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Mean platelet volume in acute pancreatitis: a systematic review and meta-analysis

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Abstract

Background Several studies have suggested there may be statistically significant differences in mean platelet volume (MPV) between the onset and remission of acute pancreatitis (AP). This systematic review and meta-analysis aimed to better characterize the correlation between MPV and AP by identifying all relevant studies and summarizing their results.

Methods A comprehensive literature review was conducted using EMBASE, PubMed/MEDLINE, Cochrane Library, ClinicalTrials.gov, and Google Scholar from January 2000 to December 2019 to identify all studies that reported MPV at the onset or remission of AP, or both. Effect estimates from each study were extracted and combined using the random-effect, generic inverse variance method of DerSimonian and Laird. The Newcastle-Ottawa quality assessment scale was used to appraise the quality of the included studies.

Results Ten observational studies, including 1019 patients and 363 controls, were included in the meta-analysis. MPV was smaller at the onset of AP than on remission (standardized mean difference= -0.33 fL, 95% confidence interval -0.54 to -0.12 fL; P=0.002); however, a moderate degree of heterogeneity (I^2=72%, P≤0.001) was observed. Subgroup analysis indicated comparable MPV in relation to the severity of AP. Similarly, no statistically significant difference was detected between AP patients and controls at either onset (P=0.760) or remission (P=0.700) of the disease. No statistically significant publication bias was detected (Eggers' regression P=0.938). Subgroup analysis suggested age (P<0.001) and sex (P=0.01) adjustment as potential sources of heterogeneity.

Conclusion MPV is smaller at the onset of AP. Further clinical evaluation is needed to assess its potential prognostic value.

Keywords Pancreatitis, mean platelet volume, blood platelets

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Introduction

It has been claimed that platelets are directly involved in the pathophysiology of acute pancreatitis (AP) [1]. An elevated activated platelet ratio has been observed at the onset of AP [2]. Moreover, greater platelet adhesiveness and aggregation has been documented in the early stages of the disease [3]. Mean platelet volume (MPV) has been proposed as a marker of platelet consumption and resulting compensatory bone marrow response during the disease process [2].

Several studies have reported statistically significant differences in MPV between the onset and remission of AP; furthermore, elevated MPV at admission has been linked with persistent organ failure in these patients [4]. However, the related literature remains obscure and thus needs further consolidation and clarification. Moreover, as properly designed prospective cohorts are still lacking, the potential prognostic value of MPV during the course of AP has so far remained elusive.

The present systematic review and meta-analysis was conducted with the aim of providing further evidence regarding a potential correlation between MPV and AP by identifying all relevant studies and summarizing their results.

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Conflict of Interest: None

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Materials and methods

A systematic literature review was conducted using EMBASE, PubMed/MEDLINE, Cochrane Library, and ClinicalTrials.gov databases from January 2000 to December 2019 to identify all studies that reported MPV at the onset or remission of AP, or both. The Google Scholar database was used as an additional pool of published data; an iterative search was performed until no additional publications could be traced. Lastly, we searched for unpublished dissertations and other unpublished work. The relevant protocol was submitted to the PROSPERO database (ID: 150901).

The review was independently conducted by 2 authors (VP and DF) using a search strategy that included the terms "mean platelet volume", "MPV" and "pancreatitis"; a third author (KM) was responsible for resolving any discordance. No software was used for study retrieval. Sources of financial support were traced where possible. The present study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines to formulate the basis of pre-specified eligibility criteria using the PICO (P—Populations/People/Patient/Problem: Patients in acute phase of AP and controls, I—Intervention(s): AP, C—Comparison: between patients at onset and remission (at discharge or at least 7 days after admission) of AP; between patients at onset of AP and controls; between patients at remission of AP and controls; between severe and mild cases at onset of AP, O—Outcome: MPV) worksheet and search strategy [5]. The AMSTAR checklist was used to confirm the high quality of the present meta-analysis [6].

Eligible studies were all that: 1) were written in English; 2) were case-control studies; 3) had a consistent outcome of interest; 4) reported a measure of statistical significance; 5) reported an effect size (means accompanied by their standard deviations); and 6) reported effect estimates not already reported.

The Newcastle-Ottawa quality assessment scale (NOS) was used to appraise the quality of the included studies in 3 areas: namely, the identification and recruitment of participants, the comparability between the 2 groups and the ascertainment of the exposure of interest [7]. Kappa statistics were used for the evaluation of inter-rater agreement in the case of NOS.

A structured data collection form was used to extract the following data from each study: title of the study, name of the first author, year of publication, country where the study was conducted, number of patients, severity of cases (if reported), number of controls (if any), correlation coefficient between paired data (if known), MPV of patients at onset of AP, MPV of patients at remission of AP, MPV of controls and adjustment for potential confounders (sex, age and body mass index). The data extraction process was carried out by 2 authors (VP and DF); a third author (KM) was responsible for cross-checking in case of any discordance.

Data analysis was performed using Revman 5.3 software from the Cochrane Collaboration (London, United Kingdom). As effect estimates, standardized mean differences (SMD) and confidence intervals (CI) expressed in fL were utilized. Effect estimates from each study were combined together using the random-effect, generic inverse variance method of DerSimonian and Laird, which assigned the weight of each study in the pooled analysis inversely to its variance [8]. In cases that median and interquartile range (IQR) were available, mean was considered equal to median and standard deviation (SD) was approached by the formula IQR/1.35 if normal distribution was reported; otherwise, the.xls tool based on the approach of Wan *et al* was applied [9].

As data between onset and remission of AP are paired, pooled SD was used, as approached by the formula $[SD_{onset}^{2} + SD_{remis}^{2} - 2 \times r \times SD_{onset} \times SD_{remis}]^{½}$, where SD_{onset}, SD_{remis} and r denote SD at onset of AP, SD at remission of AP and the correlation coefficient between data. In cases where r was unknown, it was arbitrarily given a value of 0.5 if statistical significance was reported; otherwise, the r value was nullified. Analysis of publication bias was performed through Eggers' regression, funnel plot with trim-and-fill analysis, standardized residual histogram, Galbraith plot, normal quintile plot, Rosenthal failsafe-N test, Orwin failsafe-N test and Gleser & Olkin number of unpublished studies with the aid of Meta-Essentials software [10]. Analysis of heterogeneity, as derived from the Q test and I^2 statistic (Q test P-value <0.10 was indicative of a statistically significant result; furthermore, a value of $I^2 \leq 25\%$ was indicative of insignificant heterogeneity, 26-50% of low heterogeneity, 51-75% of moderate heterogeneity and >75% of high heterogeneity), was performed through meta-regressions focusing on study characteristics, biases and confounders; multivariate analysis as well as subgroup analysis followed in case of univariate P<0.1 [11]. All statistical tests were carried out using SPSS 20.0 software (IBM Corp ©).

Results

Forty-nine potentially relevant publications were identified through a thorough search of the literature; 15 were retrieved from EMBASE, 13 from PubMed/MEDLINE, 4 from ClinicalTrials.gov, and 17 from Google Scholar databases. No relevant publication was recognized in the Cochrane Library. No unpublished data of interest were detected.

After the exclusion of 31 duplicates, all the remaining 18 publications were initially reviewed based only on title and abstract; 5 failed to fulfill the eligibility criteria based on language, type of article, study design, and measured outcomes. The remaining 13 publications were reviewed based on full text; 3 were excluded from the meta-analysis (1 letter and 2 reporting irrelevant outcomes). Finally, 10 case-control studies with 1019 patients and 363 controls were included in the meta-analysis (Fig. 1).

All the characteristics of the studies and their quality assessment are presented in Table 1. The inter-rater agreement for NOS was high (kappa=0.78). The relevant data did not reveal any profound quality handicap.

The pooled analysis demonstrated that MPV was lower at the onset of AP than at remission of the disease (SMD=-0.33 fL, 95%CI -0.54 to -0.12 fL; P=0.002); however,

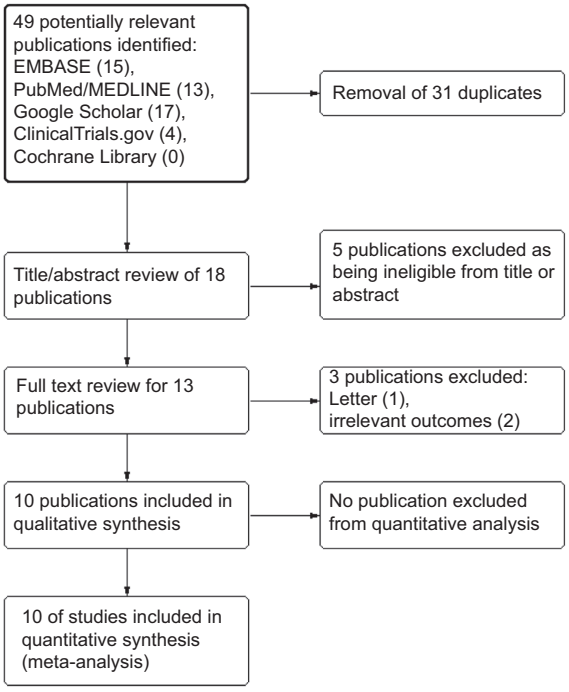

Figure 1 Flow chart

moderate heterogeneity (I^2=72%, P<0.001) was observed. Subgroup analysis indicated comparable MPV in relation to the severity of AP (SMD=-0.42 fL, 95%CI -1.02 to 0.17; P=0.170). Similarly, no statistically significant difference was detected between AP patients and controls at either onset (SMD=0.12 fL, 95%CI -0.61 to 0.84 fL; P=0.760) or remission (SMD=0.07 fL, 95%CI -0.31 to 0.46 fL; P=0.700) of the disease (Fig. 2). No statistically significant publication bias was detected (Eggers' regression P=0.938). Furthermore, the Rosenthal failsafe-N test rejected the ad-hoc rule (Failsafe-N=206), Orwin failsafe-N was null and Gleser & Olkin number of unpublished studies was 13, fairly close to the number of studies included in the present meta-analysis. Moreover, the funnel plot was not indicative of lack of symmetry and trim-and-fill analysis produced no imputed data points (Fig. 3). The Galbraith plot is depicted in Supplementary Fig. 1.

No statistically significant model analyzing study characteristics and potential confounders explained heterogeneity by meta-regression (Table 2). However, subgroup analysis suggested age (P<0.001) and sex (P=0.010) adjustment as potential sources of heterogeneity (Table 3).

Discussion

The question of whether platelets are directly involved in the pathophysiology of AP has remained controversial since it was first proposed in 2 studies of ours: the former concluded that an elevated activated platelet ratio has been observed at the onset of AP [2] and the latter that platelet adhesiveness and aggregation are greater in the early stages of the disease [3]. Furthermore, our team proposed that MPV could reflect platelet consumption and resulting compensatory bone marrow response during AP, thus being a potential candidate marker for the disease process, whose clinical usefulness remains to be tested [2]. Since then, several studies have been carried out in this area.

Three studies are in keeping with our results, having reported statistically significant differences in MPV between onset and remission of AP [13,18,19]. In 2 of them, the result was independent of the severity of the disease [18,19]. Interestingly, Beyazit *et al* [13] discriminated between mild and severe AP, concluding that MPV has a crucial value in determining disease severity; furthermore, comparisons of MPV with other inflammatory markers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell count (WBC) reported better overall accuracy for the former (72.7% at a cutoff of 7.85 fL). In keeping with the above mentioned results, Erbis *et al* proposed a very similar cutoff (7.80 fL) to discriminate between necrotizing and non-necrotizing AP [17]. Additionally, a cutoff of 12 fL was used as a prognostic indicator of persistent organ failure in patients with AP in the work carried out by Huang *et al* [4].

In contrast, Osada *et al* reported comparable MPV values between the onset and remission of AP [14]. This study underlines that platelets, which provide the cellular link between the inflammatory response and the activation of coagulation, may play an important role in the initiation of AP and the development of serious complications. The authors evaluated platelet morphology along with functional parameters in relation to the severity of AP, and concluded that patients with severe AP presented significantly lower MPV than controls at disease onset. Furthermore, they stated that patients with AP, independently of disease severity, exhibited an increase in high volume platelets at remission of the disease and proposed that this phenomenon could be explained in terms of reactive thrombocythemia. In keeping with the latter, Kefeli *et al* reported a significantly increased platelet count at remission of AP in comparison with the onset of disease; however, the authors reported comparable MPV at onset and remission of AP, as well as in controls [16]. Yarkaç *et al* also reported comparable MPV values between the onset and remission of AP and their best cutoff value for MPV to discriminate mild from severe cases of AP (9.4 fL) failed to reach statistical significance (P=0.067) [20].

Akbal *et al* reported a greater MPV at the onset of AP when compared with controls; however, they found comparable MPV values between the onset and remission of AP. Furthermore, the authors reported that MCV was correlated with D-dimers and fibrinogen levels but not with inflammation markers (CRP, ESR, and WBC) proposing that higher MPV levels in acute pancreatitis may reflect hypercoagulation associated with the disease [15].

As far as the etiology of AP is concerned, Okuturlar *et al* reported lower MPV in patients with non-biliary AP compared with biliary AP at both onset and remission of the disease,

Table 1 Eligible studies (characteristics and quality assessment)

Study	Region	Endpoint	Patients	Controls	r	MPV (Onset)	MPV (Remission)	MPV (Controls)	Adjusted confounders	NOS selection	NOS comparability	NOS exposure
Mimidis, 2004 [2]	Greece	Onset vs. Remission	52	-	0.79	9.6±1.2	10.3±1.2	-	Sex, age	☆☆☆	☆☆	☆☆☆
Yilmaz, 2011 [12]	Turkey	Onset vs. Controls	30	30		8.8±1.3	-	7.9±0.5	Sex, age, BMI	☆☆	☆	☆☆☆
Beyazit, 2012 [13]	Turkey	Onset vs. Remission vs. Controls	144	40		8.1±0.7	-	8.6±0.6	Sex, age	☆☆☆	☆☆	☆☆☆
			Mild 93		0.50	8.3±0.7	8.5±0.8					
			Severe 51		0.50	7.7±0.6	8.2±1.0					
Osada, 2012 [14]	Poland	Onset vs. Remission vs. Controls	40	25		-	-	8.9±0.8	-	☆☆☆	☆☆	☆☆☆
			Mild16		0.00	9.5±0.8	9.2±1.1					
			Severe 24		0.00	9.6±1.0	9.5±1.1					
Akbal, 2013 [15]	Turkey	Onset vs. Remission vs. Controls	24	24	0.00	8.6±1.4	8.5±1.2	7.6±0.7	Sex, age	☆☆☆	☆☆	☆☆☆
Kefeli, 2014 [16]	Turkey	Onset vs. Remission vs. Controls	140	70	0.00	7.8±1.6	7.7±0.9	7.8±1.1	Age	☆☆☆☆	☆☆	☆☆☆
Erbis, 2015 [17]	Turkey	Onset vs. Controls	76	40		7.5±0.6	-	8.3±0.9	Age	☆☆	☆☆	☆☆
			Mild 40			7.9±0.5						
			Severe 36			7.2±0.5						
Okuturlar, 2015 [18]	Turkey	Onset vs. Remission vs. Controls	332	-	0.50	8.4±1.0	8.7±1.1	8.3±0.9	Age	☆☆☆	☆☆	☆☆☆
			Biliary 195			8.1±1.0	8.4±1.0					
			Non-biliary 137									
Lei, 2017 [19]	China	Onset vs. Remission vs. Controls	117	34		8.7±2.4	10.4±1.7	11.0±1.4	Sex, age	☆☆☆	☆☆	☆☆☆
			Mild 78		0.50	8.9±2.3	9.7±1.8					
			Severe 39		0.50	8.5±2.5	10.5±1.8					
Yakac, 2019 [20]	Turkey	Onset vs. Controls	168	100		9.5±1.3		8.0±0.7	Sex, age	☆☆☆☆	☆☆	☆☆☆
			Mild 122			9.5±1.2						
			Severe 46			9.8±1.3						

MPV, mean platelet volume; NOS, Newcastle-Ottawa scale; BMI, body mass index

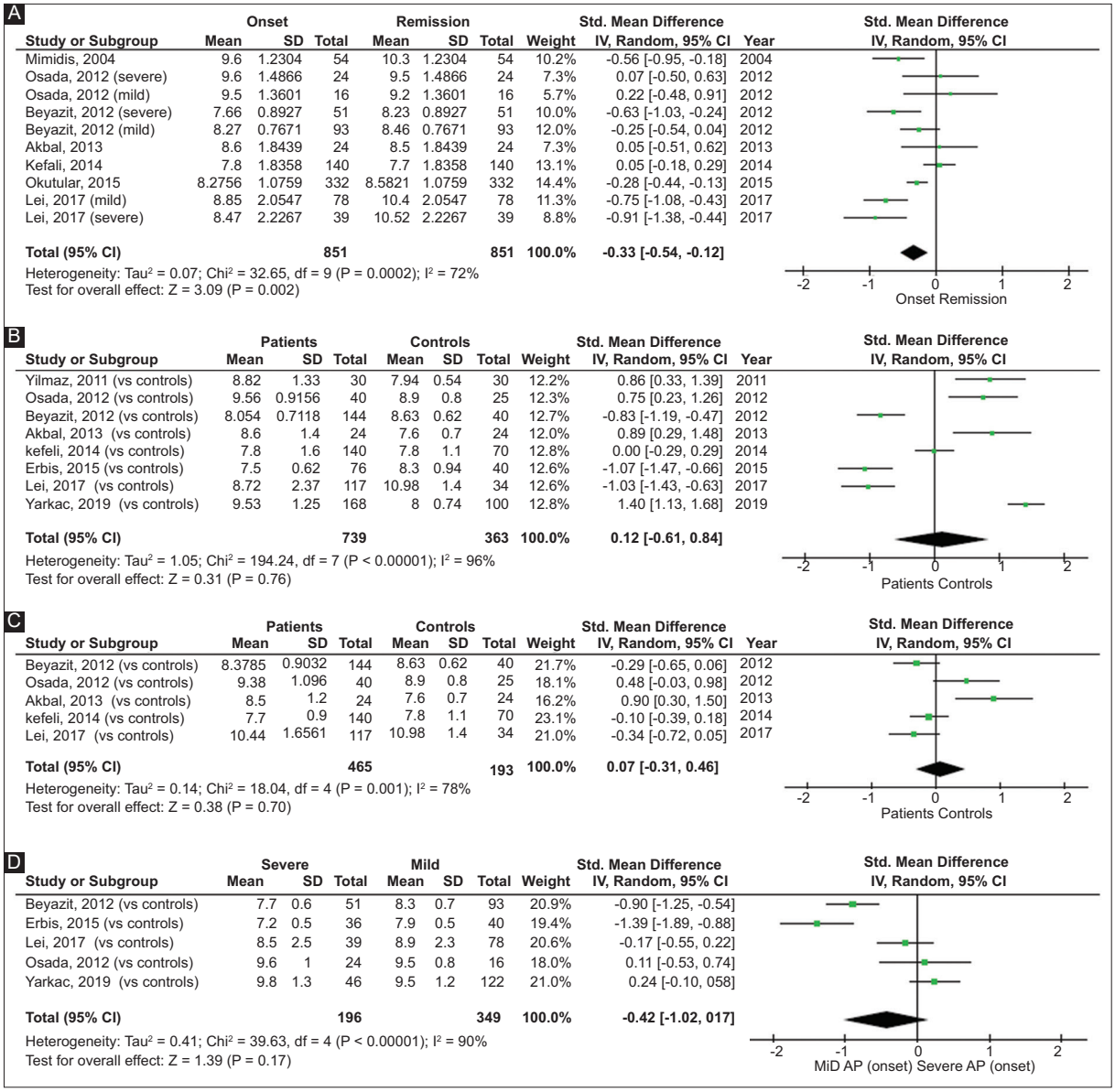

Figure 2 Meta-analysis (A) Onset vs. Remission, (B) Onset vs. Controls, (C) Remission vs. Controls and (D) Severe vs. Mild cases of acute pancreatitis (AP) at onset
CI, confidence interval; SD, standard deviation

Table 2 Meta-regression analysis

Parameter	Univariate analysis (r)	Univariate P-value	Meta-regression analysis (standardized beta)	Meta-regression P-value
Study characteristics				
Sample size	-0.014	0.969		
Years passed from publication	0.162	0.655		
Cohort study	-0.161	0.656		
Including severe cases	-0.068	0.852		
Adjustment for confounders				
Age	-0.592	0.036	-0.277	0.336
Sex	-0.684	0.015	-0.304	0.322

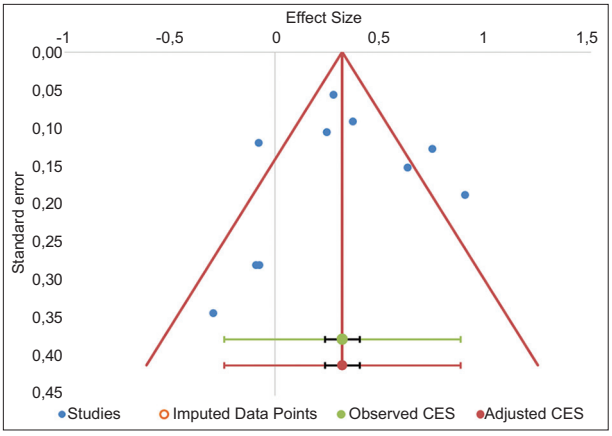

Figure 3 Funnel plot with trim-and-fill analysis
CES, combined effect size

Table 3 Subgroup analysis

Parameter	Subgroups	SMD	95%CI	I^2	P-value
Age adjustment	Yes	-0.21	-0.40 to -0.03	58%	<0.001
	No	-0.80	-1.07 to -0.54	0%	
Sex adjustment	Yes	-0.52	-0.77 to -0.27	60%	0.01
	No	-0.07	-0.32 to 0.19	60%	

SMD, standardized mean difference; CI, confidence interval

attributing the observed difference to early-onset infection in non-biliary AP patients [18]. However, Yarkaç *et al* failed to reproduce this finding [20].

Lei *at al* studied the time course of MPV alterations in AP by measuring it at admission (day 1), and on days 2, 3 and 7. The authors reported a lower MPV in AP patients at admission compared to days 2, 3 and 7, while they suggested that an MPV less than 6.65 fL at admission for AP could predict organ failure [19]. However, whether MPV could possibly serve as a predictor of the severity of AP as well as of complications of the disease needs further, carefully designed clinical studies.

Our meta-analysis incorporated all the above mentioned data, simultaneously performing quality assessment, publication bias analysis, subgroup analyses and meta-regressions. Although NOS cannot discriminate between studies of "high" and "low" quality, it constitutes a valuable tool for forming inclusion criteria for the meta-analysis, informing a sensitivity analysis or meta-regression, weighting studies, or highlighting areas of methodological quality poorly addressed by the included studies [21]. Subgroup analyses and meta-regressions focused on the potential effect of study type, sample size, region of origin, confounders, and combined outcomes.

Interestingly, no publication bias was detected, as implied by results derived from Eggers' regression, funnel plot with trim-and-fill analysis, standardized residual histogram, Galbraith plot, normal quintile plot, Rosenthal failsafe-N test, Orwin failsafe-N test and Gleser & Olkin number of unpublished studies; this result could be attributed to the fact that no clear-cut predefined or prejudged size or even direction of difference was suspected in the scientific community as a whole.

No statistically significant model analyzing study characteristics and confounders explained the observed increased heterogeneity (I^2=72%, P≤0.001) by meta-regression. However, subgroup analysis revealed age (P<0.001) and sex (P=0.010) adjustment as potential sources of heterogeneity. These findings are in keeping with the current knowledge and literature, as age and sex are known determinants for AP; the incidence of AP increases with age and it is twice more common in males than females worldwide [22]. All the above underlie the need for careful interpretation of data already published, as well as study design and performance in the future.

Summing up, the present meta-analysis suggested that MPV is higher at remission of AP than at the onset of the disease, and subgroup analysis indicated comparable MPV in relation to AP severity. However, no statistically significant difference was detected between AP patients and controls at either onset or remission of the disease. These findings are in keeping with initial platelet activation and wear, resulting in lower MPV, and subsequent reactive thrombocythemia leading to an increase of large platelets during inflammation [23].

The inconsistencies that the above-mentioned findings may seem to convey could at first be attributed to the fact that the data were derived from different studies for each comparison, as well as to the substantial heterogeneity. Seemingly, mean MPV values, despite being lower at the onset of AP than at remission of the disease, could be supposed to lie within the normal range in both cases.

The major limitation of the present study might be that the data analyzed were derived from case-control studies. Interestingly though, meta-regression did not prove any statistically significant difference regarding overall effect sizes; however, due to the fact the pooled studies were observational, residual confounding is a major limitation and even the meta-regression cannot control unknown confounders. Thus, this practice might be considered non-decisive. Furthermore, the present study failed to incorporate unpublished data; lack of this kind of source might be linked to potential publication bias, despite the fact that no prejudiced correlation between MPV and AP (positive or negative) prevailed in the literature. Such biases might not be traced in small-sized studies including less than 10 studies due to the fact that funnel plots, as well as any statistical tool used for the same purpose, are underpowered.

In conclusion, our results suggest that MPV is lower at the onset of AP than at remission of the disease, independently of the disease severity. As MPV constitutes an inexpensive and undemanding marker, it would be reasonable to further investigate its potential prognostic value. Therefore, further specially designed clinical evaluations would be needed to assess the clinical usefulness of MPV in everyday clinical practice.

Summary Box

What is already known:

- A higher activated platelet ratio has been observed at the onset of acute pancreatitis (AP)
- Greater platelet adhesiveness and aggregation has been documented in the early stages of AP
- Studies have reported statistically significant differences in mean platelet volume (MPV) between the onset and remission of AP

What the new findings are:

- MPV is smaller at the onset of AP
- MPV is independent of the severity of AP
- MPV, an inexpensive and undemanding marker, deserve further investigation of its potential prognostic value in AP

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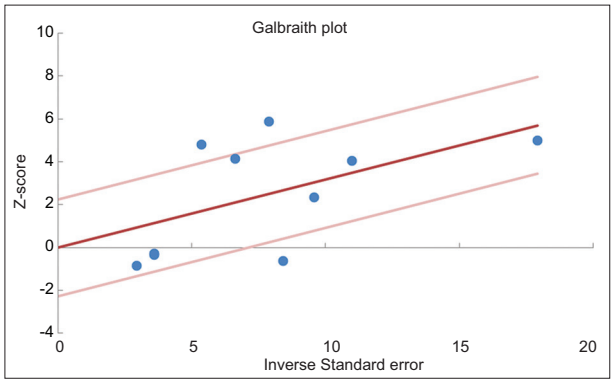
Supplementary material



Supplementary Figure 1 Galbraith plot