52 (−0.82, −0.23) 9.13
Chen, 2012 0.17 (−0.02, 0.35) 9.27
Celikbilek, 2013 −0.57 (−0.99, −0.16) 8.92
Abdel, 2016 0.17 (−0.01, 0.34) 9.28
Milovanovic, 2017 −0.56 (−0.89, −0.23) 9.08
Saremi, 2017 0.13 (−0.22, 0.47) 9.05
Oral, 2019 −0.22 (−0.43, −0.01) 9.25
Gu, 2019 −4.26 (−4.66, −3.86) 8.95
Michalak, 2021 −0.63 (−0.95, −0.30) 9.09
Overall (I−squared = 97.8%, p = 0.000) −0.66 (−1.22, −0.09) 100.00
NOTE: Weights are from random effects analysis
−4.66
0
4.66
B
Study ID
SMD (95% CI)
% Weight
Kilciler, 2010 0.10 (−0.27, 0.47) 7.67
Wang, 2010 1.11 (0.69, 1.53) 7.61
Ozhan, 2010 1.12 (0.75, 1.49) 7.67
Das, 2011 0.09 (−0.20, 0.39) 7.75
Chen, 2012 0.11 (−0.08, 0.29) 7.83
Celikbilek, 2013 0.59 (0.18, 1.01) 7.62
Cao, 2013 1.31 (0.89, 1.73) 7.61
Abdel, 2016 0.73 (0.55, 0.91) 7.83
Milovanovic, 2017 1.22 (0.87, 1.56) 7.69
Saremi, 2017 0.68 (0.32, 1.03) 7.69
Oral, 2019 −0.04 (−0.25, 0.17) 7.81
Hanafy, 2019 5.90 (5.42, 6.39) 7.53
Michalak, 2021 −1.24 (−1.59, −0.90) 7.70
Overall (I−squared = 98.3%, p = 0.000) 0.89 (0.26, 1.51) 100.00
NOTE: Weights are from random effects analysis
−6.39
0
6.39
C
Study ID
SMD (95% CI)
% Weight
Cao, 2013 1.03 (0.63, 1.44) 18.61
Abdel, 2016 0.56 (0.38, 0.73) 21.38
Milovanovic, 2017 1.14 (0.79, 1.48) 19.47
Saremi, 2017 0.20 (−0.14, 0.55) 19.48
Oral, 2019 −0.10 (−0.31, 0.11) 21.06
Overall (I−squared = 92.4%, p = 0.000) 0.55 (0.11, 0.99) 100.00
NOTE: Weights are from random effects analysis
−1.48
0
1.48
D
Study ID
SMD (95% CI)
% Weight
Kamada, 2013 −0.93 (−1.43, −0.43) 14.15
Chwist, 2014 −0.72 (−1.21, −0.22) 14.24
Goh, 2016 −0.44 (−0.66, −0.22) 18.95
Abdel, 2016 −1.34 (−1.54, −1.14) 19.17
Hirose, 2016 −0.83 (−1.27, −0.39) 15.20
Li, 2020 −0.88 (−1.15, −0.62) 18.30
Overall (I−squared = 85.9%, p = 0.000) −0.86 (−1.20, −0.52) 100.00
NOTE: Weights are from random effects analysis
−1.54
0
1.54
E
Study ID
SMD (95% CI)
% Weight
Abdel, 2016 0.86 (0.66, 1.06) 53.40
Li, 2020 0.54 (0.28, 0.80) 46.60
Overall (I−squared = 73.4%, p = 0.053) 0.71 (0.40, 1.02) 100.00
NOTE: Weights are from random effects analysis
−1.06
0
1.06

Figure 2. Forest plots for comparisons of platelet count (A), mean platelet volume (B) and platelet distribution width (C) between NAFLD versus health, and comparisons of platelet count (D) and mean platelet volume (E) between NASH versus non-NASH. SMD, standardized mean differences, CI, confidence interval.

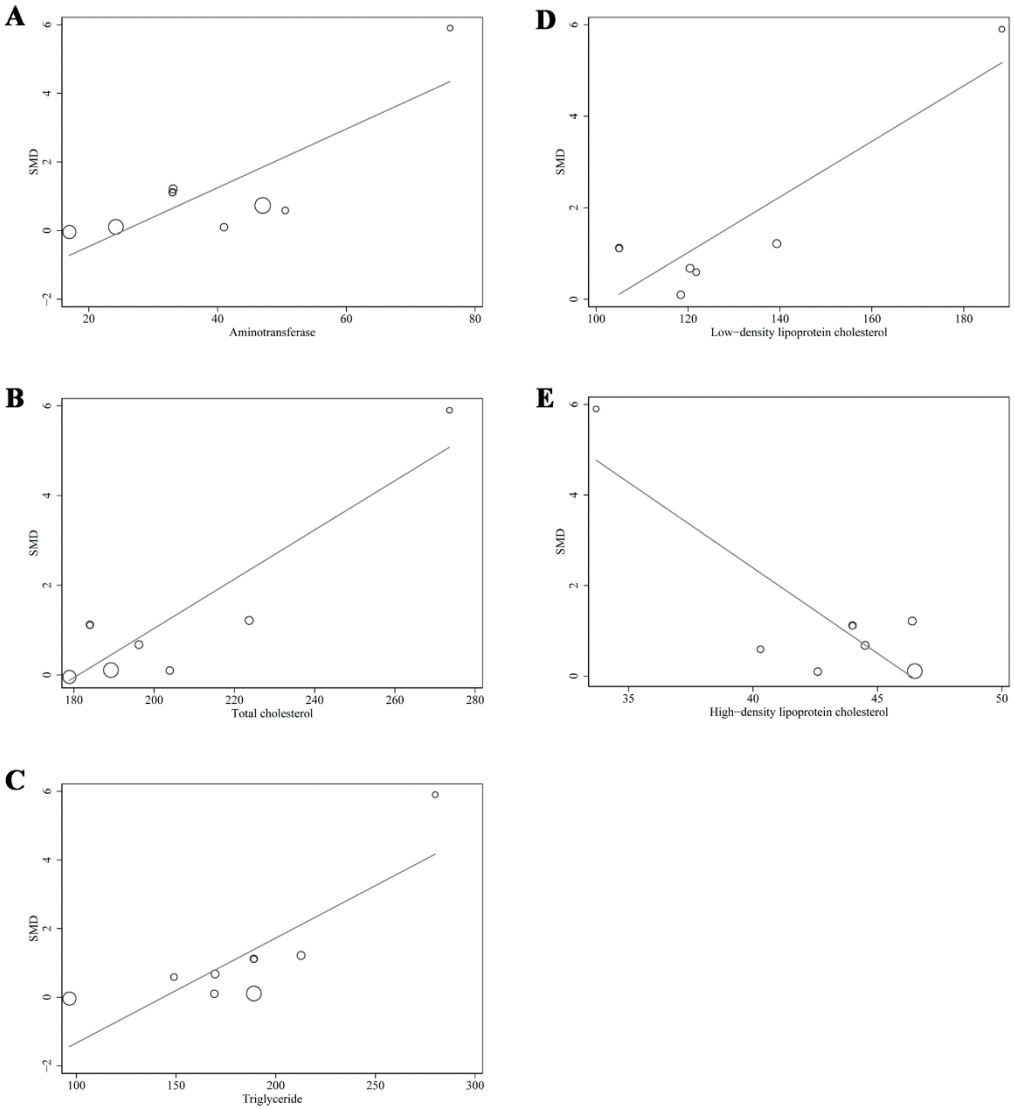
A
SMD
Aminotransferase
B
SMD
Total cholesterol
C
SMD
Triglyceride
D
SMD
Low−density lipoprotein cholesterol
E
SMD
High−density lipoprotein cholesterol

Figure 3. Meta-regression analysis demonstrating the associations between mean platelet volume and aspartate aminotransferase (A), total cholesterol (B), triglyceride (C), low-density lipoprotein cholesterol (D), and high-density lipoprotein cholesterol (E) in NAFLD patients. SMD, standardized mean differences.