Systematic Review / Meta-analysis

Role of platelet indices as a biomarker for the diagnosis of acute appendicitis and as a predictor of complicated appendicitis: A meta-analysis

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**ABSTRACT**

**Keywords:**
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**Introduction:** Acute appendicitis is one of the most common surgical emergencies worldwide. Clinical scoring systems have been developed to diagnose acute appendicitis, but insufficient to predict the complication. The amount of serum biomarkers elevates in response to acute inflammation, which could be beneficial for diagnostic tools. Accordingly, a meta-analysis was conducted to evaluate the efficacy of platelet indices, including mean platelet volume (MPV) and platelet distribution width (PDW) as potential biomarkers for the diagnosis of acute appendicitis.

**Material and methods:** The dataset was defined by searching for articles published until December 2020 from PubMed, EMBASE, Google Scholar and the Cochrane database. The meta-analysis was performed using Review Manager Software version 5.4.1.

**Results:** The final analysis was made from 9 studies, including 3124 patients. The results demonstrated that lower MPV values was significantly associated with acute appendicitis (odds ratio (OR) = 0.81, 95% confidence interval (CI) = −1.51 to −0.11, P = 0.02), but not associated with complicated appendicitis by comparing it with the control (OR = −0.13, 95% CI = −0.33 to −0.07, P = 0.19) and non-complicated appendicitis groups (OR = −0.13, 95% CI = −0.30 to −0.04, P = 0.14). The present study failed to demonstrate the diagnostic value of PDW for the prediction of appendicitis and its complication.

**Conclusion:** The results of the meta-analysis strongly indicate that a lower MVP values could function as a marker for predicting the acute appendicitis.

1. **Introduction**

Acute appendicitis (AA) is one of the most common surgical emergencies worldwide. The annual incidence of acute appendicitis is 9.4 per 10,000 people and is continuing to increase in newly industrialized countries [1,2]. Urgent appendectomy within 24 h remains a part of standard care for patients with acute appendicitis. Diagnosis and treatment delays may be associated with the development of complicated appendicitis, which increases postoperative complications and 30-day mortality by up to 8% and 0.6%, respectively [3,4].

Several clinical scoring systems have been developed to diagnose acute appendicitis with greater than 80% sensitivity and specificity among high-risk patients, such as the Alvarado score, Appendicitis Inflammatory Response (AIR) score, and RIPASA (Raja Isteri Pengiran Anak Saleha Appendicitis) score. Nevertheless, the clinical scoring system insufficiently diagnoses acute appendicitis and appears to be unreliable at differentiating between complicated and uncomplicated disease [5–7].

Radiological methods include ultrasonography and computed tomography (CT) scans which have become valuable diagnostic tools. Point of care ultrasound (POCUS) is preferable for initial investigations and has a sensitivity and specificity for diagnosing AA of 91% and 97%, respectively [8]. The low dose CT scan is effective as a standard dose in diagnosing acute appendicitis with a sensitivity of 94% and 95%, respectively. Hence, these methods are useful for the diagnosis of complicated appendicitis [9]. However, the major limitations of these examinations are their high cost and lack of availability in the majority of rural hospitals in developing countries.

Complete blood count (CBC) is one of the most common basic laboratory tests to determine inflammatory pathology. Leukocytosis and the neutrophils shift to the left are associated with acute appendicitis. The amount of several biomarkers elevate in response to acute inflammation, including C-reactive, Neutrophil-Lymphocyte ratio (NL-ratio), and Platelet-Lymphocyte ratio making them reliable tools in the
identification of non-complicated and complicated appendicitis [10–12].

Platelet indices play an important role in the response to systemic inflammation and sepsis [13]. High inflammation activity increases the activation, sequestration, and destruction of platelets which results in the release of small platelets into the bloodstream [14]. Platelet indices include mean platelet volume (MVP) and platelet distribution width (PDW) which is a measurement of platelet size determined and determined through a routine complete blood count test. Therefore, the reduction of MPV and PDW parameters may be used as a marker to reflect the acute inflammation burden and disease severity for several diseases, including rheumatoid arthritis acute pancreatitis and inflammatory bowel disease [15,16].

Although several studies report the usefulness of platelet indices in the diagnosis of acute appendicitis, there has been a significant degree of inconsistency in the findings of these studies. The present study conducts a meta-analysis based on the published literature in an attempt to clarify and evaluate the efficacy of platelet indices (MPV and PDW) as a potential biomarker for a diagnostic test of acute appendicitis and complications.

2. Material and methods

2.1. Data sources and search strategies

Electronic literature searches were performed on PubMed, Embase, Google Scholar, and the Cochrane database. The search terms ‘platelet indices’, ‘biomarkers’, ‘acute appendicitis’, and ‘complicated appendicitis’ were used as keywords to identify all English-language studies published through to December 2020 that evaluated the role of platelet indices (MPV and PDW) as a biomarker in the diagnosis of acute appendicitis and in the prediction of complicated appendicitis. Meta-analysis was performed according to the PRISMA 2020 statement, a guideline for reporting systematic reviews [17]. The quality of the meta-analysis was assessed using the AMSTAR 2 criteria critical appraisal tool for systematic reviews that include randomized or non-randomized studies of healthcare interventions [18]. The protocol of this meta-analysis was registered on Review Registry (Unique Identifying Number of reviewregistry1131) [19].

2.2. Study selection and eligibility criteria

The study inclusion criteria were as follows: (1) Studies published in English; (2) Acute appendicitis proven by the pathologic diagnosis; (3) Clarification of complicated appendicitis as gangrenous or perforated appendicitis; (4) Clarification that the control group were patients with non-diagnosis of acute appendicitis or normal appendix through operative or pathological findings; and (5) Measurement of platelet indices to compare between control and non-complicated or complicated appendicitis groups. The exclusion criteria were: (1) Non-English language articles; (2) review articles; (3) studies involving pediatric patients (aged < 15 years); and (4) no continuous variable data reported. The quality of the studies included in the meta-analysis was further evaluated using the Newcastle-Ottawa scale. The maximum possible score is 9 points which represents the highest methodological quality [20].

2.3. Statistical analysis

The two reviewers independently extracted the following information from the selected studies: Author names, country of origin, year of publication, study design, number of patients, patient characteristics, levels of MPV and PDW, and clinicopathologic diagnosis of acute appendicitis. Extracted data was cross-checked to reach consensus and then entered into a computerized spreadsheet for analysis.

Meta-analysis was performed using Review Manager software, version 5.4.1 which was provided by the Cochrane Collaboration (Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark). Cochrane’s chi-square-based Q-statistic test was applied to assess between-study heterogeneity. An I² statistic was used to test for heterogeneity between the included studies (p < 0.05 is considered for significant heterogeneity).

The association between platelet indices (MPV and PDW) with the diagnosis acute appendicitis and the prediction of complicated appendicitis by comparing with the control group was analyzed using continuous variable data (mean ± SD) with inverse variant methods to generate a pooled odds ratio (OR). The OR was considered statistically significant at the p < 0.05 level and the 95% confidential interval (CI) did not include the value 1.

The authors adopted the random-effects model, which is a more conservative way to calculate ORs, assumes a high level of variety between studies, and uses a weighted average of the effects reported in different studies to calculate levels of association. Publication bias was assessed by visual examination of a funnel plot, while asymmetry was formally assessed using both Egger’s linear regression test and the rank correlation test (Begg’s test).

3. Results

The initial search identified a total of 101 potential articles. After screening, nine articles that matched the researchers’ criteria were deemed suitable for inclusion in the meta-analysis [21–29]. The PRISMA diagram used in the search process is shown in Fig. 1. The two reviewers showed 100% agreement with the final dataset. The pooled studies included 3124 patients which was used to investigate the association between the platelet indices (MPV, PDW) values with the diagnosis of acute appendicitis by comparing acute appendicitis and complicated appendicitis against control groups.

Patients with hematologic disorder and severe comorbidities such as liver disease, heart failure, and peripheral vascular disease, which may affect the levels of MPV and PDW, were excluded from all of the included studies. Blood samples were obtained from the patient’s admission time or within 24 h after diagnosis of acute appendicitis and drawn into tubes containing EDTA or citrate to analyze complete blood count and platelet indices using an automated hematologic analyzer. The Newcastle-Ottawa scale found that all the studies included in the meta-analysis were of moderate to good quality (6–8 stars). The characteristics of the nine included studies are shown in Table 1.

3.1. Mean platelet volume (MPV) and the diagnosis of acute appendicitis

Seven studies [21–23,25,27,29] reported an association between MPV and acute appendicitis, with a total of 2142 patients (1406 patients [68%] in the acute appendicitis group and 736 patients [32%] in the control group). Pooled analysis of the seven studies demonstrated that the MPV among patients with acute appendicitis was significantly lower than the control group (OR = −0.81, 95% CI = −1.51 to −0.11, P = 0.02). There was significant heterogeneity between studies (I² = 97%, p < 0.00001). A forest plot displaying the association between MPV and diagnosis of acute appendicitis is illustrated in Fig. 2. Thus, the data was analyzed with random effect models. No evidence of publication bias was observed by either Egger’s test (P = 0.398) or the rank correlation test (P = 0.652). A funnel plot of the meta-analysis shown symmetrical distribution is illustrated in Fig. 3.

3.2. Mean platelet volume (MPV) and the prediction of complicated appendicitis

Four studies [24,26–28] reported an association between MPV and complicated appendicitis, with a total of 450 patients (235 patients [52%] in the complicated appendicitis group and 215 patients [48%] in the control group). The pooled analysis demonstrated that MPV appeared to reduce in the complicated appendicitis group, but was not
significantly different (OR = -0.13, 95% CI = -0.33 to -0.07, P = 0.19). There was no evidence of heterogeneity between the study (I² = 0%, p = 0.57) or publication bias (Egger’s test [P = 0.807] or the rank correlation test [P = 0.734]) observed in this analysis.

Additional analysis was conducted with four observational studies [24,26,28,29] that included 931 patients by comparing the MPV in complicated (200 [21%] patients) and non-complicated appendicitis group (731 [79%] patients). There was no significant difference between two patients groups (OR = -0.13, 95% CI = -0.30 to -0.04, P = 0.14). Evidence of heterogeneity (I² = 0%, p = 0.14) and publication bias [Egger’s test (P = 0.949) or the rank correlation test (P = 1.000)] was not observed.

3.3. Platelet distribution width (PDW) and the diagnosis of acute appendicitis and prediction of complication

Three studies [22,26,27] with a total of 767 patients included 513 (67%) patients in the acute appendicitis group and 254 (33%) patients in the control group. The pooled analysis did not demonstrate significant difference in PDW between both patient groups (OR = 1.19, 95% CI = -0.59 – 2.97, P = 0.19). Significant heterogeneity between the studies was found (I² = 98%, p < 0.0001). No evidence of publication bias was identified by either Egger’s test (P = 0.744) or the rank correlation test (P = 0.602).

Two studies [26,27] investigated the association between PDW and complicated appendicitis which included 153 patients (59 [39%] patients in the complicated appendicitis group and 94 [61%] in the control group). The pooled analysis demonstrates no significant difference in PDW between the complicated appendicitis and control groups (OR = -0.83, 95% CI = -2.10 – 0.44, P = 0.20). Significant heterogeneity between the studies was found (I² = 80%, p = 0.02).

The final analysis was conducted from two studies [26,27] which included 353 patients (59 [17%] in the complicated appendicitis group and 294 [83%] in the non-complicated appendicitis group). There was no significant different in PDW in both groups (OR = -1.46, 95% CI = -4.32 – 1.40, P = 0.32). Significant heterogeneity was detected (I² =
96%, \( p < 0.00001 \). A summary of the association between platelet indices (MPV and PDW) and the diagnosis of acute appendicitis and prediction of complicated appendicitis is illustrated in Table 2.

### Table 1
Characteristics of the 9 included studies included in the meta-analysis regarding the platelet indices and acute appendicitis.

| Study          | Country | Year | Study design               | Number of patients | Mean age (years)       | Blood sample obtained and analysis | Platelet indices                  | Matching | Newcastle Ottawa score |
|----------------|---------|------|----------------------------|--------------------|------------------------|-----------------------------------|-----------------------------------|----------|------------------------|
| Albayrak       | Turkey  | 2011 | Retrospective study        | 432                | 32.5 ± 15.1            | - Appendicitis group: 32.5 ± 15.1 | Mean platelet volume (MPV)        | a, b, c, f | 8                      |
|                |         |      |                            |                    | 30.8 ± 9.7             | - Control group: 30.8 ± 9.7       |                                   |          |                        |
| Fan            | China   | 2015 | Retrospective study        | 320                | 45.6 ± 19.6            | - Appendicitis group: 45.6 ± 19.6 | Mean platelet volume (MPV)        | a, b, d, f | 8                      |
|                |         |      |                            |                    | 43.0 ± 12.5            | - Non-appendicitis group: 43.0 ± 12.5 |                                   |          |                        |
| Erdem          | Turkey  | 2015 | Retrospective study        | 200                | 33.6 ± 12.2            | - Appendicitis group: 33.6 ± 12.2 | Mean platelet volume (MPV)        | a, b, c, f | 7                      |
|                |         |      |                            |                    |                        | - Control group: 30.8 ± 9.7       |                                   |          |                        |
| Bozkurt        | Turkey  | 2015 | Retrospective study        | 275                | 32.4                   | - Appendicitis group: 32.4        | Mean platelet volume (MPV)        | a, b, f   | 7                      |
|                |         |      |                            |                    |                        | - Control group: 34               |                                   |          |                        |
| Yardimci       | Turkey  | 2016 | Retrospective study        | 513                | 32.4                   | - Appendicitis group: 32.4        | Mean platelet volume (MPV)        | a, b, f   | 6                      |
|                |         |      |                            |                    |                        | - Non-appendicitis group: 31      |                                   |          |                        |
| Boshnak        | Egypt   | 2017 | Prospective non-randomised study | 200                | 22.56 ± 7.64           | - Appendicitis group: 22.56 ± 7.64 | Mean platelet volume (MPV)        | a, b, c, d, e, f | 8                      |
|                |         |      |                            |                    |                        | - Control group: 29.10 ± 16.33    |                                   |          |                        |
| Yigit          | Turkey  | 2019 | Retrospective study        | 322                | 32 ± 13                | - Appendicitis group: 32 ± 13     | Mean platelet volume (MPV)        | a, b, d, e, f | 8                      |
|                |         |      |                            |                    |                        | - Control group: 32 ± 14          |                                   |          |                        |
| Birick         | Turkey  | 2019 | Retrospective study        | 424                | 35.9 ± 16.7            | - Appendicitis group: 35.9 ± 16.7 | Mean platelet volume (MPV)        | a, b, e, f | 8                      |
|                |         |      |                            |                    |                        | - Non-appendicitis group: 35.1 ± 13.3 |                                   |          |                        |
|                |         |      |                            |                    |                        | - Control group: 32.9 ± 11.7      |                                   |          |                        |
| Haghi          | Iran    | 2019 | Retrospective study        | 438                | Mean age 26.5 ± 13.9   | - Not available                   | Mean platelet volume (MPV)        | a, b, f   | 6                      |

Abbreviations: a = age, b = sex, c = time of blood obtained d = time of blood analysis, e = type of anticoagulant in collecting tube, f = pathologic diagnosis of appendicitis, \( \text{fL} = \times 10^9/L \).

### Fig. 2.
Forest plot of the association between MPV and diagnosis of acute appendicitis.

### 4. Discussion
Appendectomy is the most common emergency surgical operation worldwide. Normal histopathologic findings of the appendix (negative appendectomy) reported an incidence of 8.47–9.5% which may increase mortality by up to 1.93% in male patients [30]. In addition, the most common mistaken diagnoses are typically correlated with young females with gynecological conditions (25–64.3%) [31]. Evaluating patients with the clinical scoring system may lower the negative appendectomy rate to 6.84% [32]. In an attempt to avoid unnecessary
acute abdominal pain such as AA and ovarian torsion which may contribute to platelet sequestration and destruction, leading to activation of megakaryocytes in the bone marrow to release young platelets into circulation. Thus, large platelets should be found in the early inflammatory phase, then the progression into the late phase of sepsis. Meanwhile, small-sized platelets should be detected in CBC analysis and indicate complicated intrabdominal infection. This finding may lead to low sensitivity of MPV and PDW in the diagnosis of AA in some previous studies [33,34].

The meta-analysis results investigated whether MVP and PDW are biomarkers for the diagnosis of acute appendicitis and the prediction of complicated appendicitis. The results demonstrate that MPV is significantly lower among acute appendicitis groups compared to control groups. Similar to Ceylan et al. the MPV value significantly decreased in non-complicated appendicitis subjects with a cutoff level of 9.95 x 10^9/L, in which sensitivity and specificity were 59.0% and 59.5%, respectively [35]. Shen et al reported the association between MPV and complicated appendicitis. The results demonstrate that MPV is significantly lower among complicated appendicitis group with a 76.3% sensitivity and 93.1% specificity [22]. The difference between studies can be described as: 1) Patient comorbidities - chronic disease that may affect platelet morphology such as obesity, hypertension, smoking, and hyperlipidemia; and 2) Pre-analytical factors - anticoagulant in collecting tubes used for blood samplings may affect the platelet morphology (EDTA-induced platelets swelling, citrate induced platelet shrinkage) may lead to unreliable outcomes [39,40].

The results of the present study were somewhat complicated since significant heterogeneity was identified in the meta-analysis of the association between MPV and PDW with the diagnosis of acute appendicitis and PDW with complicated appendicitis. The heterogeneity observed in the meta-analysis can be explained by: 1) Differentiation in the patient exclusion criteria for each study; 2) Timing of blood samples obtained varied from patients presenting time to within 24 h after diagnosis; 3) Waiting time for blood analysis varied from 10 min to 2 h; and 4) The disparity of hematology analyzers and the reference values of each study. Additionally, the data was adjusted to mimic the heterogeneity in the analysis of MPV and complicated appendicitis and adopted a

### Table 2
The result of the meta-analyses of the association between platelet indices (MPV and PDW) and the diagnosis of acute appendicitis and prediction of complicated appendicitis.

| Comparison                                                                 | Number of studies | n   | Odds Ratio | 95% confidential interval | P value | Heterogeneity between the study | Egger’s test | Rank-correlation test |
|---------------------------------------------------------------------------|-------------------|-----|------------|---------------------------|---------|-------------------------------|-------------|----------------------|
| Mean platelet volume (MPV) for prediction of complicated appendicitis: comparison with control group | 4                 | 450 | −0.13      | −0.33 to −0.07            | 0.19    | I^2 = 0%, p = 0.57           | P = 0.807   | P = 0.734           |
| Mean platelet volume (MPV) for prediction of complicated appendicitis: comparison with non-complicated appendicitis group | 4                 | 931 | −0.13      | −0.30 to −0.04            | 0.14    | I^2 = 0%, p = 0.14           | P = 0.949   | P = 1.000           |
| Platelet distribution width (PDW) for the diagnosis of acute appendicitis | 3                 | 767 | 1.19       | −0.59 to 2.97             | 0.19    | I^2 = 98%, p < 0.0001\(^1\)  | P = 0.744   | N/A                  |
| Platelet distribution width (PDW) or prediction of complicated appendicitis: comparison with control group | 2                 | 153 | −0.83      | −2.10 to −0.44            | 0.20    | I^2 = 80%, p = 0.02\(^2\)    | N/A         | N/A                  |
| Platelet distribution width (PDW) or prediction of complicated appendicitis: comparison with non-complicated appendicitis group | 2                 | 353 | −1.46      | −4.32 to 1.40             | 0.32    | I^2 = 96%, p < 0.00001\(^3\) | N/A         | N/A                  |

\(^1\) Statistical significant, N/A = Not available.
random-effects model to calculate the OR in order to compensate this effect for a more conservative result.

The major limitations of the present study include several potential sources of publication bias, for instance the inclusion of only English language publications, studies that indicate continuous variable outcomes may lead to missing relevant articles, and only observational retrospective studies were considered. Finally, most of the patients in this analysis were from Asian populations and does not represent a global clinicopathological correlation between platelet indices and acute appendicitis. Nonetheless, evidence of publication bias was not observed from the Egger’s linear regression test and rank correlation test results.

5. Conclusion

This study demonstrates that lower MPV values can have a significant role in the diagnosis of acute appendicitis, but failed to determine severity. The researchers suggest the use of MPV as a biomarker along with the clinical scoring system in patients with suspected acute appendicitis for greater diagnostic accuracy. Nevertheless, PDW was not found to be useful as a diagnostic marker and prediction of complicated appendicitis.

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Author contribution

Tullavardhana Thawatchai: Concepts, Design, Definition of intellectual content, Literature search, Clinical studies, Data analysis, Statistical analysis, Manuscript review, Guarantor, Sanguanolot Sarat: Design, Definition of intellectual content, Literature search, Data analysis, Acquisition, Statistical analysis, Manuscript preparation, Manuscript review, Guarantor, Chartkitchareon Anuwat: Definition of intellectual content, Literature search, Data acquisition, Data analysis, Manuscript editing.

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Ethical approval

This study is a systematic review and meta-analysis: no need for ethical approval.

Registration of research studies

Name of the registry: THAWATCHAI TULLAVARDHANA.
Unique Identifying number or registration ID: reviewregistry1131.
Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/60744d3e3488b8001c745bfa/

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Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

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