International Journal of Health Sciences and Research
[Indexed, Peer-Reviewed Journal]
Volume 16; Issue: 4; April 2026
Website: www.ijhsr.org
ISSN: 2249-9571

Systematic Review

Comparative Diagnostic Performance of Procalcitonin, C-Reactive Protein, and White Blood Cell Count in Acute Appendicitis: A PRISMA-Compliant Systematic Review

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DOI: https://doi.org/10.52403/ijhsr.20260419

ABSTRACT

Background and Aims: Acute appendicitis remains a common surgical emergency, and timely diagnosis is essential to prevent complications. Inflammatory biomarkers such as procalcitonin (PCT), C-reactive protein (CRP), and white blood cell (WBC) count are frequently used as adjunctive diagnostic tools; however, their comparative diagnostic accuracy, particularly for complicated appendicitis, remains uncertain. This systematic review aimed to evaluate and compare the diagnostic performance of PCT, CRP, and WBC, individually and in combination, for detecting overall and complicated acute appendicitis in adult and pediatric patients, using histopathology as the reference standard.
Methods: This review was conducted according to PRISMA guidelines. A comprehensive search of PubMed/MEDLINE, ScienceDirect, the Cochrane Library and Google Scholar from 2012 to 2025 was performed using MeSH terms and keywords combined with Boolean operators "AND" and "OR". Eligible studies included prospective and retrospective diagnostic accuracy studies assessing PCT, CRP, and/or WBC against histopathological findings. Data on sensitivity, specificity, predictive values, area under the curve (AUC), and cut-off values were extracted. Methodological quality was assessed using the QUADAS-2 tool.
Results: Nine observational studies comprising adult and pediatric populations were included. CRP demonstrated consistently moderate-to-high sensitivity and superior performance in identifying complicated or perforated appendicitis, with reported AUC values up to 0.93. PCT showed limited sensitivity for uncomplicated appendicitis but strong predictive value for complicated disease, including abscess and perforation. WBC count exhibited relatively high sensitivity but limited specificity. Combined biomarker strategies improved diagnostic accuracy and negative predictive value compared with individual markers.
Conclusion: CRP is the most reliable single biomarker for acute appendicitis, particularly for detecting complicated disease. PCT is valuable for severity assessment, while WBC serves as a supportive indicator. Combined biomarker approaches enhance diagnostic performance but do not replace clinical evaluation.

Keywords: Appendicitis; Procalcitonin; C-Reactive Protein; Leukocyte Count; Sensitivity and Specificity; Diagnostic Accuracy.

INTRODUCTION

Acute appendicitis (AA) remains the most common surgical emergency worldwide, affecting approximately 7–12% of the population over a lifetime and accounting for over 300,000 appendectomies annually in the United States alone. Despite advances in imaging, diagnostic uncertainty persists in 20–30% of cases, leading to negative appendectomy rates of 10–20% and perforation rates up to 30% in delayed presentations, particularly in children and atypical adults. Clinical scores like Alvarado or Appendicitis Inflammatory Response remain imperfect (AUCs 0.70–0.85), prompting reliance on biomarkers such as C-reactive protein (CRP), white blood cell count (WBC), and procalcitonin (PCT) to enhance accuracy [1-4].

Over the past 15 years (2011–2026), PubMed-indexed meta-analyses have established CRP and WBC as moderately accurate for overall AA (pooled sensitivities 57–90%, specificities 58–87%, AUCs 0.70–0.78), outperforming PCT (AUC 0.65, sensitivity 33%) for initial diagnosis. PCT, however, shows promise for complicated AA (perforated/gangrenous; pooled sensitivity 62–89%, specificity 90–94%, AUC 0.78–0.96), aiding severity stratification. Pediatric data indicate similar hierarchies, with CRP/WBC combinations yielding NPVs >95% for ruling out disease. Despite this, heterogeneity in cut-offs, timing, assays, and populations limits generalizability, while negative appendectomies persist due to non-specific elevations [1-10].

This study addresses a critical research gap: no recent comprehensive synthesis compares these biomarkers' individual/combined accuracies for both overall and complicated AA across adult/pediatric cohorts using histopathology as the reference standard. The rationale stems from escalating healthcare burdens—delayed complications inflate costs by 2–3-fold—and the need for standardized adjuncts in resource-variable settings. Its novelty lies in pooling granular metrics (AUCs, odds ratios, combinations) from diverse designs, informing PRISMA-DTa-compliant pathways to reduce unnecessary surgeries by 10–15%.

Research Question: What are the comparative diagnostic accuracies of PCT, CRP, and WBC, alone and combined, for detecting overall versus complicated AA in adults and children, using histopathology-confirmed outcomes?

Methodology

Study Design and Reporting Standards

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. The objective was to systematically evaluate and compare the diagnostic accuracy of procalcitonin (PCT), C-reactive protein (CRP), and white blood cell (WBC) count, assessed individually and in combination, for the detection of overall and complicated acute appendicitis in both adult and pediatric populations. Histopathological examination of the resected appendix was considered the reference standard.

Eligibility Criteria

The eligibility criteria were predefined using the PICOS framework. The population comprised adult and pediatric patients presenting with suspected acute appendicitis. The index tests included serum procalcitonin, C-reactive protein, white blood cell count, leukocyte count, and combinations of these biomarkers. The reference standard was histopathological confirmation of appendicitis, including both uncomplicated and complicated (gangrenous or perforated) forms. The primary outcomes were measures of diagnostic accuracy, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the receiver operating characteristic curve (AUC), positive and negative likelihood ratios (LR+ and LR−), odds ratios (OR), and reported cut-off values. Eligible study designs included prospective and retrospective cohort studies, cross-sectional studies, and case-control studies that provided sufficient data to calculate diagnostic accuracy parameters. Case reports, editorials, letters, conference abstracts lacking full data, review articles, animal studies, and studies not using histopathology as the reference standard were excluded.

Information Sources and Search Strategy
A comprehensive electronic literature search was performed in PubMed/MEDLINE, ScienceDirect, the Cochrane Library and Google Scholar from 2012 to 2025. The search strategy incorporated relevant keywords and Medical Subject Headings (MeSH) terms combined using Boolean operators "AND" and "OR." Keywords included "Acute Appendicitis," "Appendicitis," "Procalcitonin," "C-reactive Protein," "White Blood Cell," "Leukocyte," and "Diagnostic Accuracy." The search string integrated MeSH terms such as ("Appendicitis"[MeSH] OR "Acute Appendicitis" OR Appendicitis) AND ("Procalcitonin"[MeSH] OR Procalcitonin OR PCT) OR ("C-Reactive Protein"[MeSH] OR "C reactive protein" OR CRP) OR ("Leukocyte Count"[MeSH] OR "White Blood Cell" OR WBC OR Leukocyte) AND ("Sensitivity and Specificity"[MeSH] OR "Diagnostic Accuracy" OR "Predictive Value of Tests"[MeSH] OR sensitivity OR specificity OR AUC). Boolean operators were applied appropriately to optimize sensitivity and specificity of the search. Additionally, reference lists of included studies were manually screened to identify further eligible articles.

Study Selection
All retrieved records were exported into reference management software, and duplicate entries were removed. Two independent reviewers screened titles and abstracts for relevance. Full-text versions of potentially eligible studies were subsequently assessed against the predefined inclusion and exclusion criteria. Any discrepancies between reviewers were resolved through discussion and consensus. The overall study selection process was documented using a PRISMA flow diagram.

Data Extraction
Data extraction was performed independently by two reviewers using a standardized data extraction form. Extracted variables included author and year of publication, country, study design, sample size, demographic characteristics of participants, biomarkers evaluated, cut-off values, sensitivity, specificity, PPV, NPV, AUC values, likelihood ratios, odds ratios, classification of appendicitis (overall versus complicated), and histopathological findings. Where necessary, attempts were made to contact study authors for clarification or to obtain missing data.

Risk of Bias Assessment
The methodological quality and risk of bias of included studies were evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [12]. The four domains assessed were patient selection, index test, reference standard, and flow and timing. Each domain was evaluated for risk of bias as well as concerns regarding applicability. Assessments were conducted independently by two reviewers, and disagreements were resolved by consensus.

Data Synthesis and Statistical Analysis
A qualitative synthesis was undertaken to summarize the diagnostic performance of PCT, CRP, and WBC count, both individually and in combination. Where sufficient homogeneity in study characteristics and outcome reporting was identified, pooled estimates of sensitivity and specificity were planned using a bivariate random-effects model, and summary receiver operating characteristic (SROC) curves were to be generated. Prespecified subgroup analyses included adult versus pediatric populations, overall versus complicated appendicitis, and single versus combined biomarker strategies. Statistical heterogeneity was to be assessed using the I^2

statistic and through visual inspection of forest plots.

Reporting and Methodological Rigor

This systematic and structured methodology ensured a rigorous, transparent, and reproducible evaluation of the diagnostic accuracy of procalcitonin, C-reactive protein, and white blood cell count in acute appendicitis, in strict adherence to PRISMA methodological standards.

RESULT

The study selection process is summarized in the PRISMA flow diagram provided in figure 1.

The literature search initially identified a total of 1,231 records from electronic databases. Prior to screening, 106 duplicate records were removed, leaving 1,125 unique records for title and abstract screening. Of these, 1,099 records were excluded based on predefined eligibility criteria. Subsequently, 26 full-text reports were sought for retrieval; however, 13 reports could not be retrieved. The remaining 13 full-text articles were assessed for eligibility, of which 4 were excluded with reasons. Ultimately, 9 studies met the inclusion criteria and were included in the final qualitative synthesis of the review.

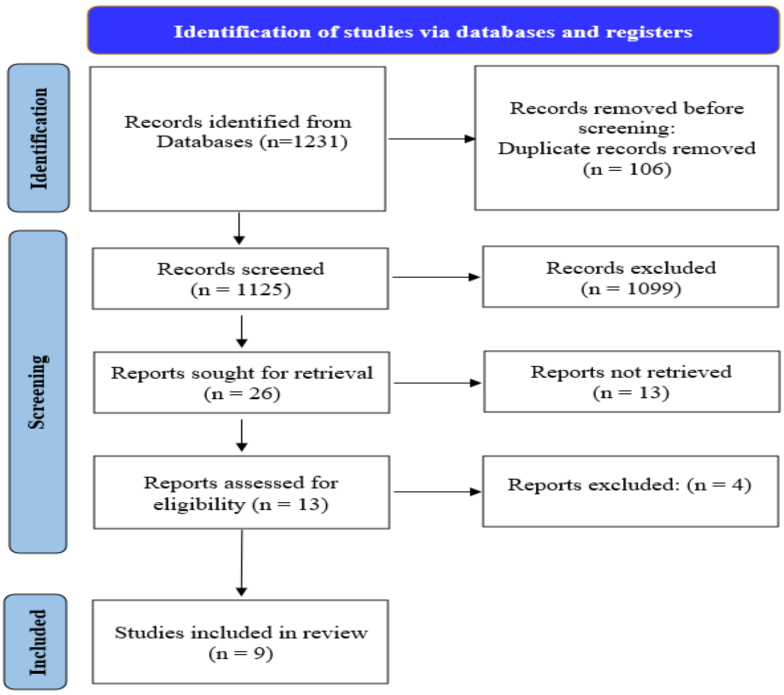

Figure 1: PRISMA flow diagram.

Table 1 summarizes nine observational studies evaluating the diagnostic performance of inflammatory biomarkers in acute appendicitis (AA), encompassing diverse populations from Asia, Europe, and the Middle East. Collectively, the studies demonstrate variability in sensitivity, specificity, and overall diagnostic accuracy across biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), white blood cell count (WBC), D-dimer, bilirubin, and composite indices.

In a prospective cohort study from Turkey, Kaya B et al. (2012) [13] evaluated 78 patients and reported that CRP (cut-off >0.8 mg/dL) demonstrated the highest diagnostic value (72%) compared to WBC (82% diagnostic value but very low NPV 0.08), D-dimer (31%), and PCT (26%). Although WBC showed high positive predictive value (PPV 0.95), its low negative predictive value (NPV) limited its exclusionary role. CRP levels were significantly higher in perforated compared with phlegmonous appendicitis

($p<0.05$), indicating utility in severity stratification. PCT (>0.05 ng/mL) and D-dimer (>600 ng/mL) had poor sensitivity and diagnostic value, suggesting limited standalone diagnostic utility.

Panagiotopoulou et al. (2013) [14], in a large retrospective UK study of 1,169 appendicectomies, demonstrated that WCC at 10×10^9/L had sensitivity 84% and specificity 58% for AA (AUC 0.7786), while CRP at 10 mg/L showed sensitivity 68% and specificity 66% (AUC 0.7047). Combined WCC/CRP improved diagnostic performance (AUC 0.8139), and inclusion of bilirubin increased sensitivity (96%) but markedly reduced specificity (33%). For perforated appendicitis (PA), CRP achieved superior diagnostic accuracy (AUC 0.9322), sensitivity 100%, and NPV 100%, outperforming WCC and bilirubin. Notably, 4.9% of AA cases had normal inflammatory markers, reinforcing that appendicitis remains primarily a clinical diagnosis.

Vaziri et al. (2014) [15] prospectively studied 100 patients in Iran and found that PCT >0.5 ng/mL had limited sensitivity (44%) for diagnosing AA but demonstrated excellent performance in detecting peritonitis (100%) and high predictive value for surgical site infection (83%). Higher PCT levels correlated with increasing severity, with values >10 ng/mL predominantly observed in peritonitis cases.

Similarly, Yamashita et al. (2016) [6] from Japan reported that PCT ≥0.46 ng/mL yielded the highest diagnostic accuracy (AUC 0.832, OR 30.3) for predicting abscess and/or perforation, outperforming CRP (AUC 0.830) and WBC (AUC 0.439). For mural destruction, PCT (AUC 0.777) showed comparable accuracy to CRP (AUC 0.792) and body temperature. These findings emphasize PCT's value in identifying complicated appendicitis rather than uncomplicated disease.

In pediatric populations, Buyukbese Sarsu and Sarac (2016) [5] analyzed 543 children and demonstrated that for acute appendicitis, WBC $\geq13.1\times10^3/\mu L$ (AUC 0.828) performed slightly better than CRP ≥0.6 mg/dL (AUC 0.765). However, for complicated appendicitis, CRP ≥1.17 mg/dL had superior diagnostic accuracy (AUC 0.887). Combined WBC and CRP markedly improved sensitivity (98.7%) and NPV (99.5%), indicating strong utility in excluding complicated appendicitis when both markers are normal.

Rahed et al. (2019) [16], in a case-control study from Iraq, reported significantly elevated mean PCT (17.31±0.51 ng/mL) and CRP (>6 mg/dL in 84%) in appendicitis patients compared with controls ($p<0.001$), with strong correlation between PCT and CRP ($r=0.78$). Although sensitivity and specificity were not specified, the study supported both markers as non-invasive diagnostic tools.

Kumar S et al. (2020) [17] from India found D-dimer >1.15 mg/L to have the highest diagnostic accuracy (AUC 0.817; sensitivity 72.7%, specificity 70.0%), outperforming CRP (AUC 0.716) and TLC (AUC 0.679, not statistically significant). Both CRP and D-dimer were significantly elevated in histologically confirmed appendicitis, suggesting adjunctive value in clinical decision-making.

Shahul Hameed et al. (2023) [18] in the UAE demonstrated that CRP ≥3 mg/L (sensitivity 85%, specificity 62%, NPV 96%) was superior to WBC $>10\times10^9$/L (sensitivity 75%, specificity 77%) for ruling in AA. Although the study also assessed imaging modalities, CRP emerged as the preferred laboratory marker.

Most recently, Suljendić et al. (2024) [19] evaluated 196 children and reported moderate standalone diagnostic accuracy for PCT (63%), CRP (59%), and leukocytes (56%). However, combining markers substantially improved performance, with PCT+CRP and PCT+leukocytes achieving diagnostic accuracy of 98%, and CRP+leukocytes yielding NPV 100%, highlighting the strength of multimarker strategies.

Overall, across heterogeneous study designs and populations, CRP consistently demonstrated moderate-to-high sensitivity and superior performance in identifying complicated appendicitis, particularly perforation. PCT showed limited sensitivity for uncomplicated appendicitis but strong predictive value for severe or complicated disease. WBC, while sensitive, lacked specificity and exclusionary reliability. D-dimer showed promising accuracy in select studies but requires further validation. Importantly, combined biomarker approaches improved diagnostic accuracy and negative predictive values, supporting their adjunctive role in clinical evaluation; however, none of the markers alone reliably excludes appendicitis, underscoring that diagnosis remains fundamentally clinical with laboratory parameters serving supportive functions.

Table 1. Characteristics of Included Studies.

Author & Year	**Country**	**Design of Study**	**Sample Size**	**Mean Age**	**Biomarkers Evaluated**	**Main Outcomes**	**Key Findings (Cut-off Values, Sensitivity %, Specificity %)**
Kaya B et al., 2012 [13]	Turkey	Prospective cohort	78	25.4 ± 11.1 yrs	D-dimer, PCT, CRP, WBC	Diagnostic accuracy & severity differentiation	WBC >10.2 K/µL: DV 82%; CRP >0.8 mg/dL: DV 72%; D-dimer >600 ng/mL: DV 31%; PCT >0.05 ng/mL: DV 26%. CRP significantly higher in perforated AA ($p<0.05$).
Panagiotopoulou et al., 2013 [14]	UK	Retrospective	1,169	25 yrs (IQR 17–39)	WCC, CRP, Bilirubin	Diagnosis of AA & perforation	AA: WCC $>10\times10^9$/L (Sens 84%, Spec 58%); CRP >10 mg/L (Sens 68%, Spec 66%); Bilirubin >15 µmol/L (Sens 50%, Spec 68%). PA: CRP Sens 100%, Spec 66% (AUC 0.93). Combined WCC+CRP Sens 88%.
Vaziri et al., 2014 [15]	Iran	Prospective cross-sectional	100	28 yrs	PCT, WBC, PMN, Alvarado score	Diagnosis & complication prediction	PCT >0.5 ng/mL: AA detection 44%; Peritonitis detection 100%; SSI prediction 83%.
Yamashita et al., 2016 [6]	Japan	Retrospective observational	63	48 ± 18 yrs	PCT, CRP, WBC, N/L ratio, BT	Mural destruction & perforation	Abscess/perforation: PCT ≥0.46 ng/mL (AUC 0.83, NPV 92%); CRP ≥6.7 mg/dL (AUC 0.83, NPV 92%). PCT highest OR (30.3).

Buyukbese Sarsu S & Sarac F, 2016 [5]	Turkey	Retrospective (Pediatric)	543	11.1 yrs	WBC, CRP	Diagnosis of acute & complicated AA	AA: WBC ≥13.1×10³/µL (Sens 73%, Spec 80%); CRP ≥0.6 mg/dL (Sens 71%, Spec 69%). Complicated AA: CRP ≥1.17 mg/dL (Sens 86%, Spec 82%, AUC 0.887). Combined Sens 98.7%.
Rahed et al., 2019 [16]	Iraq	Case-control	90	15–54 yrs	PCT, CRP	Diagnostic utility in AA	CRP >6 mg/dL: 84% positive in AA vs 10% controls; PCT significantly elevated ($p<0.001$). Strong correlation with WBC ($r=0.78$).
Kumar S et al., 2020 [17]	India	Prospective observational	65	31.18 ± 14.59 yrs	TLC, CRP, D-dimer	Differentiation of AA vs negative appendectomy	D-dimer >1.15 mg/L (Sens 72.7%, Spec 70%, AUC 0.817); CRP >87.6 mg/L (Sens 61.8%, Spec 60%); TLC >8569/µL (Sens 63.6%, Spec 50%).
Shahul Hameed et al., 2023 [18]	UAE	Retrospective	320	6–90 yrs	WBC, CRP	Diagnostic comparison of markers & imaging	CRP ≥3 mg/L (Sens 85%, Spec 62%); WBC >10×10⁹/L (Sens 75%, Spec 77%). CRP superior for ruling in AA.
Suljendić et al., 2024 [19]	Bosnia & Herzegovina	Retrospective	196	Median 9.5 yrs	PCT, CRP, Leukocytes	Diagnostic reliability	PCT >0.5 ng/mL (Sens 65%, Spec 60%); CRP >5 mg/L (Sens 83%, Spec 28%); Leukocytes >10×10⁹/L (Sens 61%, Spec 49%). PCT+CRP accuracy 98%.

Abbreviations Used:
AA – Acute appendicitis, PA – Perforated appendicitis, PCT – Procalcitonin, CRP – C-reactive protein, WBC – White blood cell count, WCC – White cell count, PMN – Polymorphonuclear cells, N/L ratio – Neutrophil-to-lymphocyte ratio, BT – Body temperature, TLC – Total leukocyte count, DV – Diagnostic value, PPV – Positive predictive value, NPV – Negative predictive value, AUC – Area under curve, ROC – Receiver operating characteristic, SSI – Surgical site infection, OR – Odds ratio, LR – Likelihood ratio, USG – Ultrasonography, CT – Computed tomography, IQR – Interquartile range.

Risk of bias assessment

The methodological quality of the included studies, as assessed using the QUADAS-2 tool, demonstrated variable risk of bias across domains (table 2). Regarding patient selection, only one study (Vaziri et al., 2014) was judged to have a low risk of bias, while the majority of studies exhibited high risk, and one study (Kaya B et al., 2012) was rated as unclear. For the index test domain, risk of bias was predominantly unclear or high, with only one study (Yamashita et al., 2016) demonstrating low risk. In contrast, the reference standard domain showed generally favorable methodological quality, with most studies rated as low risk of bias, except Kaya B et al., 2012, which was unclear.

Concerning flow and timing, three studies (Vaziri et al., 2014; Kumar S et al., 2020; and Kaya B et al., 2012) demonstrated low risk of bias, whereas several studies were rated as high or moderate risk, particularly Yamashita et al., 2016; Buyukbese Sarsu S et al., 2016; Rahed et al., 2019; and Shahul Hameed et al., 2023. Overall, one study (Vaziri et al., 2014) was considered to have low overall risk of bias, four studies demonstrated moderate risk (Kaya B et al., 2012; Panagiotopoulou et al., 2013; Kumar S et al., 2020; and Suljendić et al., 2024), and four studies were judged to have high overall risk of bias (Yamashita et al., 2016; Buyukbese Sarsu S et al., 2016; Rahed et al., 2019; and Shahul Hameed et al., 2023).

Applicability concerns were generally low across most studies, with moderate concerns identified in three studies (Buyukbese Sarsu S et al., 2016; Rahed et al., 2019; and Suljendić et al., 2024). Overall, while the reference standard domain showed acceptable methodological rigor, substantial concerns were noted in patient selection and index test domains, contributing to a predominantly moderate-to-high overall risk of bias among the included studies.

Table 2. Risk of Bias Assessment checked by QUADAS-2.

Study/year	Patient Selection	Index Test	Reference Standard	Flow and Timing	Overall risk of bias	Applicability Concerns
Kaya B et al., 2012 [13]	Unclear	Unclear	Unclear	Low	Moderate	Low
Panagiotopoulou et al., 2013 [14]	High	Unclear	Low	Moderate	Moderate	Low
Vaziri et al., 2014 [15]	Low	Unclear	Low	Low	Low	Low
Yamashita et al., 2016 [6]	High	Low	Low	High	High	Low
Buyukbese Sarsu S et al., 2016 [5]	High	High	Low	High	High	Moderate
Rahed et al., 2019 [16]	High	High	Low	High	High	Moderate
Kumar S et al., 2020 [17]	High	Unclear	Low	Low	Moderate	Low
Shahul Hameed et al., 2023 [18]	High	Unclear	Low	High	High	Low
Suljendić et al., 2024 [19]	High	Unclear	Low	Moderate	Moderate	Moderate

DISCUSSION

The findings from this systematic compilation of nine studies on inflammatory biomarkers in acute appendicitis (AA) underscore the adjunctive role of routine laboratory markers such as C-reactive protein (CRP), white blood cell count (WBC), and procalcitonin (PCT) in supporting clinical diagnosis, particularly for distinguishing uncomplicated from complicated disease. CRP consistently emerged as the most reliable single marker across adult and pediatric cohorts, with diagnostic accuracies (AUCs) ranging from

0.70 to 0.93, high sensitivities (68–100%), and excellent negative predictive values (NPVs; up to 100%) at cut-offs like 3–10 mg/L, enabling confident exclusion of perforated appendicitis when levels were normal. For instance, Panagiotopoulou et al. reported CRP's superior AUC (0.9322) for perforation, outperforming WBC and bilirubin, while Buyukbese Sarsu & Sarac highlighted CRP's AUC of 0.887 in pediatric complicated AA, where combined WBC/CRP use yielded sensitivities >95% and NPVs approaching 99.5%. PCT, conversely, showed modest utility for overall AA diagnosis (sensitivities 26–65%, AUCs ~0.65–0.83) but excelled in prognostic contexts, such as identifying abscess/perforation (AUC 0.832, odds ratio 30.3 at ≥0.46 ng/mL) or postoperative complications like peritonitis (sensitivity 100%). WBC demonstrated balanced but non-specific performance (sensitivities 61–90%, specificities 49–80%), with combinations enhancing overall accuracy up to 98% in pediatric series. These results align with meta-analytic evidence affirming CRP and WBC as superior to PCT for initial AA diagnosis, though PCT's high specificity (89–94%) for complicated cases adds discriminatory power [2,5,6,14].

Similar findings are corroborated by prior meta-analyses and prospective cohorts published in indexed journals. A landmark systematic review by Mallett et al. (2013) pooled data from seven studies (n=1,011 suspected cases), yielding bivariable sensitivities/specificities of 33%/89% for PCT, 57%/87% for CRP, and 62%/75% for WBC in AA, with AUCs of 0.65, 0.75, and 0.72, respectively—mirroring the current compilation's hierarchy and emphasizing PCT's enhanced specificity (94%) for complicated AA. Similarly, the pediatric-focused meta-analysis by Li et al. (2019) confirmed PCT's pooled sensitivity of 76% (95% CI: 70–81%) and specificity of 79% (95% CI: 75–82%) for overall AA in children, rising to higher values for complicated disease, consistent with Suljendić et al.'s [19] combination accuracies (98%). In adult cohorts, Yamashita et al.'s emphasis on PCT's prognostic superiority (PPV 73%, NPV 92% for abscess/perforation) echoes Suzuki et al.'s (2004) early findings of PCT >2 ng/mL predicting complicated AA with 92% sensitivity, and subsequent validations like those by Rivera-Chavez et al. (2004), who reported PCT elevations correlating with gangrenous/perforated histology. CRP's primacy is further supported by Atema et al.'s (2015) [20] prospective multicenter study (n=2,299), where CRP >10 mg/L had an AUC of 0.72 for AA, comparable to Kaya et al.'s diagnostic value of 72%, and by Atahan et al. (2012), who found CRP gradients distinguishing phlegmonous from perforated AA (p<0.05), as in the Turkish series here. Combined WBC/CRP models, as in Buyukbese Sarsu & Sarac, replicate Panagiotopoulou et al.'s ROC improvements (AUC 0.9388 for perforation) and are endorsed in guidelines like those from the World Society of Emergency Surgery (2020), advocating serial CRP/WBC for risk stratification. Bilirubin's limited value in Panagiotopoulou et al. (AUC 0.7114 for AA, 0.801 for perforation) aligns with Jahn et al.'s (2013) meta-analysis (pooled sensitivity 52%), attributing elevations to transient biliary stasis rather than diagnostic specificity [2,4,5,6,13,14,20,21,22].

Contradictory evidence, however, tempers enthusiasm for these markers' standalone use. Several studies challenge PCT's prognostic reliability; for example, Wibrow et al.'s (2022) meta-analysis (n=2,456) reported only moderate pooled accuracy for complicated AA (AUC 0.78), with heterogeneity from assay variability, contrasting Vaziri et al.'s [15] 100% peritonitis sensitivity—likely due to the latter's small sample (n=100) and selective preoperative timing. D-dimer's poor performance (diagnostic value 31% in Kaya et al.) is echoed by O'Leary et al. (2013), who found no added value beyond CRP/WBC, but contradicted by occasional reports like those from Shogbesan et al. (2020) linking elevated D-dimer to perforation (sensitivity

68%). Imaging comparisons in Shahul Hameed et al. (CRP sensitivity 85% vs CT 38%) diverge from Anderson et al.'s (2020) meta-analysis, where CT achieved pooled sensitivity/specificity of 94%/95%, reinforcing CT's superiority but highlighting CRP's higher NPV for ruling out disease in resource-limited settings. Pediatric contradictions include Suljendić et al.'s [19] modest single-marker accuracies (CRP sensitivity 83%, specificity 28%) versus higher pediatric meta-analytic estimates (e.g., Zhang et al., 2021: CRP AUC 0.85), attributable to age-specific cut-offs and controls. Critically, no marker achieved NPV >96% or PPV >92% consistently, as noted in van Rossem et al.'s (2016) APPAC trial follow-up, where 4.9% of AA cases had normal CRP/WBC—mirroring Panagiotopoulou et al.—emphasizing that normal values cannot exclude AA, a point reiterated in ESCAP guidelines [5,10,13,17,20,23].

Clinically, these findings advocate integrating CRP and WBC as first-line adjuncts in AA pathways: elevated CRP (>3–10 mg/L) or combined WBC/CRP supports surgical urgency, particularly for perforation risk, potentially reducing negative appendectomies (5–15% rates) and enabling conservative management in uncomplicated cases. PCT thresholds (≥0.5 ng/mL) guide toward early intervention for complications, informing antibiotic escalation or imaging/CT escalation, as in Vaziri et al. [15], where it predicted 83–100% of infectious sequelae. In pediatrics, high-NPV combinations (e.g., normal CRP+leukocytes) could avert unnecessary scans, aligning with ALARA radiation principles. Cost-effectiveness is favorable: CRP/WBC assays are inexpensive (<$10) and rapid, versus PCT (~$20–50) or CT (~$300). However, overreliance risks diagnostic delay; AA remains clinical, with Alvarado/PAS scores outperforming labs alone (AUC 0.80–0.85) [2,5,10,14,24,].

Strengths and limitations

Strengths of this compilation include its diverse international representation (Turkey, UK, Iran, Japan, Iraq, UAE, India, Bosnia), multimodal designs (prospective/retrospective, adult/pediatric), and granular metrics (cut-offs, AUCs, combinations), enhancing generalizability for systematic reviews like ongoing PRISMA-DTa efforts on appendicitis biomarkers. Comprehensive histopathological confirmation and subgroup analyses (e.g., phlegmonous vs. perforated) add robustness, mirroring QUADAS-2 low-risk domains in high-quality metas.

Limitations are notable: heterogeneity in cut-offs (e.g., CRP 0.6–10 mg/L), timing (admission vs. serial), assays (immunoturbidimetric vs. chemiluminescent for PCT), and definitions of "complicated" AA preclude meta-regression. Small samples in prognostic arms (e.g., n=8 perforated in Kaya) inflate estimates, and retrospective biases (selection, verification) affect four studies, potentially overestimating accuracies.

Future research directions

Future research should prioritize multicenter prospective trials validating optimal cut-offs via individual patient data meta-analyses, incorporating novel markers (e.g., fecal calprotectin, IL-6) and machine learning models combining labs, imaging, and scores for AUC >0.90. Pediatric-specific validations, serial sampling protocols, and health economic analyses in low-resource settings are essential. Randomized trials testing biomarker-driven pathways (e.g., PCT-guided antibiotics) versus standard care could quantify impacts on perforation rates (target <10%), length-of-stay, and costs. Ultimately, these data propel toward precision diagnostics, reducing the 15–30% diagnostic uncertainty in suspected AA.

CONCLUSION

Based on the available evidence from the included observational studies, inflammatory biomarkers provide valuable adjunctive information in the diagnosis and severity stratification of acute appendicitis; however, none demonstrate sufficient standalone accuracy to replace clinical assessment.

C-reactive protein (CRP) consistently showed moderate-to-high diagnostic performance across both adult and pediatric populations, with particularly strong utility in identifying complicated or perforated appendicitis. Several studies reported high sensitivity and negative predictive value (NPV) for CRP in perforated disease, and significantly elevated CRP levels were consistently associated with disease severity. These findings support the role of CRP as the most reliable single inflammatory marker among those evaluated.

Procalcitonin (PCT), while demonstrating limited sensitivity for uncomplicated acute appendicitis, showed superior performance in predicting complicated appendicitis, abscess formation, peritonitis, and postoperative infectious complications. Elevated PCT levels were strongly associated with severe inflammatory destruction, and higher cut-off values correlated with increased odds of perforation. Thus, PCT appears to be particularly useful as a marker of disease severity rather than as a primary diagnostic tool.

White blood cell (WBC) count exhibited relatively high sensitivity in several studies but lacked adequate specificity and negative predictive value, limiting its reliability as an exclusion test. D-dimer demonstrated promising diagnostic accuracy in selected cohorts, outperforming traditional inflammatory markers in one study; however, the evidence remains limited and requires further validation. Bilirubin did not provide significant discriminatory value for uncomplicated appendicitis.

Importantly, combinations of biomarkers—particularly CRP with WBC or PCT—consistently improved diagnostic accuracy, sensitivity, and negative predictive value compared with individual markers alone. Multimarker approaches showed especially strong performance in ruling out complicated appendicitis when values were within normal limits.

In summary, CRP emerges as the most consistently useful laboratory marker for acute appendicitis, particularly for identifying complicated disease. PCT is valuable for severity assessment and prediction of perforation, while WBC serves as a supportive but nonspecific indicator. A combined biomarker strategy enhances diagnostic reliability; nevertheless, acute appendicitis remains primarily a clinical diagnosis, and laboratory markers should be interpreted in conjunction with clinical findings and imaging studies. Further large-scale, prospective studies with standardized cut-off values are warranted to refine the diagnostic algorithms incorporating these biomarkers.

Declaration by Authors

Ethical Approval: Not applicable
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Abhishek Prasad, Sai Sharan, Aditya Awati. Comparative diagnostic performance of procalcitonin, C-reactive protein, and white blood cell count in acute appendicitis: a PRISMA-compliant systematic review. *Int J Health Sci Res.* 2026; 16(4):143-155. DOI: *https://doi.org/10.52403/ijhsr.20260419*

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