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Platelet count and mean volume in acute stroke: a systematic review and meta-analysis

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Abstract

Changes of mean platelet volume (MPV) and platelet count (PC) could be a marker or a predictor of acute stroke (AS). We conducted a systematic review and meta-analysis of the published literature on the reporting of MPV and PC in AS. Studies were included in accordance with Patient Population or Problem, Intervention, Comparison, Outcomes, and Setting framework. The PRISMA strategy was used to report findings. Risk of bias was assessed with the Newcastle-Ottawa Scale. We included 34 eligible articles retrieved from the literature. PC was significantly lower in AS patients [standardized mean difference (SMD) = − 0.30, (95% CI: − 0.49 to − 0.11), N = 2492, P = .002] compared with controls (N = 3615). The MPV was significantly higher [SMD = 0.52 (95% CI: 0.28–0.76), N = 2739, P < .001] compared with controls (N = 3810). Subgroup analyses showed significantly lower PC in both ischemic stroke (Difference SMD = −0.18, 95% CI: −0.35–0.01) and hemorrhagic stroke (−0.94, −1.62 to −0.25), but only samples by citrate anticoagulant showed significantly lower result for patients compared to controls (−0.36, −0.68 to −0.04). Ischemic stroke patients had higher MPV (0.57, 0.31–0.83), and samples by Ethylenediaminetetraacetic acid (EDTA) anticoagulant showed significantly higher result for patients compared to controls (0.86, 0.55-–1.17). PC and MPV appeared to be significantly different between patients with AS and control populations. MPV was significantly higher in ischemic stroke and PC was significantly lower in both ischemic and hemorrhagic strokes. These characteristics might be related to AS and associated with it. It is advisable to pay attention to elapsed time between phlebotomy and hematology analysis, anticoagulant and hemocytometer types in AS.
Systematic review registration: This meta-analysis is registered on the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42017067864 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=67864).

Introduction

Incidence of stroke in Europe is 95 to 290/100,000 per year and it is the fourth cause of death in the United States [1,2]. The important role of platelets in the pathogenesis of the atherothrombosis and ischemic stroke has been documented [3,4]. Mean platelet volume (MPV) is regarded as a marker of platelet turnover [5]. More immature, thereby larger platelets usually contain more granules, thus releasing more chemokines promoting further platelet aggregation as well as activation. Elevated MPV simultaneously with the elevated PC increases the risk of thrombosis [6]. Significant increased MPV in patients with deep vein thrombosis and isolated elevated PC in patients with pulmonary embolism has been revealed [7].

Modification of platelet function and consequently a hypercoagulable state has been suggested in patients with both ischemic and hemorrhagic strokes [8]. It has been shown that PC and MPV are independent predictors for poor outcome in primary intracerebral hemorrhage (PICH) [9]. There has also been a body of interest for PC and MPV in stroke patients. However, these studies have yielded inconsistent findings. Some groups reported that patients with AS had significantly increased MPV or PC compared with controls [10,11], whereas other studies found decreased MPV or PC values in AS patients [12,13]. Additionally, some studies have observed no association between these parameters and AS [14,15]. Taking these inconsistent findings into consideration, we undertook a meta-analysis to investigate the association between MPV, PC, and AS.

Methods

Protocol and Registration

The present systematic review and meta-analysis was conducted, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16] and was

demonstrated according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement [17]. The systematic review and meta-analysis protocol was registered with the PROSPERO database at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=67864

Search Strategy and Study Selection

Eligibility criteria were in accordance with the Patient Population or Problem, Intervention, Comparison, Outcomes, and Setting inclusion criteria [16]. We modified the PICOS excluding I, where I represents the Interventions, since no interventional studies were included. Studies were included if they (1) studied adult individuals, (2) included a control group, (3) involved the diagnosis or evaluation of acute stroke, (4) included the detailed data about platelet indices in both patient and control groups, and (5) were case-control or cross-sectional studies. There was no language, country or time restriction. We excluded reviews, editorials, commentaries, abstracts, and conference proceedings.

Cerebrovascular events and acute stroke were assessed in this study as the outcomes.

The basis for our analysis was the comprehensive search for the relevant studies published in Medline, EBSCOhost, Web of Science, ScienceDirect, Google Scholar and Scopus from inception to July 2017 (Supplementary file 1). The last search was performed on August 2019 and we included published studies. Google Scholar was searched by Harzing's Publish or Perish program (Harzing, A.W., 2007, Publish or Perish, available from https://harzing.com/resources/publish-or-perish). The keywords used for systematic searches were as follows: platelet indices, platelet parameters, mean platelet volume, platelet count, stroke, and cerebrovascular disease.

Data Extraction

Two reviewers independently extracted the Data (AHS and FS) by using a standard form and cross-checked. Discrepancies were resolved by consensus or through discussion with the third author (ZC). We used bibliographies of the retrieved articles for other relevant studies. All data were prospectively collected.

After the first search, reviews remained on the list to collect appropriate references. At the second step, we removed all reviews from the list of accepted publications.

We used the Newcastle-Ottawa Scale (NOS) to evaluate the quality of the eligible studies [18]. NOS includes a selection of the study population domain, comparability of the groups' domain, and ascertainment of the outcome domain. Articles identified as high quality with NOS scores 6–9, whereas scores of 0–5 were considered to indicate poor quality. In those studies that provided only median with range or interquartile range values, mean and standard deviation were calculated according to Wen et al. [19].

Data Synthesis and Statistical Analysis

This study was conducted by following the guidelines of Viechtbauer and Huzsvai and Balogh [20,21]. The meta-analysis involved between-study variances and also covariates for limiting publication biases. Standardized mean differences (SMDs) were estimated for MPV and PC within each study. We also conducted subgroup analysis by a random-effect (RE) meta-analysis for the assessment of heterogeneity using the type of anticoagulant (EDTA or citrate), type of analyzer (Sysmex or Coulter), and type of infarction [ischemic stroke (IS) or PICH] as covariates. Then, a mixed-effect (ME) meta-regression was performed using the type of infarction and type of analytes as the moderator variables. We also performed an outlier detection for MPV regarding storage time and type of analyte. Heterogeneity was quantified using the I^2 statistics across studies.

Publication bias was assessed through graphical Begg's funnel plots and Egger's regression symmetry statistical tests [22]. We performed both adjusted and unadjusted parametric bootstrap sampling with 10,000 replicates of the original data using the normal distribution. All analyses were performed by using the statistical software R 3.3.2 and its metafor package (https://cran.r-project.org).

Results

A flowchart diagram of the progression of papers through the review process is shown in Figure 1. A total of 6812 studies were identified. Supplementary Table I shows search protocols and their details for each database separately. A total of 2746 duplicates (40.3%) were excluded, and 3810 (55.9%) articles were removed after reviewing the title and/or abstract. The remaining 256 articles were assessed for eligibility criteria by screening their titles and abstracts. Following detailed evaluation, 39 studies were selected for qualitative assessment. We corresponded with authors for five studies, but data were not available. Therefore, 34 articles were included in the meta-analysis [10–15,23–50]. Three studies were carried out in the United States, 12 in Europe, ten in Asia, one in Africa, and eight studies were intercontinental. Patient populations ranged from 12 to 384 individuals.

Most of the included studies were about acute ischemic stroke (82%). Thirteen studies did not report the type of analysate (38%), and almost the same number of studies failed to report the type of hematology automated analyzer (41%) (Table I and more details at Supplementary Table II). Elapse time between phlebotomy and measurement of 20.5% of the studies was more than 2 h. Most of the studies missed to report stroke-related comorbidities (Table I).

The Dersimonian-Laird estimator was used to estimate ME and RE models for PC MPV (Supplementary Table III). Funnel plot indicates publication biases in the RE model, especially for MPV, but the ME model for both variables does not contain publication biases (Supplementary Figure 1). We applied the weighted regression model with multiplicative dispersion and t-values were calculated. Egger's test provided evidence for publication biases in RE model only for MPV ($P < .001$), but in case of PC t-statistics show stronger symmetry for the mixed effects model (Supplementary Table IV). There were no false high MPV values during our outlier detection procedure. Bootstrap sampling was used to validate both RE and ME models and to avoid the overfitting of the models in case of a low number of studies (Supplementary Table V).

PC

A total of 6107 participants were selected from 24 publications, of which 2492 were assigned to the patient group and 3615 to the control group. Three studies showed that patients with AS had higher PC than controls [24,35,36]. Eleven studies demonstrated lower PC in the patient group [12–14,23,25–27,30,32,35,43], and 11 studies found no difference in PC between patients and controls (Table I, Supplementary Table VI) [11,15,28,29,33,37,41,42,44,46,47]. One study did not provide PC results. The mean PC for all publications was 234 G/L (95% CI: 224–244) for patients and 248 G/L (95% CI 238–259) for controls. There was a marked residual heterogeneity by ME model for PC [$\chi^2 = 230.2$; df = 27; $I^2 = 88.3\%$ (95% CI: 80.0–93.1); $P < .001$]. The estimated pooled mean difference in PC was 0.48 G/L [Z = 1.61; $P = .107$] regarding the ischemic stroke for the ME model. It was −0.30 (Z = −3.15, 95% CI: − 0.49–−0.11, $P = .002$) for the RE model without moderating effects (Figure 2).

MPV

Seventeen results of the 27 studies revealed that patients with stroke had higher MPV than controls [10,12,25,27,28,34,35,39,41–43,

Records identified through database searching
n = 6812 studies
Medline: 886 studies
Web of Science: 817 studies
Scopus: 1322 studies
ScienceDirect: 138 studies
EBSCOhost: 1023 studies
Google Scholar: 2626 studies

Records after duplicates removed

n = 4066

Records after screening
n = 256 studies

Records excluded (**n** = 166):
-review
-cancer
-letter to editor
-drug effect and therapy
-animal model
-missing data
-unrelated disease

Full-text articles assessed for eligibility (**n** = 90)

Full-text articles excluded (**n** = 51):
-Insufficient data (**n** = 24)
-No control (**n** = 20)
-Data discrepancies (**n** = 2)
-Concurrent disease (**n** = 3)
-Phase contrast microscopy for platelet count (**n** = 1)
-Carotid artery disease (**n** = 1)

Studies included in qualitative synthesis (**n** = 39)

5 records excluded:
Data not available from correspondence

Studies included in quantitative synthesis (meta-analysis) (**n** = 34)

Identification

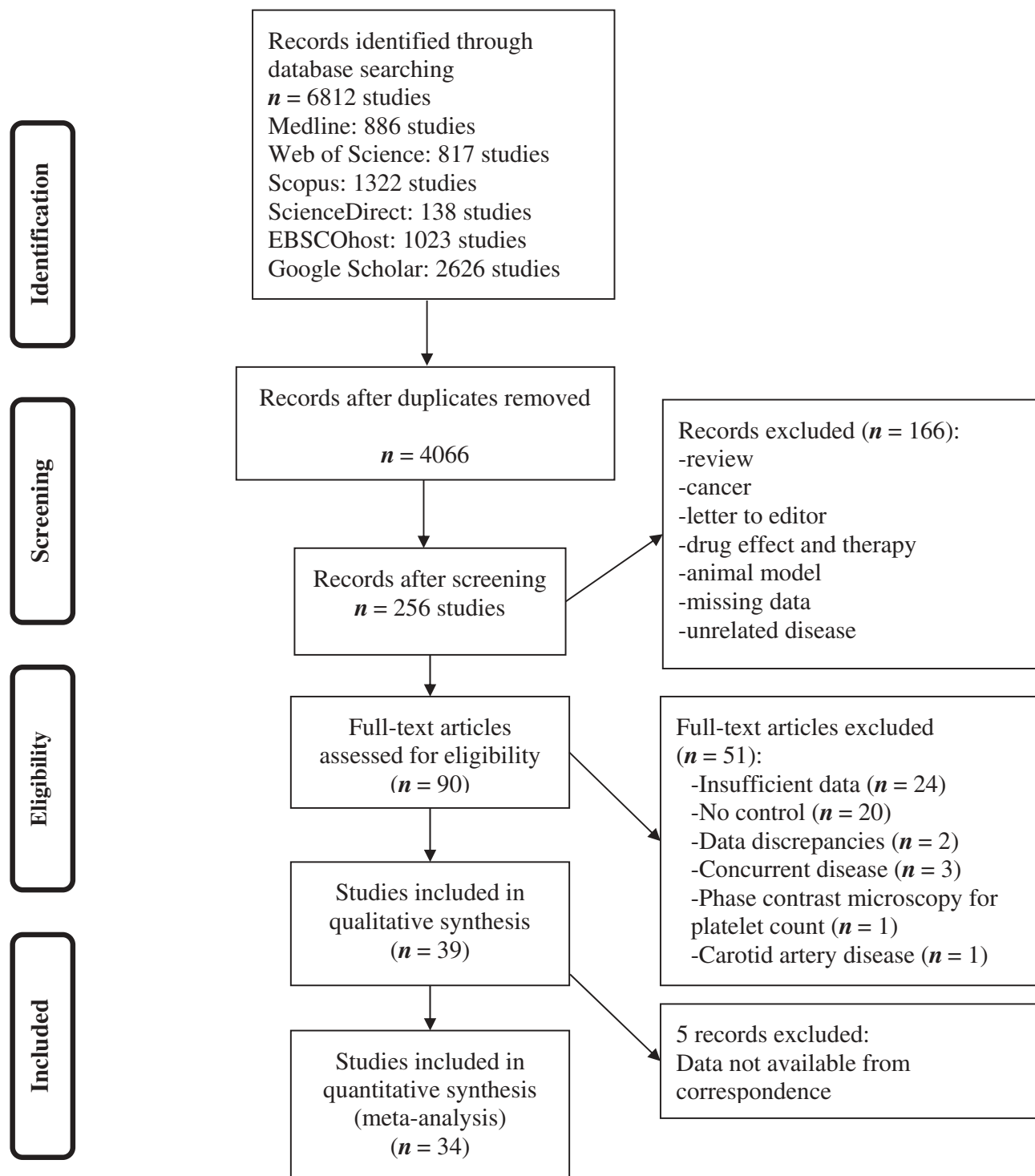**Screening**

Eligibility

Included

Figure 1. Flow chart diagram presenting the study progression.

46-48,50]. Ten studies found no difference in MPV between patients and controls [14,15,28,29,35,36,38,45,49], and two studies demonstrated a higher MPV in the control group (Table I, Supplementary Table VI) [13,40]. The mean MPV for all publications was 9.8 fL (95% CI 9.4–10.1) for patients and 9.2 fL (95% CI, 8.8–9.6) for controls. There was a marked residual heterogeneity by ME model for MPV [χ^2 = 333.5; df = 20; I^2 = 94% (95% CI: 89–97); $P < .001$]. The estimated pooled mean difference in MPV was 0.86 (Z = 5.509; $P < .001$) for the ME model regarding the type of analyte effect (EDTA compared to Citrate). It was 0.52 fL (Z = 4.29, $P < .001$) for RE model without moderating effects (Figure 3).

Subgroup Analysis

We also performed subgroup and sensitivity analyses according to the type of infarction, type of analyzer and type of analyte for MPV and PC to further evaluate the relationship between these parameters. Twelve studies measured complete blood count in 120 min or less, and seven studies assessed blood samples after 120 min. We analyzed them in a separate subgroup. Out of 34 studies which were included in this meta-analysis, three of them had divided their studies into different subgroups (Table I) [28,29,35].

Table I. Characteristic of included studies.

Author	Year	Country	NOS	Patients Age (year)	Patients MPV (fL)	Patients PLT (G/μL)	Number of patients	Number of controls	Controls Age (year)	Controls MPV (fL)	Controls PLT (G/μL)	Patients with history of hyperlipidemia (%)	Patients with history of CAD (%)	Patients with history of DM (%)	Patients with history of HT (%)	Patients with history of smoking (%)	Type of controls	Type of analyte	Sample storage time (min.)	Method of measurement	Type of Infarction
1) Farkkila	1987	Finland	8	37.8 ± 5	N/A	265 ± 37	12	13	35.3 ± 9.8	N/A	199 ± 12	N/A	N/A	N/A	N/A	N/A	Healthy	N/A	N/A	N/A	IS
2) D'Erasmo	1990	Italy	9	73 ± 10	11.3 ± 1.3	215 ± 66	36	60	72 ± 10	8.93 ± 0.9	299 ± 61	N/A	N/A	N/A	N/A	N/A	Outpatients	EDTA	240	Coulter	IS
3) D'Erasmo	1991	Italy	6	75 ± 9	N/A	215 ± 64	44	60	75 ± 9	N/A	299 ± 61	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Coulter	IS
4) Falke	1991	Sweden	9	67 ± 8	N/A	250 ± 60	37	46	61 ± 0.4	N/A	239 ± 47	N/A	N/A	N/A	N/A	N/A	Healthy	N/A	N/A	N/A	IS
5) Tohgi	1991	Japan	6	64 ± 12.9	9.8 ± 0.8	194 ± 54	22	29	55.3 ± 9.5	10.7 ± 0.6	247 ± 59	N/A	N/A	N/A	N/A	N/A	Healthy	Citrate	N/A	Sysmex	IS
6) O'Malley	1994	UK	8	79 ± 6.5	11.3 ± 1.7	255 ± 176	58	50	82 ± 8.5	10.1 ± 1.8	299 ± 160	N/A	N/A	N/A	N/A	N/A	Healthy	N/A	N/A	N/A	IS
7) Giroud	1995	France	9	63.5 ± 8.5	N/A	149 ± 59	130	130	63.5 ± 8.5	N/A	195 ± 48	8.1	8.4	13.8	68.4	14.5	N/A	N/A	N/A	N/A	PICH
8) O'Malley	1995	UK	9	79.5 ± 6.5	11.3 ± 0.8	255 ± 88	58	50	82 ± 8.5	10.1 ± 0.9	299 ± 80	N/A	54	8.6	29	14	Rehabilitation	EDTA	1440	Sysmex	IS
9) Butterworth	1998	UK	9	71.9 ± 10.8	7.3 ± 1.0	231 ± 82	137	65	68.5 ± 13	7.1 ± 0.7	236 ± 54	N/A	N/A	N/A	N/A	N/A	Healthy	Citrate	2880	Coulter	IS
		UK		71.9 ± 10.8	8.0 ± 1.0	233 ± 80	137	61	68.5 ± 13	7.7 ± 0.8	236 ± 54	N/A	N/A	N/A	N/A	N/A	Healthy	EDTA	2880	Coulter	IS
				68.5 ± 11	7.3 ± 1.0	233 ± 80	25	64	68.5 ± 13	7.1 ± 0.7	236 ± 54	N/A	N/A	N/A	N/A	N/A	Healthy	Citrate	2880	Coulter	PICH
10) Smith	2002	UK	9	73 ± 12.8	9.7 ± 0.8	225 ± 62	18	14	72 ± 7.3	9.8 ± 0.6	229 ± 43	N/A	0	0	67	38	Outpatients	Citrate	N/A	Sysmex	IS
				73 ± 12.8	10.3 ± 0.9	208 ± 41	6	14	72 ± 7.3	9.8 ± 0.6	229 ± 43	N/A	0	0	67	38	Outpatients	Citrate	N/A	Sysmex	PICH
11) Ziai	2003	USA	7	62 ± 2	N/A	220 ± 12	43	35	57 ± 3	N/A	273 ± 12	N/A	N/A	N/A	65	29	Unrelated disease	N/A	N/A	N/A	PICH
12) Cha	2004	Korea	7	58 ± 8.1	N/A	207 ± 5	29	52	62.8 ± 14.4	N/A	222 ± 50	N/A	17.2	51.7	72.4	72.4	Healthy	Citrate	N/A	N/A	IS
13) Wolf	2005	France	6	70 ± 4.3	N/A	214 ± 18	159	70	67 ± 4	8.6 ± 1	223 ± 12	26.4	18.9	22	53.5	22	No stroke	N/A	1440	Advia	IS
14) Sadreddini	2007	Iran	9	67 ± 15	9.9 ± 0.9	217 ± 80	100	100	67 ± 15	9.4 ± 0.8	208 ± 65	N/A	N/A	N/A	N/A	N/A	Healthy	EDTA	15	Sysmex	IS
15) Ilhan	2010	Turkey	6	65 ± 11	10.4 ± 1.3	N/A	30	30	60 ± 8.3	8.3 ± 0.8	N/A	N/A	N/A	N/A	N/A	N/A	Healthy	EDTA	N/A	Coulter	IS
16) Mayda-Domac	2010	Turkey	9	65.6 ± 12.6	9.9 ± 1.81	281 ± 93	384	208	63.2 ± 13.7	9.5 ± 3.9	269 ± 70	23.9	34.7	41.4	61.5	19.8	Healthy	EDTA	120	Sysmex	IS
				62.2 ± 13.1	9.6 ± 1.7	247 ± 77	208	208	63.2 ± 13.7	9.5 ± 3.9	269 ± 70	26.4	21.1	29.8	75.4	22.1	Healthy	EDTA	120	Sysmex	PICH
17) Al-Tameemi	2012	Iraq	9	64.7 ± 8.5	10.9 ± 1.3	254 ± 76	25	20	62.4 ± 9.5	11 ± 0.98	235 ± 60	N/A	16	56	68	44	Healthy	N/A	1440	Sysmex	IS
18) Järemo	2012	Sweden	6	74 ± 10	N/A	265 ± 84	72	24	66 ± 8	N/A	260 ± 78	N/A	9.7	15.2	44.4	13.8	Healthy	N/A	90	Coulter	IS
19) Cho	2013	Korea	6	51.5 ± 13	8.6 ± 1	N/A	166	311	N/A	8.6 ± 1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	EDTA	120	Sysmex	IS
20) Dogan	2013	Turkey	7	68 ± 14	9.9 ± 0.9	N/A	143	60	58 ± 17	9.4 ± 0.8	N/A	22.4	37.1	36.4	77.6	42	Healthy	EDTA	15	Sysmex	IS
21) Celikbilek	2014	Turkey	6	69.5 ± 13.4	9.8 ± 1.2	N/A	70	70	60 ± 10	10.2 ± 1.1	N/A	N/A	N/A	N/A	N/A	N/A	Healthy	N/A	N/A	N/A	IS
22) Li	2014	USA	7	53.3 ± 10.4	10.4 ± 1.3	224 ± 59	375	1840	48.9 ± 10	9.2 ± 1.2	228 ± 59	N/A	N/A	24.8	34.1	36.3	No disease	EDTA	30	Sysmex	IS
23) Wang	2015	China	9	63 ± 11	10.5 ± 0.8	214 ± 50	50	50	51 ± 12	10.2 ± 0.6	221 ± 34	N/A	N/A	N/A	N/A	N/A	Healthy	EDTA	N/A	Sysmex	IS
24) Ciancarelli	2016	Italy	7	72.3 ± 1.1	11 ± 0.2	N/A	24	24	72.4 ± 1.1	9.4 ± 0.3	N/A	N/A	N/A	N/A	N/A	N/A	Healthy	EDTA	120	Sysmex	IS
25) Lee	2016	USA	8	68 ± 6.5	N/A	238 ± 56	73	74	68 ± 6.6	N/A	242 ± 58	N/A	N/A	N/A	N/A	52	N/A	EDTA	N/A	N/A	PICH
26) Oz	2016	Turkey	6	63 ± 10	8.5 ± 0.9	240 ± 68	52	40	57 ± 12	8.3 ± 0.8	245 ± 83	N/A	N/A	N/A	N/A	N/A	Healthy	EDTA	30	N/A	IS
27) Özkan	2016	Turkey	9	67 ± 10	8.9 ± 1.1	262 ± 61	74	90	65.5 ± 11	8.3 ± 1	260 ± 48	27	N/A	32.4	43.2	21.6	Healthy	EDTA	30	Sysmex	IS
28) Elsayed	2017	Egypt	9	61 ± 13.5	8.99 ± 1.5	266 ± 83	50	20	53.6 ± 10.5	7.7 ± 0.9	266 ± 61.3	N/A	N/A	N/A	N/A	N/A	Healthy	EDTA	120	N/A	IS
29) Gokdemir	2017	Turkey	8	67.4 ± 10.8	9.5 ± 2.4	303 ± 124	48	46	66 ± 9.94	9.2 ± 2.3	328 ± 85	N/A	N/A	32	N/A	N/A	Healthy	Heparin	N/A	N/A	IS
30) Wan	2017	China	7	63.6 ± 7.5	11.3 ± 1.7	188 ± 69	100	80	62.7 ± 8.1	10.6 ± 1.1	191 ± 72	N/A	N/A	26	64	30	Healthy	N/A	N/A	Symex	IS
31) Ayas	2018	Turkey	7	73 ± 9	9.8 ± 1.6	249 ± 78	67	67	73 ± 9	9.6 ± 1.7	257 ± 73	11.9	36.4	38.8	77.6	17.9	Healthy	EDTA	60	Coulter	IS
32) Patel	2108	India	6	58 ± 14	9.8 ± 1.2	N/A	50	50	58 ± 14	8.3 ± 1.1	N/A	N/A	N/A	N/A	N/A	N/A	outpatient	EDTA	60	N/A	IS
33) Farah	2018	Israel	7	68.4	8.7 ± 1.2	N/A	200	30	N/A	9.2 ± 1.3	N/A	N/A	N/A	N/A	N/A	N/A	Healthy	N/A	N/A	N/A	IS
34) Sarkar	2018	India	9	55 ± 7.1	12.9 ± 1.3	N/A	70	40	52 ± 5.4	10.5 ± 1.3	N/A	N/A	N/A	N/A	65	N/A	Healthy	EDTA	N/A	Sysmex	IS

MPV, mean platelet volume; PLT, platelet count; NS, not significant; S, stroke; IS, ischemic stroke; PICH, primary intracerebral hemorrhage; NOS, Newcastle-Ottawa Scale; N/A, not available; CAD, coronary artery disease; DM, diabetes mellitus; HT, hypertension.
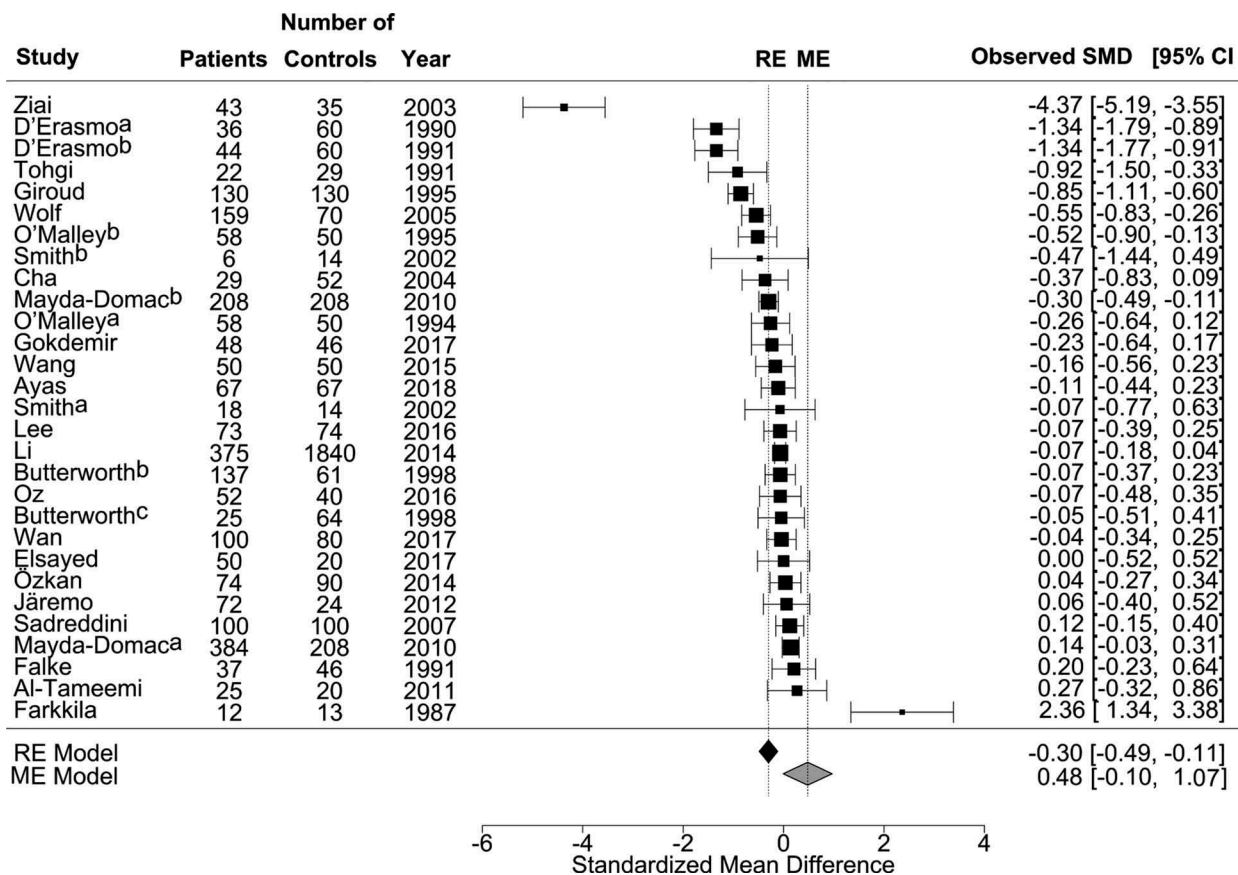
Figure 2. Forest plot of standard mean difference (SMD) for association between platelet count and occurrence of acute stroke.

In 23 studies about acute ischemic stroke, 2007 cases demonstrated significantly lower PC compared to 3090 control individuals (SMD = −0.18; 95% CI: − 0.35 to −0.01, $P < .001$) (Figure 4 panel A, Supplementary Table VII). Six studies about PICH revealed more significant results with 485 patients by comparison with 525 controls (SMD = −0.94; 95% CI: −1.62 to −0.25, $P < .001$) (Figure 4 panel B, Supplementary Table VII). Citrated samples for PC measurement showed significantly higher results in 100 patients compared with 173 controls (SMD = −0.36; 95% CI: −0.68 to −0.04, $P < .05$).

MPV was significantly higher in 2444 patients who suffered acute ischemic stroke compared to 3405 controls (SMD = 0.57; 95% CI: 0.31–0.83, $P < .001$) (Figure 4 panel C, Supplementary Table VIII). MPV was lower in patients compared with controls in case of acute hemorrhagic stroke, but this difference was not significant (SMD = 0.07; 95% CI: −0.10–0.25, $P > .05$) (Figure 4 panel D, Supplementary Table VIII). MPV from EDTA-anticoagulated samples was measured in 17 studies, and it was significantly higher in 1974 cases compared to 3209 control individuals (SMD = 0.86; 95% CI: 0.55–1.17, $P < .001$). Citrated samples from 208 cases showed lower MPV compared to 186 controls (SMD = −0.13; 95% CI: −0.69–0.42, $P < .001$). Sysmex hematology analyzers in 14 studies with 2727 controls measured significantly higher MPV in 1557 patients (SMD = 0.64; 95% CI: 0.28–1.01, $P < .001$). Coulter hematology analyzers in six studies with 432 patients measured significantly higher MPV compared with 347 controls (SMD = 0.58; 95% CI: 0.08–1.08, $P < .001$) (Supplementary Table VIII). We also examined MPV results in two subgroups of elapsed time more than 120 min or less than/equal to 120 min. This is the time delay between venipuncture and analysis (Supplementary Table VIII). Compared to control group, MPV was significantly higher in both ≤120 min and >120 min groups (SMD = 0.72; 95% CI: 0.36–1.08, $P < .001$) and (SMD = 0.70; 95% CI: 0.08–1.32, $P < .001$), respectively.

Discussion

We conducted a systematic review and meta-analysis of the literature to evaluate PC and MPV in patients with AS. To the best of our knowledge, this is the first meta-analysis assessing results of MPV and PC on AS while considering the type of stroke and some pre-analytical factors.

Larger platelets are more metabolically and functionally active, platelets with high MPV contain more glycogen, ADP, ATP, and reacting more readily to stimulating agents [51]. Platelet dysfunction is described to be associated with PICH [52]. Platelets also have a prominent role in thromboemboli formation that may initiate the symptoms of stroke. Recent meta-analysis showed elevated MPV in different pathological conditions [53,54].

Hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, and smoking habits are among the most important medical pre-conditions and stroke-related comorbidities. Several lines of evidence from the literature suggest that a direct correlation exists between MPV and these traditional cerebrovascular risk factors [55–60]. MPV was significantly higher (0.65 fL) in individuals with coronary artery disease and patients with high MPV had 17% higher chance of having cardiovascular events compared to patients with low MPV [61]. Another meta-analysis concluded that MPV was significantly higher in those with acute myocardial infarction than those without acute myocardial infarction [62].
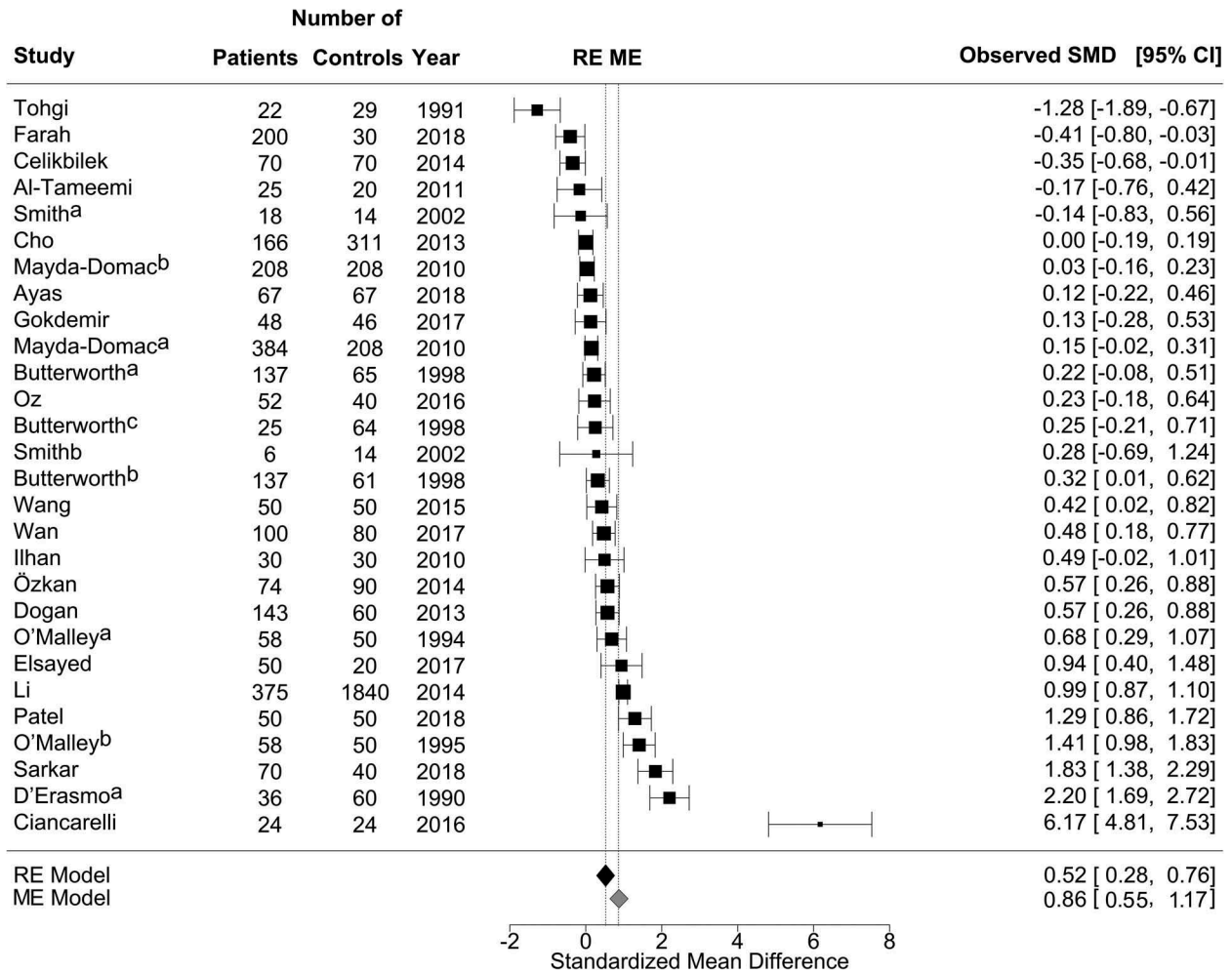
Figure 3. Forest plot of standard mean difference (SMD) for association between mean platelet volume and occurrence of acute stroke.
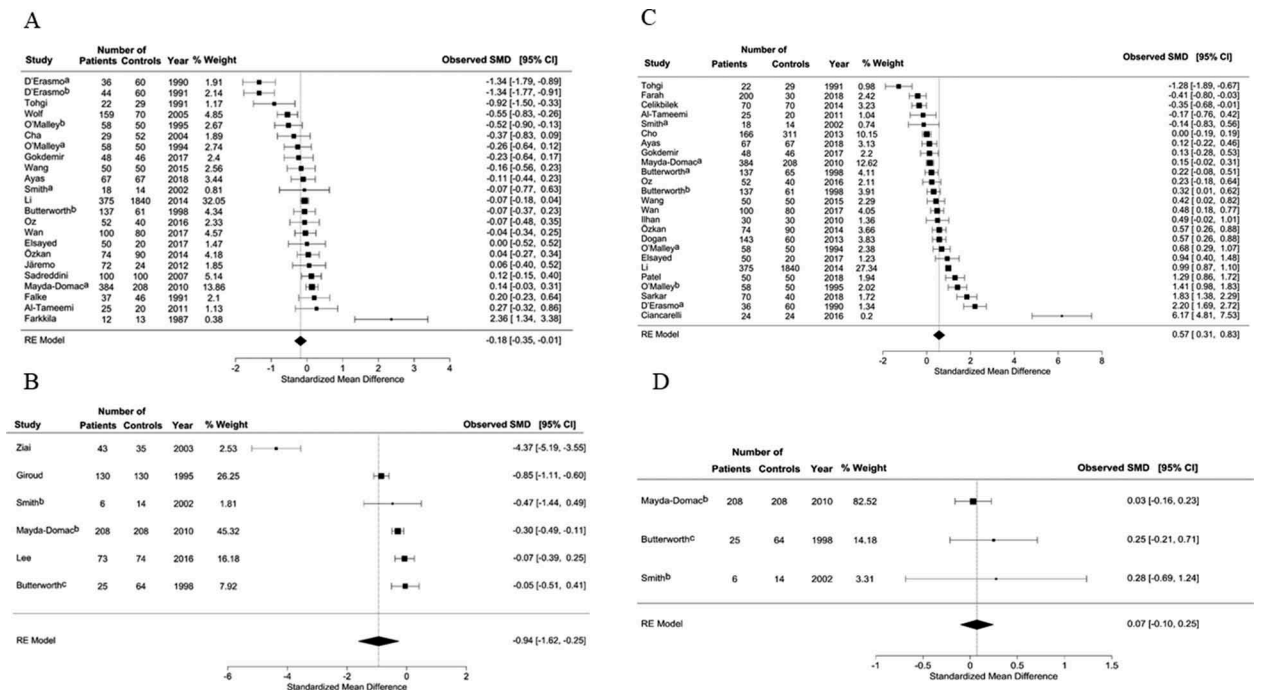

Figure 4. Subgroup analysis for A – platelet count in patients with acute ischemic stroke, or B – platelet count in patients with acute hemorrhagic stroke; and C – mean platelet volume in patients with acute ischemic stroke, or D – mean platelet volume in patients with acute hemorrhagic stroke.

In our study, significantly higher MPV was found in acute ischemic stroke and PC was significantly decreased in both acute ischemic and hemorrhagic strokes.

Some authors consider a possible use of MPV assessments as a potential biomarker of AS or as a prognostic marker in patients after AS [10,12]. An association of MPV with stroke is possibly due to higher platelet activity, aggregation, and turnover in patients with elevated MPV. It has been shown that increased MPV is linked to more hemostatically active platelets with higher avidity to aggregate [63]. Additionally, increased turnover of platelets causes the release of young, more active and larger platelets from bone marrow [64]. The estimated pooled mean difference of MPV was 0.51 fL and significantly higher in patients with AS than controls. Moreover, MPV was significantly higher in patients than controls after adjustment for the type of analyte or analyzer. It should be acknowledged that these differences are rather small in absolute terms. Therefore, they might reflect some changes of specific characteristics of the platelet population and may also show the presence of more reactive platelets within the blood stream in this group of patients.

Since the normal lifespan of platelets is between 8 and 10 days, the contribution of the elevated MPV in a prothrombotic state and an increased risk of stroke is likely to be present prior to stroke onset. Platelet activation measured by the levels of CD62P (*P*-selectin) and circulating monocyte-platelet complex was increased in stroke patients [65]. On the other hand, the level of reticulated platelets as a marker of platelet production was the same as controls in stroke patient [66]. These results suggest the presence of continuous stimulation for platelet activation without excessive platelet production after stroke. Monitoring stroke patients revealed constant elevated MPV results post-stroke, even three to 6 months after the event [25,28]. Low number of studies related to acute hemorrhagic stroke and hyporeactive platelets, as determined by significantly decreased platelet aggregation rates induced by ADP [67], could explain partly constant level of MPV in acute hemorrhagic stroke. Lower PC in acute ischemic stroke could be contributed to platelet consumption during acute phase of stroke [13]. Decreased PC number in patients with acute hemorrhagic stroke is difficult to explain. Consumption of platelets to produce effective lower PC requires significantly larger hemorrhage than that usually seen in nontraumatic acute hemorrhagic stroke. Medications such as antiepileptics, or antibiotics may have attributed to lower PC. It seems that modification of PC as an acute phase reactant requires additional time than duration of AS.

Pre-analytical conditions of MPV assessment have a great effect on the results of platelet size. If MPV would apply as a risk factor AS, its measurement should be standardized. This fact is not only important for laboratory, but also for clinicians.

Type of anticoagulant for blood samples has also a significant effect on platelet parameters measured by conventional hematology analyzers [68]. It has been demonstrated previously that the addition of EDTA anticoagulant to the sample causes artificial platelet swelling [69]. However, this modification could be partly explained by the alterations of both platelet cell wall and the membranes lining the canalicular system and the change of phosphorylation patterns of platelet proteins by exposure to EDTA [70,71]. Sixty-one percent of the studies included in this meta-analysis applied EDTA as an anticoagulant and it shows significantly higher MPV for patients. It is important to mention that almost half of the studies failed to report the type of analyte they used for their study. Type of anticoagulant for blood samples could also modify substantially PC results [72]. This phenomenon can be manifested by small-scale platelet micro-aggregate formation with the usage of the citrate anticoagulant [73]. Our results demonstrated that the estimated pooled mean difference of PC was −0.30 G/L in total patients compared to controls.

Hematology analyzers may differ in the method they incorporate for the measurement of the platelet parameters. These constitute mostly impedance or optical methods, and neither of them take into account the shape change of platelets [74]. As a result, these methods do not agree with each other. Sample storage time is another parameter which influences MPV [75]. Although not all studies stated sample storage time in their investigation, MPV was significantly higher than controls in both ≤120 min and >120 min groups. One possibility to increase the chance to harmonize the reporting of MPV is standardizing the elapse time between venipuncture and MPV measurement.

There are some limitations to this study. Several reasons may account for inconsistent results on the association between MPV and stroke in the literature. Pooled estimates demonstrated large heterogeneity. This can be explained by vast differences in pre-analytical factors and demographic characteristics of the studied population. Most of the studies failed to mention these characteristics and it could be a potential source of heterogeneity. Only a limited number of studies evaluated the potential confounding effects of the traditional cerebrovascular risk factors, and pre-analytical factors were profoundly diverse among them. Significant heterogeneity exists among some studies, and the results should be interpreted cautiously. Different results could be related to the time difference between the stroke and blood tests, failure to report the type of analyte or type of analyzer. False results could be obtained as blood samples remain in contact with anticoagulant for a long time. The difference in the analyte used to anticoagulant the samples or assay methods might also partly contribute to the high heterogeneity among the studies.

We recommend future studies design to include a set of standard covariates and pre-analytical factors. This can be achieved by implanting specific time frame to measure the sample results, define the type of anticoagulant in sample tube and specify method of measurement. Lack of thorough documentation of patient-related pre-analytical factors leads to higher variability among studies.

In conclusion, MPV as a part of a routine complete blood count is easily accessible and could be a surrogate marker of platelet turnover. The results of this study emphasize that platelets play a role in the pathogenesis of stroke, PC and MPV appeared to be significantly different from control populations. Acute ischemic stroke demonstrated significantly higher MPV, nonetheless both acute ischemic and hemorrhagic strokes revealed significantly lower PC. These features might be associated with AS and related to its occurrence.

Declaration of interest statement

The authors report no conflicts of interest.

Supplementary material

Supplemental data for this article can be accessed here.

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