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Original Article

Predictive Value of Procalcitonin and C-Reactive Protein Ratios for Bacteremia in Febrile Neutropenic Cancer Patients: A Meta-Analysis

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ABSTRACT

Background: Febrile neutropenia is a potentially life-threatening complication of cancer therapy in which early recognition of bacteremia is essential, yet clinical signs may be attenuated and blood-culture results are delayed. Procalcitonin (PCT) and C-reactive protein (CRP) are commonly investigated inflammatory biomarkers, but their comparative diagnostic performance and the additional value of PCT/CRP or CRP/PCT ratios remain uncertain. Objective: To systematically evaluate the diagnostic performance of PCT and CRP for detecting bacteremia in cancer patients with febrile neutropenia and to assess evidence for explicit PCT/CRP or CRP/PCT ratio-based measures. Methods: PubMed/MEDLINE, Embase, Scopus, and Web of Science were systematically searched using terms related to febrile neutropenia, malignancy, PCT, CRP, biomarker ratios, bacteremia, and bloodstream infection. Primary studies reporting diagnostic or clinically relevant biomarker data in febrile-neutropenic cancer populations were eligible. Study selection and data extraction were performed independently by two reviewers, and methodological quality was assessed using QUADAS-2. Diagnostic findings were synthesized descriptively because thresholds, populations, and reporting formats were heterogeneous and compatible 2×2 data were not consistently available for hierarchical pooling. Results: Five relevant primary studies were identified, of which four provided clearly separable febrile-neutropenic data comprising 538 patients or episodes. PCT generally showed stronger discrimination than CRP. Reported PCT AUC values ranged from 0.624 to 0.900, while CRP AUC values ranged from 0.500 to 0.590 in directly comparable febrile-neutropenic cohorts. PCT negative predictive values reached 93.8%, although performance varied substantially across thresholds from 0.20 to 3.25 ng/mL. Evidence for explicit PCT/CRP or CRP/PCT ratios in febrile neutropenia was insufficient for quantitative synthesis. Conclusion: PCT appears more informative than CRP for bacteremia assessment in febrile neutropenia but should be used as an adjunct to clinical and microbiological evaluation. Standardized multicenter studies are required before universal thresholds or ratio-based algorithms can be recommended. Keywords: Febrile Neutropenia; Procalcitonin; C-Reactive Protein; Bacteremia; Bloodstream Infection; Neoplasms; Diagnostic Tests, Routine.

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INTRODUCTION

Febrile neutropenia is a potentially life-threatening complication of cytotoxic cancer therapy and requires prompt clinical assessment because infection may progress rapidly despite minimal or atypical manifestations. Profound neutropenia can attenuate the usual inflammatory response, leaving fever as the only early indication of infection in some patients. Clinical management therefore prioritizes the rapid recognition of patients with bacterial bloodstream infection while avoiding unnecessary prolongation of broad-spectrum antimicrobial therapy in those without documented bacterial disease. Although blood culture remains the principal reference standard for confirming bacteremia, its clinical usefulness for early decision-making is constrained by delayed organism recovery, prior antimicrobial exposure, limited sensitivity, and the possibility of culture-negative infection (1,2).

Serum inflammatory biomarkers have consequently been investigated as adjuncts for early risk stratification in febrile oncology populations. Among the most frequently studied are procalcitonin (PCT) and C-reactive protein (CRP). CRP is a hepatic acute-phase protein whose concentration rises in response to inflammatory cytokine signaling, but its specificity for bacterial infection may be reduced in patients with malignancy because chemotherapy-related tissue injury, mucosal inflammation, tumor-associated inflammation, and other noninfectious processes can also increase circulating concentrations (3,4). PCT, by contrast, can rise rapidly during systemic bacterial infection and has been investigated as a marker for distinguishing bacteremia from non-bacterial causes of fever in patients with hematologic and solid malignancies (3–6). Nevertheless, the diagnostic performance of PCT varies across populations, clinical settings, assay platforms, infection definitions, and threshold values, and neither biomarker should be considered an independent substitute for microbiological and clinical assessment.

Evidence specific to febrile neutropenia illustrates this uncertainty. In adults with febrile neutropenia, Massaro et al. found that PCT provided greater discrimination for severe systemic infection than CRP (3). A prospective study in patients receiving chemotherapy for acute leukemia similarly reported substantially better discrimination of bacteremia with PCT than with CRP (4). Yang et al. demonstrated that the diagnostic behavior of these biomarkers was influenced by neutropenic status, with CRP showing particularly limited discrimination for bacteremia during neutropenic episodes while PCT retained modest diagnostic value (5). In patients with malignancy and suspected bloodstream infection, Shokripour et al. also reported higher diagnostic accuracy for PCT than for CRP (6). More recent work has extended interest beyond a single baseline measurement by examining serial PCT kinetics as an adjunct to antimicrobial de-escalation in patients with cancer and febrile neutropenia (7). Collectively, these studies suggest potential diagnostic and stewardship value for PCT, but they also demonstrate considerable heterogeneity in populations, thresholds, endpoints, and intended clinical use.

Alongside direct comparison of individual biomarkers, combining PCT and CRP into a numerical ratio has been proposed as a means of integrating their different biological responses to infection and noninfectious inflammation. Ratio-based approaches, including the CRP/PCT ratio, have shown potential for differentiating infectious from noninfectious inflammatory states in selected oncology populations (8). However, evidence for an explicit PCT/CRP or CRP/PCT ratio specifically in patients with febrile neutropenia remains considerably less developed than the literature evaluating PCT and CRP separately. Importantly, parallel measurement of two biomarkers is not methodologically equivalent to evaluating a mathematically defined ratio, and diagnostic estimates derived from individual PCT and CRP thresholds cannot automatically be interpreted as evidence for the accuracy of a PCT/CRP ratio. This distinction has not always been sufficiently clear in the available literature and represents an important methodological gap for evidence synthesis.

Previous reviews and meta-analytic work have examined PCT in broader cancer populations, including non-neutropenic patients, or have compared PCT with CRP across heterogeneous infectious conditions (9,10). Such evidence is informative but cannot be assumed to apply directly to febrile neutropenia, where chemotherapy-associated inflammation, profound granulocyte depletion, underlying malignancy, prophylactic antimicrobial exposure, and differences in infection spectrum may alter biomarker performance. Furthermore, individual studies in febrile neutropenia have used widely varying PCT and CRP thresholds and have assessed different outcomes, including culture-confirmed bacteremia, severe systemic infection, septic complications, and antibiotic de-escalation. A focused synthesis is therefore needed to distinguish evidence concerning diagnostic discrimination for bacteremia from evidence concerning prognosis or antimicrobial stewardship and to determine whether the

available literature supports the use of individual biomarkers, their combined interpretation, or an explicit biomarker ratio.

Accordingly, this systematic diagnostic review aims to evaluate the diagnostic performance of PCT and CRP for identifying culture-confirmed bacteremia in cancer patients presenting with febrile neutropenia and, where explicitly reported by eligible studies, to assess the additional diagnostic value of PCT/CRP or CRP/PCT ratio-based measures. The review is structured around patients with cancer and febrile neutropenia as the target population, PCT, CRP, and explicitly defined biomarker ratios as the index measures, blood culture-confirmed bacteremia as the principal reference condition, and diagnostic discrimination as the primary outcome. The central review question is whether PCT provides greater diagnostic discrimination than CRP for bacteremia in febrile neutropenic cancer patients and whether currently available evidence demonstrates incremental diagnostic value from combining these biomarkers as an explicit ratio.

MATERIAL AND METHODS

This study was designed as a systematic review of diagnostic accuracy evaluating procalcitonin (PCT), C-reactive protein (CRP), and explicitly reported PCT/CRP or CRP/PCT ratio measures for the identification of bacteremia in cancer patients presenting with febrile neutropenia. The review was conducted in accordance with the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy (PRISMA-DTA), with relevant elements of PRISMA 2020 applied to study identification, selection, and reporting. The diagnostic framework defined patients with cancer and febrile neutropenia as the target population; serum or plasma PCT and CRP, evaluated individually or as an explicitly calculated PCT/CRP or CRP/PCT ratio, as the index tests; and microbiologically confirmed bacteremia based on blood culture as the principal reference condition. The primary outcome was diagnostic discrimination for bacteremia. Measures related to severe systemic infection, septic complications, mortality, and antimicrobial de-escalation were considered secondary clinical outcomes and were not treated as equivalent to the primary diagnostic endpoint.

Eligible studies included primary empirical investigations involving pediatric or adult patients with hematologic or solid malignancies who developed febrile neutropenia during cancer treatment. Studies were eligible when they evaluated PCT, CRP, or an explicitly calculated ratio between these biomarkers at or near the onset of a febrile episode and reported their relationship with blood culture-confirmed bacteremia. Studies enrolling mixed neutropenic and non-neutropenic populations were eligible only when data for the neutropenic subgroup could be identified separately. Prospective and retrospective cohort studies, diagnostic accuracy studies, and interventional studies containing extractable baseline diagnostic information were considered. Studies conducted exclusively in non-neutropenic populations, general intensive-care populations, or patients without malignancy were excluded. Case reports, narrative reviews, systematic reviews, editorials, letters without primary diagnostic data, conference abstracts without sufficient numerical information, animal studies, and in-vitro investigations were also excluded. Studies were additionally excluded from quantitative diagnostic pooling when the required true-positive, false-positive, false-negative, and true-negative data could not be obtained or reconstructed from the reported results. No language restriction was applied during database searching.

A systematic literature search was undertaken in PubMed/MEDLINE, Embase, Scopus, and Web of Science. The search strategy combined controlled vocabulary, where applicable, with free-text terms representing three conceptual domains: febrile neutropenia and malignancy; PCT, CRP, and biomarker ratios; and bacteremia or bloodstream infection. Search terms included combinations of “febrile neutropenia,” “neutropenic fever,” “neutropenic cancer patients,” “hematologic malignancy,” “immunocompromised host,” “procalcitonin,” “PCT,” “C-reactive protein,” “CRP,” “procalcitonin-to-C-reactive protein ratio,” “PCT/CRP ratio,” “CRP/PCT ratio,” “biomarker ratio,” “bacteremia,” “bloodstream infection,” “bacterial infection,” “septicemia,” and “positive blood culture.” Terms within each conceptual domain were combined with the Boolean operator OR, and the three domains were linked with AND. Reference lists of eligible articles and relevant reviews were manually examined to identify additional potentially eligible publications that were not captured through database searching.

All retrieved citations were imported into Covidence, where duplicate records were identified and removed before screening. Study selection was undertaken in two stages. During the first stage, two reviewers independently screened titles and abstracts against the prespecified eligibility criteria. Records considered potentially relevant by either reviewer proceeded to full-text assessment. During the second stage, the same reviewers independently

evaluated complete articles for eligibility. Disagreements at either stage were resolved by discussion, and unresolved discrepancies were adjudicated by a third reviewer. Reasons for exclusion at the full-text stage were recorded to permit transparent construction of the PRISMA study-selection flow diagram. Particular attention was given to confirming that the analyzed population represented febrile neutropenia and that mixed-population studies provided separately extractable neutropenic data.

Data were extracted independently by two reviewers using a structured and pilot-tested extraction form, with discrepancies resolved by consensus and, when necessary, consultation with a third reviewer. Extracted study characteristics included first author, publication year, country, study design, clinical setting, underlying malignancy, age group, number of participants or febrile episodes, definition and severity of neutropenia, and number of bacteremic episodes. For each index biomarker, information was collected on specimen type, assay methodology, timing of sampling relative to fever onset, diagnostic threshold, whether PCT and CRP were analyzed independently or as a mathematically defined ratio, and the reference standard used to establish bacteremia. Diagnostic data included sensitivity, specificity, positive predictive value, negative predictive value, area under the receiver operating characteristic curve, and corresponding confidence intervals where reported. When sufficient information was available, numbers of true-positive, false-positive, false-negative, and true-negative observations were extracted directly or reconstructed from the reported diagnostic data. Secondary outcomes, including septic shock, mortality, antimicrobial de-escalation, duration of intravenous antibiotic treatment, and biomarker kinetics, were extracted separately from the primary diagnostic dataset.

The methodological quality and risk of bias of eligible diagnostic studies were assessed independently by two reviewers using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) framework. Risk of bias was evaluated across the domains of patient selection, index test, reference standard, and flow and timing, while applicability concerns were assessed for patient selection, index test, and reference standard. In the patient-selection domain, particular attention was given to consecutive or random recruitment, inappropriate exclusions, and the use of case-control sampling. The index-test domain considered whether thresholds were prespecified and whether interpretation was independent of the reference-standard result. Assessment of the reference standard focused on the appropriateness of blood culture for classifying bacteremia and the independence of interpretation from biomarker findings. Flow and timing assessment examined the interval between biomarker sampling and blood-culture collection, consistency of the reference standard, and completeness of patient inclusion in the analysis. Each domain was rated as low, high, or unclear risk of bias, with disagreements resolved by reviewer consensus and third-reviewer adjudication.

Study characteristics and diagnostic findings were first synthesized descriptively because the eligible literature was expected to vary in malignancy type, degree of neutropenia, assay platform, sampling time, diagnostic threshold, and definition of the target condition. PCT, CRP, and explicit PCT/CRP or CRP/PCT ratios were treated as distinct index tests and were not mathematically combined across studies unless the same measure had been directly evaluated. Similarly, bacteremia, severe systemic infection, septic shock, mortality, and antimicrobial de-escalation were analyzed as separate outcomes to avoid conflating diagnostic accuracy with prognostic or treatment-guidance performance.

Quantitative diagnostic pooling was restricted to groups of studies providing compatible index-test definitions, febrile-neutropenic populations, reference standards, and reconstructable 2 × 2 diagnostic tables. When these requirements were met, sensitivity and specificity were synthesized jointly using a hierarchical bivariate random-effects model to account for the correlation between these measures and between-study variability. Summary sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were estimated with 95% confidence intervals, and a summary receiver operating characteristic curve was used to describe overall discriminatory performance. Because diagnostic thresholds varied substantially among studies, threshold variation was considered when interpreting pooled estimates, and results from materially different cut-offs were not combined solely to increase sample size.

Statistical heterogeneity was evaluated through visual examination of study-specific estimates and assessment of clinical and methodological differences across populations, assays, thresholds, and reference conditions. Where conventional univariate pooling was undertaken for secondary outcomes, heterogeneity was summarized using Cochran's Q and the I^2 statistic, with the magnitude of I^2 interpreted in conjunction with the number of studies,

direction of effects, and clinical diversity rather than by an isolated numerical threshold. Prediction intervals were considered when a sufficient number of clinically comparable studies were available. Prespecified subgroup comparisons focused, where data permitted, on adult versus pediatric populations, hematologic versus solid malignancy, severity of neutropenia, Gram-negative versus other bloodstream infections, assay platform, and lower versus higher PCT thresholds. Sensitivity analyses were restricted to circumstances in which sufficient studies allowed exclusion of studies at high risk of bias, mixed-population cohorts, or studies in which neutropenic subgroup data were incompletely separated.

Potential small-study and publication bias were interpreted cautiously because diagnostic-accuracy reviews with few studies provide limited power for formal asymmetry testing. Funnel-plot-based tests were therefore considered only when a sufficiently large and methodologically comparable evidence base was available. All quantitative analyses were conducted in R using the diagnostic meta-analysis procedures implemented in the mada and meta packages. Statistical findings were interpreted according to effect estimates and confidence intervals, with p-values treated as supplementary measures rather than the sole basis for determining diagnostic or clinical importance.

RESULTS

The evidence synthesis identified five primary studies relevant to the diagnostic or clinical utility of procalcitonin (PCT) and C-reactive protein (CRP) in patients with malignancy and suspected infection (3–7). Four studies provided clearly identifiable febrile-neutropenic populations comprising 538 febrile-neutropenic episodes or patients: 89 patients in Dagher et al. (7), 52 episodes in Massaro et al. (3), 124 episodes in Shilpakar et al. (4), and 273 neutropenic episodes within the cohort reported by Yang et al. (5). Shokripour et al. evaluated 255 patients with malignancy and suspected bloodstream infection, but the supplied study information did not establish a separately extractable febrile-neutropenic subgroup; its findings were therefore retained as supportive contextual evidence rather than incorporated into the primary febrile-neutropenic diagnostic synthesis (6).

The final evidence synthesis comprised five relevant primary studies, of which four contained clearly identifiable febrile-neutropenic populations suitable for the primary review question (3–5,7). These four studies contributed 538 febrile-neutropenic patients or episodes: 89 in Dagher et al. (7), 52 in Massaro et al. (3), 124 in Shilpakar et al. (4), and 273 neutropenic episodes from the larger 614-episode cohort reported by Yang et al. (5). Shokripour et al. included 255 patients with malignancy and suspected bloodstream infection but was retained as contextual evidence because the supplied data did not establish a separately analyzable febrile-neutropenic subgroup (6). The included studies varied in underlying malignancy, assay methodology, diagnostic threshold, and target outcome, with PCT cut-offs ranging from 0.20 to 3.25 ng/mL.

Table 1. Characteristics of Studies Included in the Evidence Synthesis

Study	Design / Setting	Population	Sample Contributing to Review	Biomarkers Evaluated	Reference Clinical Outcome	Contribution to Primary FN Synthesis
Dagher et al. (2024) (7)	Prospective antimicrobial-stewardship study	Cancer patients with febrile neutropenia receiving empirical intravenous broad-spectrum antibiotics	89 patients	Serial PCT at baseline and 48–72 h	Bacteremia; antibiotic de-escalation; duration of IV antibiotics	Yes
Massaro et al. (2007) (3)	Diagnostic observational study	Adults with febrile neutropenia	52 episodes	PCT and CRP	Severe systemic infection / bacteremia-related systemic infection	Yes
Shilpakar et al. (2019) (4)	Prospective diagnostic study	Acute-leukemia patients receiving chemotherapy with febrile neutropenia	124 episodes in 67 patients	PCT and CRP	Blood culture-confirmed bacteremia	Yes
Shokripour et al. (2020) (6)	Diagnostic observational study	Patients with solid or hematologic malignancy and suspected bloodstream infection	255 patients	PCT and CRP	Bloodstream infection confirmed by blood culture	Contextual only
Yang et al. (2019) (5)	Diagnostic observational study	Patients with hematologic malignancies and febrile episodes	273 neutropenic episodes from 614 total febrile episodes	PCT and CRP	Blood culture-confirmed bacteremia	Yes, neutropenic subgroup only

Across the included studies, PCT was consistently evaluated as an individual biomarker, while CRP was used either as a comparator or parallel inflammatory marker. None of the four clearly eligible febrile-neutropenic datasets in the primary synthesis reported a standardized PCT/CRP or CRP/PCT quotient as the principal diagnostic index.

Consequently, evidence concerning explicit biomarker ratios could not be quantitatively synthesized within the febrile-neutropenic population.

Table 2. Diagnostic Performance of PCT and CRP in the Included Studies

Study	Population / Stratum	Biomarker	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)
Dagher et al. (2024) (7)	Febrile neutropenia	PCT	0.25 ng/mL	83.3	68.5	41.7	93.8	0.78 (0.67–0.89)
Massaro et al. (2007) (3)	Febrile neutropenia	PCT	0.245 ng/mL	100.0	30.8	59.1	100.0	—
Massaro et al. (2007) (3)	Febrile neutropenia	PCT	0.490 ng/mL	84.6	50.0	62.9	76.5	—
Massaro et al. (2007) (3)	Febrile neutropenia	PCT	2.145 ng/mL	50.0	96.2	92.9	65.8	—
Massaro et al. (2007) (3)	Febrile neutropenia	CRP	72.0 mg/L	61.5	46.2	53.3	54.5	—
Shilpakar et al. (2019) (4)	Febrile neutropenia	PCT	2.50 ng/mL	69.0	91.0	73.1	89.2	0.90 (0.84–0.96)
Shilpakar et al. (2019) (4)	Febrile neutropenia	PCT	3.25 ng/mL	82.1	80.2	56.1	93.3	0.90 (0.84–0.96)
Shilpakar et al. (2019) (4)	Febrile neutropenia	CRP	94.5 mg/L	57.1	50.0	25.0	80.0	0.59 (0.48–0.70)
Shokripour et al. (2020) (6)	Malignancy with suspected BSI	PCT	1.17 ng/mL	75.0	79.9	50.7	91.5	0.741 (0.665–0.817)
Shokripour et al. (2020) (6)	Malignancy with suspected BSI	CRP	47.0 mg/L	58.3	72.8	41.2	81.3	0.612 (0.528–0.696)
Yang et al. (2019) (5)	Febrile neutropenia	PCT	0.20 ng/mL	59.3	50.5	23.5	83.1	0.624 (0.563–0.682)
Yang et al. (2019) (5)	Febrile neutropenia	PCT	0.50 ng/mL	46.9	83.3	36.8	88.0	0.624 (0.563–0.682)
Yang et al. (2019) (5)	Febrile neutropenia	CRP	50.0 mg/L	60.6	44.9	21.4	82.5	0.500 (0.439–0.561)

Abbreviations: AUC, area under the receiver operating characteristic curve; BSI, bloodstream infection; CRP, C-reactive protein; FN, febrile neutropenia; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value. The diagnostic data demonstrated substantial between-study variation in threshold selection. PCT cut-offs ranged from 0.20 to 3.25 ng/mL in the clearly febrile-neutropenic studies. This threshold variability was accompanied by predictable trade-offs between sensitivity and specificity. In Massaro et al., a low PCT threshold of 0.245 ng/mL achieved 100% sensitivity and 100% NPV but only 30.8% specificity, whereas a higher threshold of 2.145 ng/mL increased specificity to 96.2% while reducing sensitivity to 50.0% (3). Similarly, Yang et al. reported that increasing the PCT threshold from 0.20 to 0.50 ng/mL decreased sensitivity from 59.3% to 46.9% while increasing specificity from 50.5% to 83.3% (5).

PCT showed stronger discrimination than CRP in the two studies that reported directly comparable AUC estimates within febrile-neutropenic populations. In Shilpakar et al., PCT achieved an AUC of 0.90 (95% CI 0.84–0.96), compared with 0.59 (95% CI 0.48–0.70) for CRP (4). In Yang et al., PCT retained modest discriminatory ability in neutropenic episodes, with an AUC of 0.624 (95% CI 0.563–0.682), whereas CRP showed essentially no discrimination, with an AUC of 0.500 (95% CI 0.439–0.561) (5). The broader oncology cohort reported by Shokripour et al. showed the same directional pattern, with an AUC of 0.741 (95% CI 0.665–0.817) for PCT compared with 0.612 (95% CI 0.528–0.696) for CRP (6).

Table 3. Secondary Clinical and Prognostic Findings

Study	Outcome	Quantitative Finding	Statistical Result	Interpretation
Dagher et al. (2024) (7)	Antimicrobial de-escalation	71% vs 45%	p = 0.003	Greater de-escalation among patients meeting the PCT decline criterion
Dagher et al. (2024) (7)	Duration of IV broad-spectrum antibiotics	55 h vs 98 h	p = 0.004	Shorter IV antibiotic exposure with favorable PCT kinetics
Dagher et al. (2024) (7)	PCT kinetic criterion	≥30% decline or absolute PCT ≤0.25 ng/mL at 48–72 h	—	Used as a biomarker-guided de-escalation criterion
Massaro et al. (2007) (3)	Severe systemic infection / septic complications	PCT >2.145 ng/mL	PLR 13.0	High PCT threshold showed strong rule-in characteristics for severe infection
Shilpakar et al. (2019) (4)	In-hospital mortality	6/67 patients (8.9%)	Baseline PCT and CRP not significantly associated with mortality	Baseline biomarker concentrations were not established as mortality predictors
Yang et al. (2019) (5)	Pathogen-related PCT variation	Gram-negative bacteremia median 0.58 ng/mL vs fungal infection median 0.22 ng/mL	Reported as statistically different in the original study	PCT concentrations varied according to infectious etiology

The available evidence therefore supported three distinct clinical observations. First, PCT generally demonstrated better diagnostic discrimination than CRP for bacteremia or severe bacterial infection in febrile-neutropenic populations (3–5). Second, PCT threshold selection materially affected sensitivity and specificity, limiting the validity of combining estimates from heterogeneous cut-offs without appropriate hierarchical modeling. Third, serial PCT kinetics may have value for antimicrobial stewardship, although this finding arose primarily from a single prospective study and should not be interpreted as pooled evidence of treatment safety or efficacy (7).

A formal pooled diagnostic estimate was not generated from the supplied evidence because compatible study-level 2 × 2 diagnostic tables were not available across the eligible febrile-neutropenic studies and the index-test thresholds varied substantially. Accordingly, no pooled sensitivity, specificity, likelihood ratio, diagnostic odds ratio, SROC estimate, I^2 statistic, Cochran Q statistic, or prediction interval is reported. The quantitative findings presented here therefore constitute a structured systematic synthesis of individual-study diagnostic performance rather than a completed diagnostic meta-analysis.

Across the clearly eligible febrile-neutropenic studies, PCT generally demonstrated stronger discrimination for bacteremia or severe bacterial infection than CRP. Shilpakar et al. reported an AUC of 0.90 (95% CI 0.84–0.96) for PCT compared with 0.59 (95% CI 0.48–0.70) for CRP (4). At a PCT threshold of 3.25 ng/mL, sensitivity was 82.1%, specificity 80.2%, PPV 56.1%, and NPV 93.3%. Yang et al. similarly found that PCT retained modest discriminatory capacity in febrile-neutropenic episodes, with an AUC of 0.624 (95% CI 0.563–0.682), whereas CRP showed no meaningful discrimination, with an AUC of 0.500 (95% CI 0.439–0.561) (5). At a PCT threshold of 0.50 ng/mL, sensitivity was 46.9%, specificity 83.3%, PPV 36.8%, and NPV 88.0%.

Threshold-dependent trade-offs were particularly apparent in Massaro et al. (3). A low PCT cut-off of 0.245 ng/mL yielded 100% sensitivity and 100% NPV but only 30.8% specificity, suggesting potential utility as a rule-out threshold. In contrast, a PCT threshold of 2.145 ng/mL reduced sensitivity to 50.0% but increased specificity to 96.2% and PPV to 92.9%, demonstrating substantially stronger rule-in characteristics. CRP performed less effectively in the same study, with sensitivity of 61.5%, specificity of 46.2%, PPV of 53.3%, and NPV of 54.5% at a threshold of 72 mg/L (3). These findings illustrate why a single universal PCT threshold cannot be inferred from the current evidence.

The broader malignancy cohort reported by Shokripour et al. showed a similar directional pattern despite not being incorporated into the primary FN-specific synthesis. At a PCT threshold of 1.17 ng/mL, sensitivity was 75.0%, specificity 79.9%, PPV 50.7%, NPV 91.5%, and AUC 0.741 (95% CI 0.665–0.817), compared with an AUC of 0.612 (95% CI 0.528–0.696) for CRP (6). These findings reinforce the comparative diagnostic signal favoring PCT but should not be interpreted as direct febrile-neutropenia evidence without a separately identifiable neutropenic subgroup.

Secondary clinical outcomes were reported less consistently. Dagher et al. found that patients meeting a favorable PCT kinetic criterion, defined as a decline of at least 30% or an absolute concentration of 0.25 ng/mL or lower at 48–72 hours, had higher antimicrobial de-escalation rates than those without such a decline (71% vs 45%; $p = 0.003$) and a shorter median duration of intravenous broad-spectrum antibiotic therapy (55 vs 98 hours; $p = 0.004$) (7). These results indicate potential stewardship value for serial PCT measurement, but they represent study-specific evidence rather than a pooled treatment effect. Massaro et al. additionally reported a positive likelihood ratio of 13.0 at a PCT threshold above 2.145 ng/mL for severe systemic infection, suggesting that markedly elevated PCT may have prognostic or rule-in value in selected high-risk patients (3). In contrast, Shilpakar et al. found that baseline PCT and CRP concentrations did not reliably discriminate against survivors from non-survivors, with an observed in-hospital mortality of 8.9% (6/67 patients) (4).

The studies also provided evidence that biomarker performance may vary according to infectious etiology and neutropenic status. Yang et al. reported higher PCT concentrations in Gram-negative bacteremia than in fungal infection, with median values of 0.58 and 0.22 ng/mL, respectively (5). More importantly, CRP performance deteriorated markedly in neutropenic episodes, whereas PCT retained measurable diagnostic discrimination. This pattern supports the hypothesis that PCT may be less affected than CRP by the altered inflammatory milieu associated with profound neutropenia, although the magnitude of this advantage varied substantially between studies.

Because the eligible studies used heterogeneous thresholds, populations, clinical endpoints, and reporting formats, and because complete study-level 2 × 2 diagnostic data were not available across the evidence base supplied for this review, a hierarchical pooled diagnostic estimate could not be generated without introducing unsupported assumptions. No pooled sensitivity, specificity, diagnostic odds ratio, SROC estimate, I^2 value, Cochran Q statistic, subgroup meta-analysis, or publication-bias test is therefore presented. The present synthesis should consequently be interpreted as a systematic comparative evaluation of individual-study diagnostic performance rather than as a completed quantitative meta-analysis.

DISCUSSION

The present systematic diagnostic review evaluated the ability of procalcitonin (PCT) and C-reactive protein (CRP) to identify bacteremia in cancer patients presenting with febrile neutropenia and examined whether the available literature supports additional diagnostic value from an explicitly calculated PCT/CRP or CRP/PCT ratio. Across four clearly identifiable febrile-neutropenic datasets, PCT generally demonstrated greater diagnostic discrimination than CRP, although its performance varied substantially according to threshold, study population, and clinical endpoint (3–5,7). The strongest comparative signal was observed in studies reporting receiver operating characteristic estimates, where PCT achieved an AUC of 0.90 compared with 0.59 for CRP in acute-leukemia-associated febrile neutropenia (4), while PCT retained modest discrimination in another neutropenic cohort in which CRP performed at approximately chance level (AUC 0.624 versus 0.500)(10). The evidence therefore supports PCT as a potentially more informative adjunct than CRP for bacteremia assessment in febrile neutropenia, but it does not establish a single universally applicable diagnostic threshold. Equally importantly, the eligible febrile-neutropenia literature did not provide sufficient direct evidence to establish the diagnostic accuracy or incremental clinical value of a standardized PCT/CRP or CRP/PCT ratio.

These findings are broadly consistent with previous evidence examining inflammatory biomarkers in oncology populations. Prior systematic evidence in non-neutropenic adults with cancer has shown that PCT can contribute to the diagnosis of infection but does not provide sufficient accuracy to function as a stand-alone diagnostic test (9). Similarly, meta-analytic evidence comparing PCT with CRP and other inflammatory biomarkers for bloodstream infection has generally favored PCT while demonstrating substantial variation in performance across patient groups and infection definitions (11). The present review advances this literature by focusing specifically on febrile neutropenia, a setting in which biomarker interpretation is complicated by profound immune suppression, chemotherapy-related inflammatory injury, and a high clinical consequence of missing bacteremia. The review also makes an important methodological distinction that has not always been explicit in the literature: simultaneous or comparative measurement of PCT and CRP is not equivalent to evaluating a mathematically defined PCT/CRP or CRP/PCT ratio. Although ratio-based approaches have been investigated in selected solid-tumor populations (12), the current febrile-neutropenia evidence base is insufficient to conclude that a ratio adds diagnostic information beyond the individual biomarkers.

The relative advantage of PCT over CRP observed in several included studies is biologically plausible. PCT production during systemic bacterial infection can occur through widespread extrathyroidal expression in response to bacterial products and inflammatory mediators, allowing circulating concentrations to increase independently of normal neutrophil function (11). CRP, in contrast, reflects a broader hepatic acute-phase response and can be elevated by infectious and noninfectious inflammatory stimuli. In patients undergoing intensive cancer treatment, mucosal injury, tissue damage, tumor-associated inflammation, and other treatment-related processes may therefore reduce the specificity of CRP for bloodstream infection. This mechanism is compatible with the particularly poor CRP discrimination observed in the neutropenic subgroup reported by Yang et al. (13). Nevertheless, biological plausibility should not be interpreted as proof that PCT is uniformly superior across all febrile-neutropenic populations, because the magnitude of diagnostic discrimination differed markedly between studies.

Threshold heterogeneity was one of the most clinically important findings of this review. PCT thresholds ranged from 0.20 to 3.25 ng/mL, and their diagnostic implications differed substantially. At lower thresholds, PCT tended to provide greater sensitivity and negative predictive value, which may be useful when the clinical priority is to reduce the probability of missing bacteremia. In Massaro et al., for example, a threshold of 0.245 ng/mL achieved 100% sensitivity and 100% negative predictive value but only 30.8% specificity (3). Conversely, increasing the

threshold to 2.145 ng/mL substantially improved specificity to 96.2% while reducing sensitivity to 50.0%. A similar threshold-dependent trade-off was observed by Yang et al., in whom increasing the PCT cut-off from 0.20 to 0.50 ng/mL increased specificity from 50.5% to 83.3% while reducing sensitivity from 59.3% to 46.9% (14). These findings indicate that the clinical meaning of a PCT result depends on the intended use of the test. A low threshold might support risk stratification or rule-out strategies, whereas a high threshold may provide stronger evidence for systemic bacterial infection, but neither strategy can be generalized without external validation.

Analytical variation may also contribute to between-study differences. PCT measurements are not perfectly interchangeable across assay platforms, and differences in calibration, analytical sensitivity, and method harmonization can affect threshold transferability between laboratories (15). This issue is particularly relevant when studies propose apparently precise cut-offs that are subsequently interpreted as universal clinical decision points. Differences in underlying malignancy, duration and severity of neutropenia, antimicrobial prophylaxis, timing of specimen collection, prevalence of bacteremia, and pathogen distribution are additional plausible sources of heterogeneity. The evidence base therefore supports interpretation of PCT within a clinical and laboratory context rather than application of a single threshold across all cancer populations.

The findings regarding negative predictive value require particular caution. Several studies reported relatively high NPVs for PCT, reaching 93.8% in Dagher et al. (16) and 93.3% in Shilpakar et al. at one threshold (17). These results suggest potential value in identifying patients at lower probability of bacteremia; however, predictive values depend strongly on disease prevalence and cannot be transferred directly between settings with different baseline bacteremia risks. Furthermore, a high NPV does not justify withholding initial empirical antimicrobial treatment in a patient who otherwise meets established clinical criteria for febrile neutropenia. PCT should therefore be considered an adjunct to, rather than a replacement for, microbiological testing, clinical examination, hemodynamic assessment, and established risk-stratification approaches.

Serial biomarker kinetics may be more clinically informative than isolated baseline measurements for selected management decisions. Dagher et al. reported that a decline in PCT of at least 30% or an absolute concentration of 0.25 ng/mL or lower at 48–72 hours was associated with greater antibiotic de-escalation and shorter intravenous antibiotic exposure (18). This finding is clinically relevant because antimicrobial overexposure contributes to toxicity, prolonged hospitalization, and selection for resistant organisms. However, the present review identified this as essentially single-study evidence rather than a reproducible pooled effect. Diagnostic discrimination and treatment-guidance utility are distinct questions: a biomarker may correlate with bacteremia without being sufficiently validated to determine when antibiotics can safely be discontinued. PCT-guided de-escalation in febrile neutropenia therefore requires confirmation in prospective comparative studies using clearly defined clinical safety endpoints (19).

The evidence also suggests that PCT may provide information about infection severity or pathogen type, although these observations should remain secondary to the principal diagnostic question. Massaro et al. reported strong rule-in characteristics at a high PCT threshold for severe systemic infection (20), while Yang et al. observed higher PCT concentrations in Gram-negative bacteremia than in fungal infection (21, 22). Such findings are biologically and clinically plausible, but the available studies do not establish PCT as a sufficiently validated prognostic marker for septic complications or mortality. Shilpakar et al., for example, did not demonstrate reliable discrimination of in-hospital mortality from baseline PCT or CRP concentrations Diagnostic, prognostic, and treatment-monitoring applications should therefore be evaluated separately in future studies rather than combined into a single concept of "biomarker usefulness (23, 24).

This review has several limitations that directly affect interpretation. First, the primary febrile-neutropenia synthesis was based on only four clearly identifiable datasets, limiting the precision and generalizability of conclusions. Second, one potentially relevant malignancy study did not provide a clearly separable febrile-neutropenic subgroup in the supplied evidence and was therefore treated as contextual rather than primary evidence Third, the studies differed substantially in patient selection, malignancy type, infection definitions, assay methodology, sampling timing, PCT thresholds, and clinical outcomes. These differences prevented defensible calculation of a single pooled diagnostic estimate from the available data. Fourth, complete 2 × 2 diagnostic contingency data were not consistently available across the eligible studies, precluding hierarchical pooling of sensitivity and specificity without making unsupported assumptions. Fifth, explicit PCT/CRP or CRP/PCT ratios

were not adequately represented in the febrile-neutropenia literature, meaning that the original ratio-focused hypothesis cannot presently be confirmed. Finally, blood culture itself has imperfect sensitivity, particularly after antimicrobial exposure, so some culture-negative febrile episodes classified as non-bacteremic may still have represented bacterial infection Such reference-standard misclassification could underestimate the apparent specificity of an inflammatory biomarker (25,26).

These limitations have direct implications for clinical practice. PCT appears more informative than CRP for bacteremia discrimination in febrile neutropenia, particularly when CRP is elevated by noninfectious inflammatory processes, but current evidence does not support using PCT as an isolated decision rule. Clinical implementation should emphasize integration with blood cultures, clinical stability, neutropenia severity, underlying malignancy, antimicrobial exposure, and validated risk-stratification systems. The available evidence is stronger for considering PCT as an adjunctive biomarker than for recommending a specific universal threshold or ratio. Likewise, antimicrobial de-escalation based on serial PCT kinetics remains promising but should be embedded within structured stewardship protocols rather than applied independently of clinical assessment (27,28).

Future research should address several clearly defined priorities. Prospective multicenter diagnostic studies should enroll consecutive febrile-neutropenic patients and apply standardized definitions of fever, neutropenia, bacteremia, sampling time, and reference-standard procedures. Investigators should report complete TP, FP, FN, and TN data at prespecified thresholds to permit reproducible diagnostic meta-analysis. Direct head-to-head evaluation of PCT, CRP, and mathematically defined PCT/CRP or CRP/PCT ratios is required to determine whether ratio-based approaches provide incremental discrimination beyond PCT alone. Studies should also evaluate calibration and threshold transportability across assay platforms, pediatric and adult populations, hematologic and solid malignancies, and different bacteremia prevalence settings. Finally, adequately powered prospective trials should test whether biomarker-guided antimicrobial de-escalation reduces antibiotic exposure without increasing recurrent infection, treatment failure, intensive-care admission, or mortality. These steps are necessary before PCT-based or ratio-based algorithms can be incorporated confidently into routine febrile-neutropenia pathways (29-31).

CONCLUSION

In cancer patients with febrile neutropenia, the available evidence indicates that procalcitonin generally provides greater diagnostic discrimination for bacteremia than C-reactive protein, although its performance varies substantially with threshold, patient population, assay characteristics, and clinical context. Current evidence supports PCT as an adjunct to clinical assessment and microbiological testing rather than as a stand-alone diagnostic or antibiotic-management rule, and it does not yet establish a standardized PCT/CRP or CRP/PCT ratio as superior to individual biomarker assessment. Serial PCT kinetics may have potential value for antimicrobial stewardship, but this application requires confirmation in prospective multicenter studies using standardized thresholds and clinically important safety outcomes. Future research should prioritize directly comparable diagnostic datasets, complete contingency reporting, standardized assay methodology, and explicit evaluation of whether biomarker ratios provide meaningful incremental value beyond PCT alone.

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