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C-reactive protein and procalcitonin use in adults in low- and middle-income countries: a narrative review

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Objectives: C-reactive protein (CRP) and procalcitonin (PCT) are widely used biomarkers in high-income countries. However, evidence for their use in low- and middle-income countries (LMICs) is scant. Because many factors, including rates of endemic disease, comorbidities and genetics, may influence biomarkers' behaviour, we aimed to review available evidence generated in LMICs.

Methods: We searched the PubMed database for relevant studies within the last 20 years that originated in regions of interest (Africa, Latin America, Middle East, South Asia or South East Asia), and full-text articles involving diagnosis, prognostication and evaluation of therapeutic response with CRP and/or PCT in adults ($n = 88$) were reviewed and categorized in 12 predefined focus areas.

Results: Overall, results were highly heterogeneous, at times conflicting, and often lacking clinically useful cut-off values. However, most studies demonstrated higher levels of CRP/PCT in patients with bacterial versus other infections. HIV and TB patients had consistently higher levels of CRP/PCT versus controls. In addition, higher CRP/PCT levels at baseline and follow-up in HIV, TB, sepsis and respiratory tract infections were associated with poorer prognosis.

Conclusions: Evidence generated from LMIC cohorts suggests that CRP and PCT may have potential to become effective clinical guiding tools particularly in respiratory tract infections, sepsis and HIV/TB. However, more studies are needed to define potential scenarios for use and cost-effectiveness. Consensus across stakeholders regarding target conditions, laboratory standards and cut-off values would support the quality and applicability of future evidence.

Introduction

The biomarkers C-reactive protein (CRP) and procalcitonin (PCT) have been used in clinical practice as tools to guide both diagnosis (negative predictive value of low CRP/PCT for bacterial infection), prognosis and antibiotic de-escalation (decreasing trend of CRP/PCT, mainly in acute respiratory infection). However, most of the evidence comes from high-income countries (HICs).[1–3]

Low- and middle-income countries (LMIC) settings are heterogeneous, with differing baseline rates of endemic disease and comorbidities such as malaria, which, combined with genetic factors, may mean that biomarkers behave differently than in HICs, where most evidence has been generated. For example, healthy adult males in Ghana were found to have a slightly lower baseline CRP compared with European counterparts (0.98 versus 1.52 mg/L).[4] However, evidence from populations in LMICs suggests that use of CRP and PCT may avert unnecessary antibiotic use and improve patient outcomes in these settings as well.[5–9] There are barriers to implementation, including cost. More recently, point-of-care testing (POCT), e.g. immunochromatographic methods, have been piloted also in primary care settings with evidence of potential feasibility also on a larger scale due to their reduced costs. More evidence to support the use of point-of-care CRP/PCT in acute febrile illnesses in sub-Saharan Africa and LMICs elsewhere is urgently needed.[10]

We performed a narrative review of existing evidence from LMICs on the utility of CRP and PCT in various clinical conditions.

Methods

Using MeSH (Medical Subject Headings) terms and a Cochrane Database LMIC filter,[11] we aimed at identifying studies from within the last 20 years that used biomarkers in adult populations (19 years and above) in LMIC settings for diagnosis, prognostication and evaluation of therapeutic response. The initial search yielded 83 376 articles using PCT or CRP in humans. After using the LMIC filter and excluding paediatric studies, the remaining 10 598 articles were considered for inclusion if they fell into 1 of 12 predefined focus areas (Table S1, available as Supplementary data at *JAC-AMR* Online) and selected 2033 articles. We subsequently excluded studies that were not from LMICs, publications not in English, French or Spanish, reviews, case reports, studies outside geographical regions of interest (Africa, Latin America, Middle East, South Asia or South East Asia), articles where full text was unavailable, and articles focusing on COVID-19. Abstracts of the remaining 108 relevant publications were screened by three independent reviewers, and 88 of these were included in the final review (Figure 1). The articles were categorized by use of biomarkers in diagnosis and prognostication, and further assigned to at least 1 of 12 predefined focus areas.

Given the heterogeneity of the results, key findings were summarized in a narrative format. Laboratory values were converted to units of mg/L for CRP and ng/mL for PCT. When available, our review focused on objective and clinically applicable measures of diagnostic validity, such as biomarker cut-offs, sensitivity, specificity and predictive values (Table 1).

Results

CNS infections

Diagnosis

CRP was higher in patients with bacterial meningitis (mean 209.25 mg/L) compared with viral meningitis (mean 67.05 mg/L) (Thailand).[12] PCT was higher in bacterial compared with aseptic meningitis (Egypt).[13]

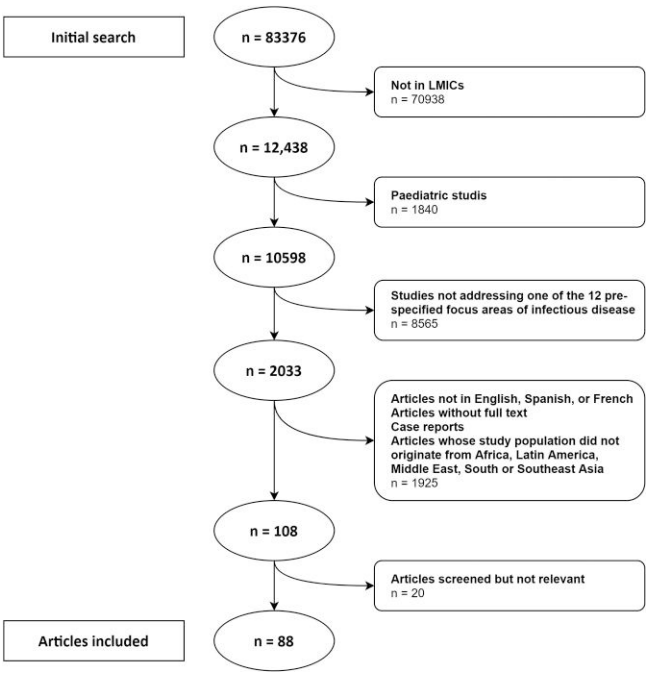

Figure 1. Flowchart of inclusion/exclusion of publications for review.

Treatment response

Patients with bacterial meningitis who responded to treatment had a decline in PCT after 24 h whereas those failing treatment had an increase (Iran).[14]

Cardiovascular infections

Diagnosis

Among patients with suspected endocarditis, elevated CRP was 97.9% sensitive for bacterial endocarditis (negative predictive value 87.5%) (South Africa).[15] In *Brucella* endocarditis, the average CRP was 22.1 mg/L and, together with ESR (erythrocyte sedimentation rate), it was the only significant altered blood test in the study cohort (Turkey).[16]

Prognosis

Infective endocarditis with a CRP greater than 40 mg/L had a sensitivity of 76% and a specificity of 99% for complications (including need for urgent surgery due to embolic phenomena), and was associated with increased in-hospital mortality and 6 month mortality (India).[17]

Respiratory tract infections

Diagnosis, outpatients

A CRP below 20 mg/L was associated with a low likelihood of acute bacterial aetiology requiring antibiotics, and using this cut-off decreased antibiotic prescribing by 14% (Vietnam).[18] Using a threshold of 40 mg/L led to a reduction in antibiotic use with no difference in clinical outcomes (Myanmar, Thailand).[9]

Diagnosis, inpatients

A CRP above 71 mg/L was associated with pneumococcal infection in patients admitted with community-acquired pneumonia (CAP) (Togo).[19] PCT was mildly elevated among patients with acute chronic obstructive pulmonary disease (COPD) exacerbations compared with COPD patients without exacerbations (mean 0.27 versus 0.07 ng/mL) (Iran).[20] Among people living with HIV (PLWH), PCT was higher in bacterial pneumonia compared with TB and *Pneumocystis jirovecii* pneumonia (PJP) (South Africa).[21] A more recent study found significant differences in both biomarkers among bacterial pneumonia, TB and PJP in PLWH, but with too much overlap between groups to reliably differentiate cause of infection (South Africa).[22]

Prognosis

CRP and PCT were significantly higher in non-survivors compared with survivors (mean 76 versus 36 mg/L, and 2 versus 1.08 ng/mL) (India).[23] CRP was higher in CAP among PLWH compared with HIV-negative patients (59.5 versus 20.1 mg/L), and higher CRP was associated with short-term mortality (Uganda).[24] High mean admission CRP indicated risk of bacterial pneumonia (above 180 mg/L), septic shock (above 210 mg/L) and requirement of mechanical ventilation (above 280 mg/L), and lack of CRP decline within 3 days of hospitalization was associated with high risk of complications (Chile).[25] Higher PCT was associated with risk of death in bacterial CAP (13.2 versus 3.4 ng/mL in survivors)

Table 1. Summary of publications included for review

Citation/ref.	Year	Study country	Study location	Study design	Disease tested	Study population	Biomarker(s)	Ranges (CRP/PCT)	Comparison	Outcomes tested
Sirijaichingkul *et al.*[12]	2005	Thailand	Inpatient	Prospective cohort	CNS infections	32	CRP	Not specified	Non-comparative	Diagnostic value of CRP for bacterial meningitis
Abdelkader *et al.*[13]	2014	Egypt	Emergency department	Prospective cohort	CNS infections	40	PCT	Not specified	Non-comparative	Diagnostic value of PCT at admission and 3 days after treatment for bacterial meningitis
Alavi *et al.*[14]	2012	Iran	Inpatient	Prospective cohort	CNS infections	36	PCT	0.5 ng/mL	Non-comparative	Prognostic value of early (24 h) decrease in PCT
Koegelenberg *et al.*[15]	2004.	S Africa	Inpatient	Prospective cohort	Endocarditis	92	CRP	Not specified	Non-comparative	Diagnostic value of CRP for infective endocarditis
Inan *et al.*[16]	2010	Turkey	Inpatient (cardiac surgery)	Retrospective	Endocarditis (*Brucella*)	31	CRP	Not specified	Non-comparative	Diagnostic value of CRP for *Brucella* endocarditis
Mohanan *et al.*[17]	2018	India	Inpatient	Prospective cohort	Endocarditis	178	CRP	<3 mg/L	Non-comparative	Prognostic value of CRP for infective endocarditis
Do *et al.*[18]	2016	Vietnam	Outpatient	Randomized controlled trial	Acute respiratory tract infection	2036	CRP	20 mg/L	No biomarker (routine care)	Diagnostic value of CRP in non-severe acute respiratory tract infection
Blake *et al.*[19]	2017	Togo	Inpatient	Prospective cohort	Acute respiratory tract infection	1684	CRP	Not specified	Lyt A rtPCR, blood culture, CXR	Diagnostic value of CRP in community-acquired pneumonia
Borsi *et al.*[20]	2019	Iran	Emergency department, and outpatient	Retrospective	Acute respiratory tract infection	50	PCT	Not specified	Non-comparative	Diagnostic value of PCT in acute exacerbation of COPD
Nyamande *et al.*[21]	2006	S Africa	Inpatient	Prospective cohort	Acute respiratory tract infection	266	PCT	Not specified	Non-comparative	Diagnostic value of PCT for community-acquired pneumonia/and TB in HIV patients
Mendelson *et al.*[22]	2018	S Africa	Inpatient	Prospective cohort	Acute respiratory tract infection	210	CRP, PCT	CRP 10 mg/L, PCT 0.02 μg/L	Composite reference standards	Diagnostic value of PCT and CRP for respiratory tract infections in HIV patients
Sharma *et al.*[23]	2016	India	ICU	Prospective cohort	ARDS	64	CRP, PCT, IL-1β, IL-6, TNF-α	Not specified	Non-comparative	Prognostic value of PCT and CRP for ARDS patients
Wang *et al.*[24]	2019	Uganda	Inpatient	Cross-sectional	Acute respiratory tract infection	173	CRP	Not specified	Non-comparative	Prognostic value of CRP for respiratory tract infections in HIV patients
Saldias-Penafiel *et al.*[25]	2019	Chile	Inpatient	Prospective cohort	Acute respiratory tract infection	823	CRP	0–0.5 mg/dL	Non-comparative	Diagnostic and prognostic value of CRP for community-acquired pneumonia
El Maghraby *et al.*[26]	2020	Egypt	Inpatient	Cross-sectional	Acute respiratory tract infection	240	PCT	Not specified	Non-comparative	Diagnostic and prognostic value of PCT for community-acquired pneumonia
Tokman *et al.*[27]	2014	Uganda	Inpatient	Prospective cohort	Acute respiratory tract infection	635	PCT	0.02–0.5 ng/mL	Non-comparative	Prognostic value of PCT for lower respiratory tract infections in HIV patients
Seligman *et al.*[28]	2011	Brazil	ICU	Observatonal cohort	Acute respiratory tract infection	71	PCT, CRP, MR-proANP, copeptin	CRP not specified, PCT 0.1 ng/mL, copeptin 2.25 pmol/L, MR-proANP 1 pmol/L	Non-comparative	Prognostic value of PCT and CRP for ventilator-associated pneumonia
Kiaei *et al.*[29]	2015	Iran	ICU	Retrospective	Acute respiratory tract infection	50	PCT, CRP	Not specified	Non-comparative	Efficacy of PCT and CRP in determining antibiotic therapy duration in patients with ventilator-associated pneumonia
Wongsurakiat and Tulatamakit[30]	2018	Thailand	ICU	Prospective non-randomized controlled study	Acute respiratory tract infection	71	PCT	0.02–100 ng/mL	No biomarker (clinical score)	Efficacy of PCT in determining antibiotic therapy duration in patients with ventilator-associated pneumonia
Mohd *et al.*[31]	2021	Malaysia	ICU	Prospective interventional single-blinded	Acute respiratory tract infection	85	PCT	< 0.25 ng/mL	No biomarker (routine care)	Efficacy of PCT in determining antibiotic therapy duration in patients with ventilator-associated pneumonia
El-Amin *et al.*[32]	2017	Egypt	Inpatient	Cross-sectional descriptive study	Intra-abdominal infections	100	CRP	Not specified	Non-comparative	Diagnostic value of CRP for infection among patients with liver cirrhosis
Godinez-Vidal *et al.*[33]	2019	México	Inpatient	Retrospective, descriptive, cross-sectional	Intra-abdominal infections	99	PCT	>10.1 ng/mL	Non-comparative	Prognostic value of PCT in abdominal sepsis
Orati *et al.*[34]	2013	Brazil	ICU	Retrospective cohort	Intra-abdominal infections	345	CRP	Not specified	Non-comparative	Diagnostic value of CRP in abdominal sepsis
Trivedi *et al.*[35]	2016	India	Inpatient	Retrospective	Urinary tract infections	122	CRP	Not specified	Non-comparative	Diagnostic value of CRP in urinary sepsis
Ndamason *et al.*[36]	2019	Cameroon	Inpatient	Cross-sectional	Urinary tract infections	128	CRP	Not specified	Non-comparative	Diagnostic value of CRP in urinary sepsis
Arjunlal *et al.*[37]	2020	India	Inpatient	Prospective	Urinary tract infections	64	CRP	Not specified	Non-comparative	Prognostic value of CRP in urinary sepsis

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Table 1. *Continued*

Citation/ref.	Year	Study country	Study location	Study design	Disease tested	Study population	Biomarker(s)	Ranges (CRP/PCT)	Comparison	Outcomes tested
Agrawal *et al.*[38]	2015	India	Inpatient	Retrospective	Bone and joint infection	81	CRP	Not specified	Non-comparative	Diagnostic value of CRP in osteoarticular infections
George *et al.*[39]	2019	India	Inpatient	Retrospective	Bone and joint infection	70	CRP	Not specified	Non-comparative	Diagnostic value of CRP in septic arthritis
Waheed *et al.*[40]	2019	Egypt	Inpatient	Prospective	Bone and joint infection	44	CRP	Not specified	Non-comparative	Prognostic value of CRP in patients with spondylodiscitis
Sharma *et al.*[41]	2012	India	Inpatient	Prospective	Bone and joint infection	20	CRP	11 mg/dL	Non-comparative	Prognostic value of CRP in patients with severe odontogenic infections
Umapathy *et al.*[42]	2018	India	Inpatient	Cross-sectional case-control	Skin and soft tissue infections	185	PCT	30 pg/mL	Biomarkers (CRP, ESR, WBC)	Prognostic value of PCT in diabetic patients with foot ulcers
Bammigatti *et al.*[43]	2019	India	Inpatient	Prospective observational	Skin and soft tissue infections	327	PCT	0.03 ng/mL	Non-comparative	Prognostic value of PCT in patients with snake bites
Yousef *et al.*[44]	2010	Egypt	ICU	Prospective observational	Sepsis and bloodstream infections	106	CRP, leptin, IL-6 and TNF-α	Not specified	Non-comparative	Prognostic value of CRP in patients with sepsis
Mamani *et al.*[45]	2012	Iran	Inpatient	Case-control	Sepsis and bloodstream infections	90	CRP, fibronectin	Not applicable	Non-comparative	Prognostic value of CRP in patients with sepsis
Ali *et al.*[46]	2017	Pakistan	ICU	Case series	Sepsis and bloodstream infections	32	CRP, lactate	Not specified	Non-comparative	Prognostic value of CRP in patients with sepsis
Talebi-Taher *et al.*[47]	2014	Iran	Emergency department	Prospective	Sepsis and bloodstream infections	150	CRP	PCT: 0.5 ng/mL; IL-6: 10 pg/μL, ESR: 17 mm/h for men and 25 mm/h for women; CRP ≥12 mg/L	ESR, PCT, IL-6	Diagnostic value of CRP in elderly patients with sepsis
Premaratna *et al.*[48]	2015	Sri Lanka	Inpatient	Prospective	Sepsis and bloodstream infections	40	CRP	Not specified	Non-comparative	Diagnostic value of CRP for sepsis in patients with dengue fever
Gupta *et al.*[49]	2019	India	Inpatient	Prospective	Sepsis and bloodstream infections	305	PCT	>0.5 ng/mL	Non-comparative	Diagnostic value of PCT in patients with sepsis
Sinha *et al.*[50]	2011	India	ICU	Prospective	Sepsis and bloodstream infections	40	PCT	>0.5 ng/mL	Non-comparative	Diagnostic value of PCT in patients with sepsis
Ghorbani[51]	2009	Iran	Emergency department	Cross-sectional	Sepsis and bloodstream infections	100	PCT	0.05 ng/mL	Non-comparative	Diagnostic value of PCT in patients with sepsis
Jain *et al.*[52]	2014	India	ICU	Prospective	Sepsis and bloodstream infections	54	PCT	Not specifed	CRP	Prognostic value of PCT in patients with sepsis
Rebello *et al.*[53]	2017	India	Inpatient, ICU	Prospective observational	Sepsis and bloodstream infections	112	PCT	Not applicable	Non-comparative	Prognostic value of PCT in patients with sepsis
Mehta *et al.*[54]	2016	India	ICU	Retrospective observational study	Sepsis and bloodstream infections	100	PCT, BNP	Not specified	Non-comparative	Prognostic value of PCT and NTproBNP in ICU-admitted patients
Dolatabadi *et al.*[55]	2015	Iran	Emergency department	Cross sectional	Sepsis and bloodstream infections	170	PCT	0.5 ng/mL	PCT before, 6 h after and 24 h after ATBs	Prognostic value of PCT in patients with sepsis
Najafi *et al.*[56]	2015	Iran	ICU	Prospective, single-blind randomized	Sepsis and bloodstream infections	60	PCT	Not specified	No biomarker	Prognostic value of PCT in patients with sepsis
Lubell *et al.*[57]	2015	Thailand, Cambodia, Laos	Inpatient/ outpatient	Retrospective	Undifferentiated fever	1372	CRP, PCT	Not specified	Non-comparative	Diagnostic value of CRP, PCT in patients with undifferentiated fever
Wangrangsimakul *et al.*[58]	2018	Thailand	Inpatient	Prospective	Undifferentiated fever	200	CRP, PCT	Not specified	Non-comparative	Diagnostic value of CRP, PCT in patients with undifferentiated fever
Phatlhane *et al.*[59]	2016	S Africa	Outpatient	Cross-sectional	HIV	110	PCT, IL-6, LBP, CRP, IgG, albumin	Not specified	Non-comparative	Prognostic value of CRP, PCT in HIV-infected patients with diarrhoea
Ramana *et al.*[60]	2013	India	Outpatient	Prospective	HIV	250	CRP	Not specified	ESR, TLC, Hb, AEC	Prognostic value of CRP in HIV-infected patients with diarrhoea
Zulu *et al.*[61]	2008	Zambia	Not specified	Retrospective	HIV	80	CRP, TNFR p55, MIF, IL-6, IL-12, IFN-γ	0.2 mg/L	Non-comparative	Prognostic value of CRP and cytokines in HIV-infected patients with diarrhoea
Koethe *et al.*[62]	2011	Zambia	Outpatient	Prospective observational cohort	HIV	142	CRP, albumin, ferritin	Not specified	Non-comparative	Prognostic value of CRP and other biomarkers in patients with malnutrition and advanced HIV
Bedell *et al.*[63]	2018	Malawi	Outpatient	Retrospective	HIV	469	CRP	3.0 - 480 mg/L	Non-comparative	Diagnostic value of CRP for tuberculosis and bloodstream infections in HIV-infected patients

Ledwaba *et al.*[64]	2012	S Africa	Outpatient	Case-control	HIV	187	CRP, IL-6, D-dimer	CRP 1 mg/mL, IL-6 0.428-8.870 pg/L, D-Dimer 0.5 mg/L	Non-comparative	Prognostic value of CRP and other biomarkers in patients with advanced HIV
Woodd *et al.*[65]	2016	Zambia, Tanzania	Outpatient	Prospective	HIV	1815	CRP	Not specified	Non-comparative	Prognostic value of CRP in patients with advanced HIV
Haddow *et al.*[66]	2012	S Africa	Outpatient	Prospective	HIV	498	CRP	Not specified	Non-comparative	Prognostic value of CRP in patients with advanced HIV
Sereti *et al.*[67]	2020	Kenya, Thailand, USA	Outpatient	Prospective observational	HIV	506	CRP	Not specified	Non-comparative	Prognostic value of CRP in patients with advanced HIV
Kroeze *et al.*[68]	2019	Kenya, Nigeria, South Africa, Uganda, Zambia	Not specified	Retrospective	HIV	398	sCD14, sCD163, CRP, CXCL10, IL-6, CCL2, CXCL	Not specified	Non-comparative	Prognostic value of CRP in patients with advanced HIV
Kiefer *et al.*[69]	2018	Rwanda	Outpatient	Prospective	HIV	695	CRP, D-dimer, transthyretin	Not specified	Non-comparative	Prognostic value of CRP in patients with advanced HIV
Chegou *et al.*[70]	2016	S Africa, Uganda, Gambia, Malawi, Namibia	Outpatient	Prospective	716	TB	CRP, PCT	Not specified	IL-1ra, TGF-α, IFN-γ, IP-10, TNF-α, IFN-α2, VEGF, MMP-2, MMP-9, ApoA-1, Apo-CIII, transthyretin, CFH, SAA, SAP, fibrinogen, ferritin, TPA, haptoglobulin, α-2-macroglobulin	Diagnostic value of CRP, PCT and other biomarkers in patients with pulmonary TB
Jacobs *et al.*[71]	2016	S Africa	Outpatient	Prospective	TB	55	CRP, PCT	Not specified	NCAM, SAP, IL-1β, sCD40L, IL-13 and Apo A-1	Diagnostic value of CRP, PCT and other biomarkers in patients with pulmonary TB
Berrocal-Almanza *et al.*[72]	2016	India	Outpatient	Prospective cohort	TB	119	CRP	Not specified	S100A12, sRAGE, esRAGE, HMGB-1, TNF-α, IFN-γ	Prognostic value of CRP in TB
Worodria *et al.*[73]	2011	Uganda	Outpatient	Prospective	TB	247	CRP	<5 mg/L	Non-comparative	Diagnostic value of CRP, in HIV patients with pulmonary TB
Yoon *et al.*[74]	2017	Uganda	Outpatient	Prospective	TB	1237	CRP	>10 mg/L	Non-comparative	Diagnostic value of CRP for TB in people living with HIV/AIDS
Rajopadhye *et al.*[75]	2017	India	Not specified	Prospective	TB	50	CRP, NO, TBARS, SOD	Not specified	Non-comparative	Diagnostic value of CRP for TB in people living with HIV/AIDS
Yoon *et al.*[76]	2019	Uganda	Outpatient	Prospective	TB	1245	CRP	8 mg/L	No biomarker (symptom-based screening)	Diagnostic value of CRP for TB in
Ciccacci *et al.*[77]	2019	Mozambique	Outpatient	Retrospective	TB	155	CRP	10 mg/L	Neopterin, IP-10	Diagnostic value of CRP for TB in people living with HIV/AIDS
Olsson *et al.*[78]	2019	Ethiopia	Outpatient	Prospective	TB	260	CRP, PCT	Not specified	CCL5, IP-10, IL-6, IL-12, IL-18, IL-27, IFN-γ, suPAR	Diagnostic value of CRP, PCT for TB in people living with HIV/AIDS
Wilson *et al.*[79]	2011	S Africa	Outpatient	Prospective	TB	364	CRP	Method 1: 0–8 mg/L Method 2: 0–5 mg/L	Non-comparative	Diagnostic value of CRP for TB in people living with HIV/AIDS
Lawn *et al.*[80]	2013	S Africa	Outpatient	Prospective	TB	496	CRP	50 mg/L	Non-comparative	Diagnostic and prognostic value of CRP for TB in people living with HIV/AIDS
Farr *et al.*[81]	2018	Uganda	Not specified	Retrospective	TB	865	CRP, cytokines	Not specified	Non-comparative	Diagnostic value of CRP and cytokines for TB in people living with HIV/AIDS
de Oliveira *et al.*[82]	2019	Brazil	Not specified	Retrospective	TB	50	CRP	<1 mg/dL	No biomarker (3D reconstructed lung imaging)	Prognostic value of CRP in TB
Wilson *et al.*[83]	2018	S Africa	Outpatient	Prospective cohort	TB	421	CRP	Not specified	Non-comparative	Prognostic value of CRP in TB
Rasmussen *et al.*[84]	2011	Guinea-Bissau	Outpatient	Prospective	TB	218	PCT CRP	PCT 0.02–50 ng/mL CRP not specified	CRP	Prognostic value of PCT in TB
Janssen *et al.*[85]	2017	S Africa	Inpatient	Prospective cohort	TB	60	PCT	Not specified	Non-comparative	Prognostic value of PCT for TB among HIVpatients
Soedarsono *et al.*[86]	2019	Indonesia	Outpatient	Prospective cohort	TB	30	CRP	0.3–0.5 mg/dL	Non-comparative	Prognostic value of CRP in TB

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Table 1. *Continued*

Citation/ref.	Year	Study country	Study location	Study design	Disease tested	Study population	Biomarker(s)	Ranges (CRP/PCT)	Comparison	Outcomes tested
Epelboin L *et al.*[87]	2013	French Guiana	Emergency department	Retrospective	Undifferentiated febrile illness	416	CRP	>5 mg/L	No biomarker (clinical score)	Diagnostic value of CRP for malaria and dengue fever
Sanchez-Arcila *et al.*[88]	2014	Brazil	Outpatient	Prospective	Malaria	264	CRP	0.01–320 μg/mL	Non-comparative	Diagnostic value of CRP for malaria and intestinal parasites coinfection
Peto *et al.*[89]	2016	Cambodia	Outpatient	Prospective	Malaria	328	CRP	Not applicable	Non-comparative	Diagnostic value of CRP for malaria
Gibson and Huddle[90]	1998	Malawi	Outpatient	Prospective	Malaria	152	CRP	Not specified	Non-comparative	Diagnostic value of CRP for malaria in pregnancy
Mockenhaupt *et al.*[91]	2000	Ghana	Outpatient	Cross-sectional	Malaria	530	CRP	>0.6 mg/dL	Non-comparative	Diagnostic value of CRP for malaria in pregnancy
Hinderaker *et al.*[92]	2002	Tanzania	Outpatient	Prospective	Malaria	2547	CRP, ferritin, iron, TIBC, cobalamin, folate, vitamin A, LDH, TFsat	10 mg/L	Non-comparative	Diagnostic value of CRP for malaria in pregnancy
Adegnika *et al.*[93]	2006	Gabon	Inpatient	Prospective	Malaria	145	CRP	0.5 –6 mg/L	Non-comparative	Prognostic value of CRP for malaria in pregnancy
Conroy *et al.*[94]	2011	Malawi	Inpatient	Case-control	Malaria	465	CRP, C3a, C5a, angiopoietin-1, -2, sTie-2, sEndoglin, VEGF, sFlt-1, tissue factor, leptin	Not specified	Non-comparative	Prognostic value of CRP for malaria
Paul *et al.*[95]	2012	India	Outpatient	Prospective	Malaria	71	CRP	≤5 mg/L	Non-comparative	Prognostic value of CRP for malaria
Mendonca *et al.*[96]	2013	Brazil	Outpatient	Retrospective	Malaria	530	CRP, liver transaminases, bilirubins, creatinine, fibrinogen, SOD-1, HO-1, cytokines, chemokines	Not specified	Non-comparative	Prognostic value of CRP for malaria
Bhardwaj, *et al.*[97]	2019	India	Inpatient	Prospective	Malaria	96	CRP	Not applicable	Non-comparative	Prognostic value of CRP for malaria
Lima-Junior *et al.*[98]	2012	Brazil	Outpatient	Prospective	Malaria	71	CRP, NO, platelets, neutrophils	0.01–320 μg/mL	Non-comparative	Prognostic value of CRP for malaria

AEC, absolute eosinophil count; ApoA-1, apolipoprotein A1; Apo-CIII, apolipoprotein CIII; ARDS, acute respiratory distress syndrome; ATB, antibiotic; BNP, brain natriuretic peptide; CCL, C motif chemokine ligand; CFH, complement factor H; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CXCL10, CXC motif chemokine 10; CXR, chest X-ray; ESR, erythrocyte sedimentation rate; esRAGE, endogenous secretory receptor for advanced glycation end products; Hb, haemoglobin; HMGB-1, high-mobility group protein 1; HO-1, haem oxygenase 1; IL-1ra, interleukin-1 receptor antagonist; IP-10, interferon gamma inducible protein 10; LBP, lipopolysaccharide-binding protein; LDH, lactate dehydrogenase; Lyt A, autolysin A; MIF, macrophage migration inhibitory factor; MMP, matrix metalloproteinase; MR-proANP, midregional pro-atrial natriuretic peptide; NCAM, neural cell adhesion molecule; NO, nitric oxide; PCT, procalcitonin; S100A12, S100 calcium binding protein A12; SAA, serum amyloid A; SAP, serum amyloid P-component; sCD, soluble cluster of differentiation; sCD40L, soluble CD40 ligand; sFlt-1, soluble Fms-like tyrosine kinase-1; SOD-1, superoxide dismutase 1; sRAGE, soluble receptor for advanced glycation end products; sTie-2, soluble tyrosine-kinase-receptor; suPAR, soluble urokinase-type plasminogen activator receptor; TBARS, thiobarbituric acid reactive substances; TFsat, transferrin saturation; TGF-α, transforming growth factor-α; TIBC, total iron-binding capacity; TLC, total leukocyte count; TNFR p55, tumour necrosis factor receptor p55; TPA, tissue polypeptide antigen; VEGF, vascular endothelial growth factor.

(Egypt).[26] PCT elevation greater than 0.5 ng/mL was an independent predictor of mortality for PLWH with pneumonia (Uganda).[27] PCT was a significant predictor of in-hospital mortality in ventilator-acquired pneumonia (VAP) (Brazil).[28]

Treatment response

In patients with VAP responding to treatment, PCT and CRP began declining at 48 and 72 h, respectively (Iran).[29] The combination of a low clinical pulmonary infection score (a validated score to predict the likelihood of VAP) plus a PCT below 0.5 ng/mL on Day 8 was a safe indication for discontinuation of antibiotics in VAP (Thailand).[30] Patients with VAP and serial PCT measurements had on average 1.25 fewer days on antibiotics without increased mortality when compared with controls when discontinuation was based on 80% decrease to below 0.5 ng/mL, or any decrease below 0.25 ng/mL (Malaysia).[31]

Intra-abdominal infections including gastrointestinal and hepatobiliary

Diagnosis

Elevated CRP was an independent predictor of bacterial infection among admitted patients with liver cirrhosis (Egypt).[32] Elevated PCT was associated with abdominal sepsis (most commonly appendicitis) (Mexico).[33] Patients with abdominal sepsis had higher CRP than those with pulmonary sepsis (mean 178 versus 149 mg/L) (Brazil).[34]

Genitourinary

Diagnosis

CRP levels in pyelonephritis were often greater than 200 mg/L and were not affected by the presence of diabetes (India).[35] CRP levels in lower urinary tract infection (UTI) were not altered by pregnancy (Cameroon).[36] In males admitted with UTI the median CRP level was 22.3 mg/L (India).[37]

Musculoskeletal infections

Diagnosis

Patients with acute osteomyelitis and joint infections caused by MRSA had CRP levels greater than 13.9 mg/L (India).[38] Patients with septic arthritis all had CRP levels greater than 75 mg/L (mean 132.5 mg/L) (India).[39]

Treatment response

CRP was elevated (mean 257 mg/L, range 60–980 mg/L) in patients with spondylodiscitis (bacterial, brucellar, mycobacterial, culture-negative) of more than 4 months duration, and decreased after 2 weeks of treatment to indicate response (Egypt).[40] CRP decreased with treatment in severe odontogenic infections (India).[41]

Skin and soft tissue infections

Diagnosis

A PCT above 0.5 ng/mL had moderate sensitivity (54%) and excellent specificity (100%) for the diagnosis of infected diabetic foot ulcers, and outperformed CRP, WBC count and erythrocyte sedimentation rate in this setting (India).[42] In patients with severe snake bites, PCT did not increase over time (0.29 ng/mL), supporting clinical suspicion of toxin-mediated inflammation and withholding antibiotics in patients with local manifestation mimicking those due to bacterial infection (India).[43]

Sepsis and bloodstream infections

Diagnosis, CRP

CRP was elevated on average to 67 mg/L in septic patients in their first day of admission to the ICU (Egypt).[44] Patients with sepsis in the setting of UTI, pneumonia or soft tissue infection had a mean CRP of 89 mg/L (Iran).[45] Patients with septic shock from pneumonia or UTI had a mean CRP of 29 mg/L (Pakistan).[46] Patients older than 65 years with sepsis had a mean CRP of 58 mg/L (Iran).[47] Prolonged fever in dengue (>5 days) with subsequent bacteraemia was associated with higher peak CRP (mean 600 compared with 160 mg/L in prolonged fever without bacteraemia) (Sri Lanka).[48]

Diagnosis, PCT

PCT was higher in sepsis with confirmed positive culture in blood, urine, sputum or other body fluid (2.2 versus 1.3 ng/mL), and a cut-off of 2.2 ng/mL was 98% sensitive and 89% specific for culture positivity (India).[49] A PCT cut-off of 2 ng/mL was moderately sensitive (86%) and specific (95%) for sepsis (India).[50] A PCT greater than 10 ng/mL (mean 30 ng/mL) was associated with septic shock, and higher PCT was associated with positive blood cultures (Iran).[51]

Prognosis

A PCT greater than 7 ng/mL on ICU admission was associated with mortality (India).[52] Non-survivors in sepsis had rising PCT on Days 1–5 compared with those surviving (India).[53] Among patients with acute respiratory distress syndrome from pneumonia and malaria, PCT was lower in survivors versus non-survivors (1.1 versus 2 ng/mL), as was CRP (36 versus 76 mg/L) (India).[23] PCT did not predict all-cause mortality in an ICU population admitted for infectious and non-infectious conditions (India).[54]

Treatment response

Patients responding to treatment had a decrease in mean PCT from 9 to 5 ng/mL at 24 h (Iran).[55] No difference in mortality was noted compared with standard care by withholding antibiotics in patients with suspected sepsis admitted to ICU with a low value of PCT at admission (less than 2 ng/mL) and serial follow-up measurements (Iran).[56]

Undifferentiated febrile illness

Diagnosis

A CRP cut-off of 10 mg/L was 95% sensitive and 49% specific for bacterial versus viral illness; increasing the cut-off to 20 mg/L lowered the sensitivity (86%) and increased the specificity (67%), and a PCT cut-off of 0.1 ng/mL was 90% sensitive and 39% specific (Laos, Thailand).[57] In patients with undifferentiated fever on presentation, a low CRP (median 12.5 mg/L) was associated with viral compared with bacterial aetiology (median 139.5 mg/L). Median PCT in viral and bacterial undifferentiated febrile illness was 0.3 and 2.6 ng/mL, respectively (Thailand).[58]

HIV

This section includes publications addressing CRP and PCT related to HIV itself. Data on specific other conditions in PLWH have been described in other sections.

General issues and prognosis

PCT levels were not elevated in asymptomatic untreated HIV infection compared with controls (South Africa).[59] A CRP above 12 mg/L was associated with a CD4 count of <350 cells/mm^3 (India).[60] Elevated CRP was linked with disease severity in AIDS-related diarrhoea, and associated with short-term mortality in PLWH (Zambia).[61] A CRP above 15 mg/L was associated with increased 90 day mortality among malnourished adults initiating ART (Zambia).[62] A CRP above 10 mg/L at the time of ART initiation was associated with TB, bloodstream infection and early mortality (Malawi).[63] A pre-ART elevated CRP was a strong predictor of death in advanced HIV (South Africa).[64] The mortality rate in malnourished PLWH increased with baseline CRP and was five times higher with a measurement above 160 mg/L compared with below 10 mg/L (Tanzania, Zambia).[65] Elevated baseline CRP was associated with immune reconstitution inflammatory syndrome and increased mortality after ART initiation (Thailand, Kenya, South Africa).[66,67]

Treatment response

PLWH had elevated CRP prior to initiating ART compared with HIV-negative controls; this varied by country of origin, and post-ART CRP declined but did not completely normalize (Kenya, South Africa, Nigeria, Uganda, Zambia).[68] Higher CRP was associated with HIV infection with more advanced immune suppression, but ART was not associated with a decrease in CRP (Rwanda).[69]

TB

Diagnosis

Patients with TB had elevated CRP compared with controls (South Africa, Malawi, The Gambia, Namibia, Uganda),[70] with a sensitivity of 82% and specificity of 90% when using a cut-off of 9 mg/L (South Africa).[71] Mean baseline CRP in smear-positive TB was elevated compared with controls (6.74 compared with 3.18 mg/L) (India).[72]

Diagnosis, PLWH

A CRP above 5 mg/L was associated with TB unmasking at ART initiation (Uganda).[73] CRP above 10 mg/L was 89% sensitive and 72% specific for TB in PLWH with CD4 <350 cells/mm^3 (Uganda) and was associated with TB (Malawi).[63,74] CRP was elevated in TB, and more so in HIV-positive (mean 44.7 mg/L) than HIV-negative (mean 3.67 mg/L) patients, compared with controls (1.4 mg/L) (India).[75] Using a CRP above 8 mg/L as a criterion for TB testing with GeneXpert in PLWH decreased cost and number of tests by around 50% without lowering overall sensitivity (Uganda).[76] Average CRP among GeneXpert-positive PLWH was 15.7 mg/L compared with 1.1 mg/L in GeneXpert-negative controls (Mozambique).[77] PLWH with TB had higher CRP levels if smear- or GeneXpert-positive (50 mg/L and 49.5 mg/L, respectively) compared with patients who were only positive by culture (9.1 mg/L), and PCT was low amongst all patients (Ethiopia).[78] A CRP above 5 mg/L had sensitivity of 98% and specificity of 59% for smear-negative TB in a population with high HIV prevalence (South Africa).[79] A CRP below 1.5 mg/L excluded TB among a cohort of PLWH (South Africa).[80] Average CRP among PLWH with TB admitted to the hospital was 140 mg/L compared with 69 mg/L in PLWH without TB (Uganda).[81] CRP elevation correlated with volume of TB-affected lung on 3D CT reconstructions (Brazil).[82]

Prognosis

In PLWH with TB, a CRP above 50 mg/L was associated with higher mortality, disseminated disease and increased mycobacterial load (South Africa).[80] Failure of CRP to decrease to below 55% of baseline value at Week 2 predicted hospitalization or death among symptomatic TB patients initiating treatment (South Africa).[83] CRP correlated with disease severity and mortality (Guinea Bissau).[84] Among PLWH with TB, non-survivors had higher PCT than survivors (mean 8.28 versus 1.31 ng/mL) (South Africa).[85]

Treatment response

Mean baseline CRP in smear-positive TB decreased to 4.4 mg/L at 2 months of treatment (India).[72] After 2 months of treatment for smear-positive TB, the mean CRP decreased from 64 to 12 mg/L (Indonesia).[86] CRP declined with treatment (South Africa).[71]

Malaria

Diagnosis

CRP was higher in malaria than dengue fever, and a cut-off of 5 mg/L had a sensitivity of 99.5% and specificity of 35% (French Guiana).[87] Patients with intestinal protozoan and malarial coinfection did not have increased CRP compared with those infected with malaria alone (Brazil).[88] Median CRP was similar in patients with subclinical parasitaemia (0.66 mg/L) and healthy matched controls (0.52 mg/L) (Thailand).[89]

Diagnosis, pregnancy

Of asymptomatic pregnant women, 31.3% tested positive for malaria, yet only 6% of these had a CRP above 15 mg/L (Malawi).[90] Of 528 pregnant women, 51% had a CRP above 6 mg/L, and 82% of these had a positive test for malaria

compared with 31% in the total cohort (Ghana).[91] A higher CRP level was associated with a degree of anaemia but not with a microscopic diagnosis of malaria in pregnant women (Tanzania).[92] CRP was elevated in microscopic but not submicroscopic *Plasmodium falciparum* malaria (average 34 versus 7 mg/L) (Gabon).[93] In patients with asymptomatic placental *P. falciparum* malaria, average CRP was 60.2 compared with 18.5 mg/L in those without infection, and a cut-off of 30.5 mg/L had a sensitivity of 73.9% and a specificity 68.3% (Malawi).[94]

Prognosis

In patients with *P. falciparum* malaria, CRP increase was associated with severity of organ dysfunction and mortality (mean 47.1 mg/L compared with 16.4 mg/L in survivors), and a CRP greater than 35 mg/L had a sensitivity above 95% for mortality (India).[95] Mean CRP varied with severity of *Plasmodium vivax* malaria: deaths 34.4 mg/L, severe malaria survivors 13.2 mg/L, uncomplicated cases 15.5 mg/L, asymptomatic cases 7.9 mg/L, and endemic controls 5.2 mg/L (Brazil).[96] The CRP level was slightly higher in severe *P. falciparum* malaria (20 mg/L) compared with uncomplicated malaria (14 mg/L) and healthy controls (1 mg/L) (India).[97]

Treatment response

Of symptomatic patients with *P. vivax* or *P. falciparum* malaria, 87% had elevated CRP (mean 27.8 mg/L), which decreased with successful therapy (mean 3 mg/L on Day 15) (Brazil).[98]

Discussion

CRP and PCT both have the potential to improve clinical outcomes and antimicrobial stewardship in LMICs. Notable areas where available data are particularly promising are the diagnosis of bacterial respiratory infections, sepsis and TB, and in monitoring response to treatment in these infections.

In the outpatient setting, using low CRP measurements to support withholding antibiotics for respiratory symptoms is perhaps the most straightforward specific area of implementation, although it would require POCT in order to be practically useful and have added value compared with clinical indicators alone. High concentrations of both CRP and PCT could also help identify patients at risk of adverse outcome of respiratory tract infection who are in need of admission or closer outpatient follow-up.

In the inpatient setting, CRP and PCT should be interpreted in the light of clinical findings and ideally together with a range of additional tests such as culture of blood and respiratory specimens and biochemical markers of organ dysfunction. The absence of these additional paraclinical safety nets in many LMICs is an important limitation in the implementation of CRP/PCT for both diagnosis and monitoring purposes. This is particularly important in the diagnostic workup and treatment monitoring in sepsis, where mortality is high and the consequence of withholding effective treatment can be fatal.

In TB, CRP has the specific potential to rationalize the use of more expensive diagnostic tests, and WHO recently recommended CRP as one of the screening tools for TB.[99] The cost-effectiveness of this strategy should be evaluated.

There are important limitations to this review. The general lack of well-defined cut-off values validated in more than one setting will be an important limiting factor in the practical implementation of both CRP and PCT. Half of the included publications were carried out in only three countries—South Africa, India and Uganda (Table 1). In addition, there was a high degree of methodological heterogeneity between studies. Some studies used different definitions of normal range measurements, most studies did not include laboratory cut-offs for normal, different assays were used, some studies used non-standard units when reporting CRP and PCT, and some did not include any units and authors had to be contacted for this information. Finally, studies with a focus on COVID-19 were excluded from the review. The impact of the pandemic may change the future generalizability of studies of respiratory tract infections and may also mean less available funding for implementation of new laboratory tests in LMICs.

Despite numerous limitations, there were consistent results across many areas, and almost half of identified publications were from the last 5 years, perhaps indicating increasing interest and availability of CRP and PCT in LMICs. Consensus across stakeholders regarding target-conditions and laboratory standards, in particular cut-off values, would support the quality and applicability of future evidence.

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Supplementary data

Table S1 is available as Supplementary data at *JAC-AMR* Online.

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