Research Article

An Exploratory Study to assess the Feasibility and Acceptability of Clinical Infection Score Estimation in Patients with Suspected Infection at a tertiary care hospital

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Abstract

Background: The Global Action Plan to combat antimicrobial resistance highlights the need for sustainable investment in diagnostic development. A major cause of irrational antibacterial prescribing is the absence of rapid tests to accurately identify pathogens. Neutrophil receptor expression has recently been proposed to differentiate bacterial from viral infections through estimation of the Clinical Infection Score (CIS). This study evaluated the feasibility and acceptability of estimating CIS operationally in clinical settings.

Methods: In Phase I, operational feasibility was assessed in healthy participants, while in Phase II, operational acceptability was assessed in patients with suspected infection who had not yet received empiric antimicrobials. Operational feasibility of CIS estimation was assessed based on successful completion of all required steps of score calculation and acceptability was assessed in terms of operational convenience from obtaining consent to calculation of CIS score. To assess objectives, blood samples were collected to measure absolute neutrophil count, erythrocyte sedimentation rate, C-reactive protein, and mean fluorescence intensity of CD35-FITC (CR1) and CD11b-PE (CR3). CIS was calculated using the algorithm proposed by Lilius and Nuutila.

Results: Phase I was done in 12 healthy participants. In phase 2, 36 patients were enrolled but only samples of 30 patients were included in analysis as 6 samples got lysed. The time from sample collection to reporting CR1 and CR3 values was 1.5–2 hours, and 1.75–2.25 hours for CIS calculation. Among healthy subjects, CIS ranged from 0–2, while in patients, 20 had CIS <2 and 10 had CIS ≥2, consistent with previous reports.

Conclusion

The findings demonstrated that measuring CR1 and CR3 expression and computing CIS is feasible operationally in healthcare settings. The CIS range in healthy controls and patients with suspected infection was consistent with findings reported in the earlier studies. However, randomized controlled studies are needed to validate the diagnostic utility of CIS and to assess its impact on reducing empirical antimicrobial therapy.

Introduction

Antimicrobial resistance (AMR) was recognized by the World Health Assembly in 2014 as a major global health threat, leading to the 2015 Global Action Plan that emphasizes sustainable investment in developing new antimicrobials, diagnostics, and vaccines [1].

The limited investment in developing new antimicrobials makes preserving the effectiveness of existing drugs increasingly urgent [1]. Although antibacterials target bacterial infections, similar symptoms across infections caused by different pathogens and the ≥48-hour turnaround of the gold-standard culture-susceptibility test often lead to empirical prescribing of antibacterials based on clinical suspicion [2].

A key driver of irrational antibacterial prescribing is the lack of rapid diagnostic tests to identify pathogens and their antimicrobial susceptibility at the point of care, limiting timely, appropriate treatment decisions [3,4].

There has been increasing focus on the use of acute-phase reactants (APRs) like erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), procalcitonin (PCT) in the management of infections. However, they are known to get elevated in non-infectious, inflammatory conditions, thereby are associated with risk of false positive and false negative results for diagnosis of infections [5,6,7].

Lilius EM. and Nuutila J. proposed that neutrophil receptor expression can help differentiate bacterial from viral infections. Complement receptors CR1 (CD35) and CR3 (CD11b) are weakly expressed on resting neutrophils but are upregulated in bacterial infections; in viral infections, CR1 is downregulated while CR3 remains upregulated. They suggested that a clinical infection score (CIS), based on ESR, CRP, mean fluorescence intensity (MFI) of CR1, and the total neutrophil complement receptor (TNCR) index, can distinguish microbiologically confirmed bacterial from viral infections at a cutoff >2, with 98% sensitivity and 97% specificity [8].

Therefore, given the need for novel biomarkers to distinguish bacterial from viral infections and reduce unnecessary antibacterial use and antimicrobial resistance, this exploratory study assessed the feasibility and acceptability of estimating the Clinical Infection Score (CIS) operationally in clinical settings.

Methods

This prospective study was conducted in accordance with Good Clinical Practice guidelines after obtaining Institutional Ethics Committee approval and written informed consent from all participants.

This study was conducted in two phases: phase I assessed the operational feasibility of CIS estimation using a standardized protocol adapted from method described by Lilius et al [8], and phase II evaluated operational acceptability based on ease of use, time required to calculate the score, and explored its preliminary clinical utility in patients with suspected infection.

In phase I, for assessing operational feasibility of CIS estimation, healthy adults aged ≥ 18 years of either sex who had not taken any medication in the previous two weeks were included. Individuals with any significant medical history, hepatic or renal impairment, and pregnant or lactating women were excluded.

In phase II, to assess operational acceptability of CIS, adult immunocompetent patients aged ≥ 18 years of either sex with suspected bacterial or viral infection who had not started empirical antimicrobial therapy were included. Exclusions were suspected fungal infections, medications affecting leukocyte counts, hepatic or renal impairment, and pregnancy or lactation.

Eligible participants in both phases underwent clinical examination and in phase II, clinical details and relevant investigation reports were recorded. Blood (5 mL) was collected for ESR, CRP, and Absolute Neutrophil Count (ANC). An additional 5 mL was collected in EDTA tubes for measuring CR1 and CR3 MFI, transported at 2–4 °C within 45 minutes, and processed immediately on arrival for MFI estimation.

Procedure for estimation of MFI of CR1 and CR3

EDTA blood samples were processed to measure CR1 and CR3 expression on granulocytes by flow cytometry. From each sample, 100 µL was transferred to a flow tube and incubated with 10 µL each of CD45KR, CD35-FITC, and CD11b-PE antibodies (Immunotech SAS a Beckman Coulter company) for 15–20 min in the dark at room temperature. Erythrocytes were then lysed with 500 µL Optilyse, followed by a second dark incubation (10–15 min), centrifugation at 1500 rpm for 5 min, and washing with PBS. After a final wash, events were acquired on a Beckman Coulter Navios 3-laser, 10-color flow cytometer. Granulocytes were gated on the CD45 vs. side-scatter plot, and mean fluorescence intensity (MFI) of CD35-FITC (CR1) and CD11b-PE (CR3) was obtained from histogram analysis.

All the samples were processed in only one laboratory in which two technicians underwent training from service providers to estimate MFI of CR1 and CR3.

Estimation of CIS point

The total neutrophil complement receptor (TNCR) index was calculated as the base-10 logarithm of the product of ANC, MFI of CD35-FITC (CR1), and MFI of CD11b-PE (CR3) [8].

For each variable, values below the cutoff (CRP 77 mg/L, ESR 28 mm/h, CR1 MFI 8.7, TNCR 3.4) scored 0; values between the cutoff and a second threshold (CRP 161 mg/L, ESR 42 mm/h, CR1 MFI 13.5, TNCR 3.9) scored 1; and values above the second threshold scored 2. The CIS was calculated by

summing the scores for CRP, ESR, CR1 MFI, and TNCR index [8].

Operational feasibility of CIS estimation

Operational feasibility of CIS estimation was assessed based on successful completion of all required steps of score calculation, including blood sample collection and processing, measurement of MFI of CR1 and CR3 by flow cytometry using standardized test protocol, derivation of the TNCR index using algorithm and calculation of the final CIS using predefined cut-offs as proposed by Lilius et al [8].

Operational acceptability of CIS

Operational acceptability of CIS estimation was assessed in terms of practical implementation, including patient consent for sample collection; sample stability during transport; ease of procurement of reagents, setting up of flow cytometer for measurement of MFI of complement receptors; simplicity of CIS calculation; turnaround time from sample collection to final score estimation and cost of the test.

In addition to operational acceptability, the preliminary clinical utility was also explored by comparing CIS of cases with CIS of healthy participants.

Statistical analysis

Demographic and clinical characteristics were summarized as mean ± SD for quantitative variables. The TNCR index and CIS were calculated for all participants, and mean ± SD values were determined for healthy subjects, cases with CIS <2, and cases with CIS ≥2. Between group comparison of quantitative variables was done by One-Way ANOVA followed by pairwise comparisons.

A feasibility sample of 12 healthy subjects and 36 patients with suspected bacterial or viral infection was planned. Assuming a 20% screen failure rate, 57 subjects were required to recruit 48 participants. As this was the first study that explored the feasibility and acceptability of CIS estimation, the sample size was calculated based on feasibility.

Results

In phase I, the flow cytometer was successfully configured for estimation of MFI of CD35-FITC (CR1) and CD11b-PE (CR3) in a single sitting by the instrument service providers following procurement of the reagents. However, procurement of reagents through the institutional rate contract process required approximately two months, which delayed assay establishment. Once the assay was established, 15 healthy adults were screened; 12 males were included and 3 excluded due to recent medication use. The median age of participants was 28 year. All recruited participant samples were collected, transported at 2–4 °C to the laboratory. The time from sample collection to delivery to the laboratory ranged from 0.5 to 0.75 h. Once received at the laboratory, all the samples were processed and test execution was carried out according to the procedure briefed in methodology and MFI of CR1 and CR3 were obtained in all participants. The turnaround time from sample collection to reporting of CR1 and CR3 MFI was 1.5–2 hours. Mean CR1 and CR3 values were observed to be 5.4 and 53.7, respectively (Table 1).

The TNCR index and CIS were computed for all samples according to the algorithm proposed by Lilius et al without any missing data or assay failure. CIS calculation required approximately 1.75–2.25 hours from sample collection. In healthy subjects, CIS ranged from 0–2; 11 of 12 had CIS <2, and one had CIS =2 (Figure 1). The 11/12 obtained values were within the range previously reported in the study by Lilius et al [8]. No major logistical or technical challenges were encountered after assay establishment, indicating that implementation of CIS assay was feasible in our setting.

In phase II, 41 patients were screened and 36 enrolled. Three were excluded due to recent antimicrobial use and two declined consent. Among the 36 cases, suspected diagnoses included acute undifferentiated fever (17), upper respiratory tract infection (12), pneumonia (2), malaria (2), acute gastroenteritis (2), and dengue (1). However, in one female inpatient with clinical suspicion of pneumonia, sputum culture reported *Klebsiella pneumoniae* and one female patient with clinical suspicion of dengue was found positive for NS1 antigen. Rest all the cultures were reported sterile. Blood samples from all eligible cases were collected, transported, processed and analyzed according to the standardized protocol established in phase 1.

Six (6) samples were excluded due to lysis, resulting in successful CIS estimation in 30 of 36 cases (83.3%) with median age of 30 years (19 males and 11 females). CIS point ranged from 0–4 with 20 cases having a CIS <2 and 10 cases having CIS ≥2 (Figure 2). Mean CR1 and CR3 were 5.7 and 62.1 in cases with CIS <2, and 8.3 and 86.9 in cases with CIS ≥2 (Table 1). The CIS score of patient with *K pneumoniae* infection was 3 and for patient with dengue was 0. A dot plot of healthy subjects and cases is shown in Figure 1 and 2 respectively.

Figure 1: Showing a dot plot of CIS scores in healthy subjects.

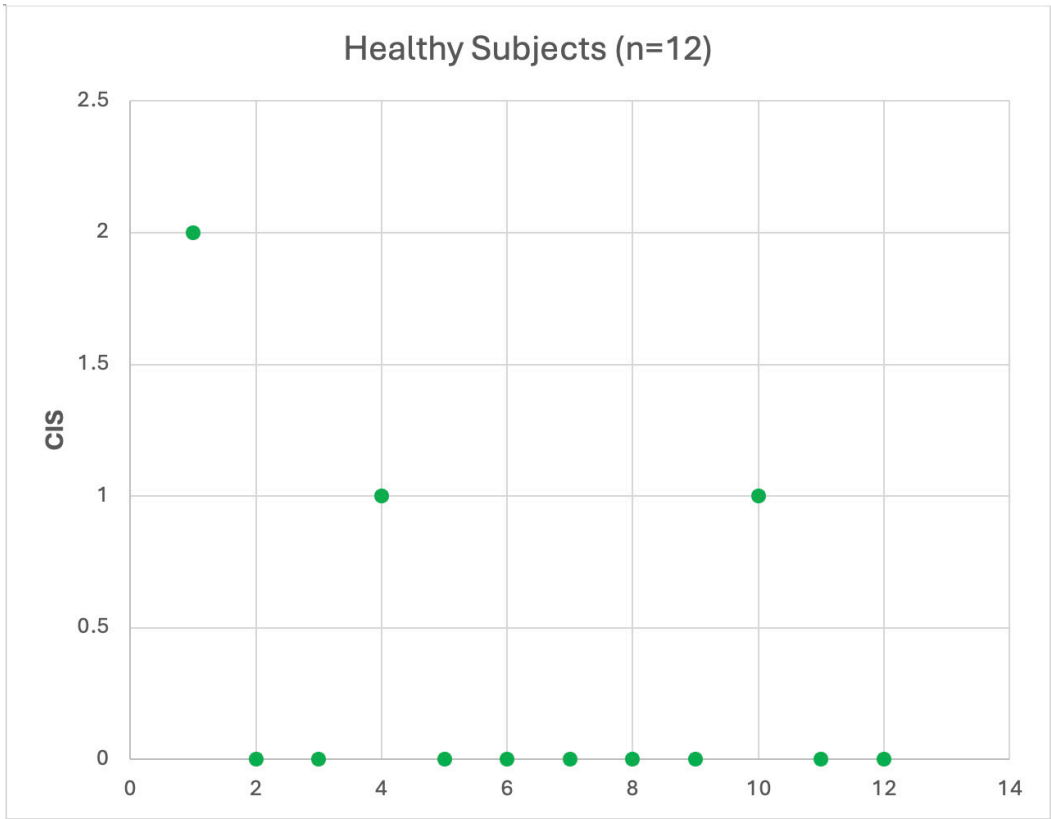
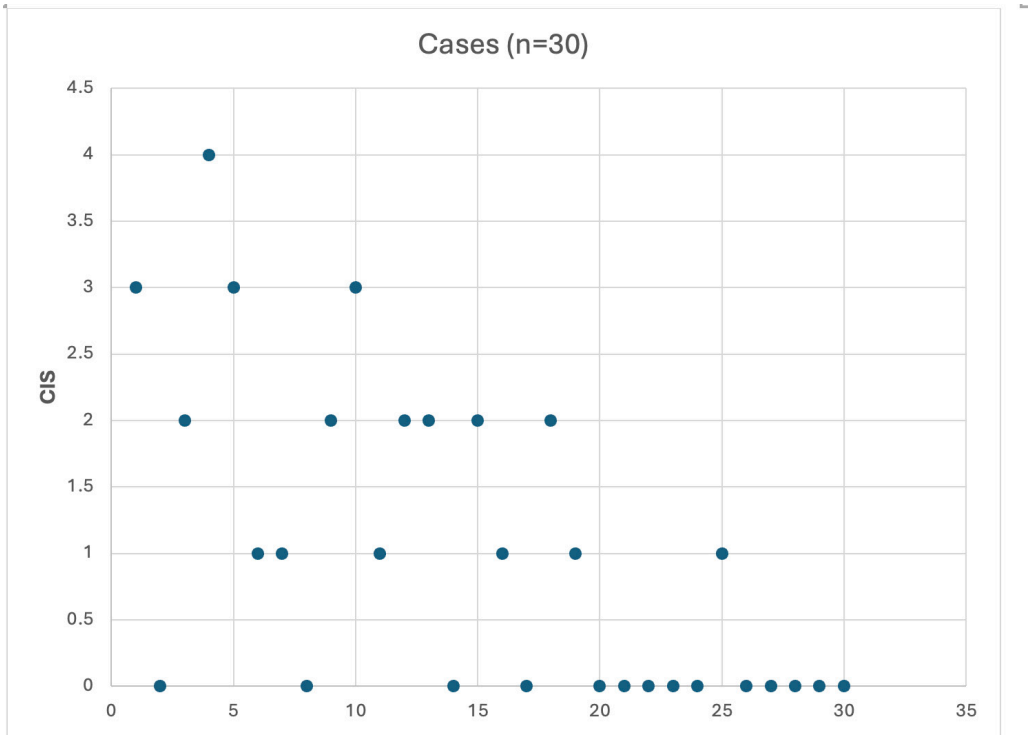


Figure 2: Showing a dot plot of CIS scores in cases.



The mean and standard deviation of ANC, ESR, CRP, MFI of CR1, MFI of CR3, TNCR index, and CIS for healthy subjects, cases with CIS <2, and cases with CIS ≥2 are presented in Table 1.

Table 1: Showing the Mean (SD) of variables in healthy subjects, cases with CIS ≥ 2 and CIS<2.

Variables	Healthy Subjects (n=12)	Cases with CIS ≥ 2 (n=10)	Cases with CIS<2 (n=20)	pvalue (One Way ANOVA)
ANC	4.6 (1.2)	4.7 (2.1)	3.6 (1.8)	0.17
ESR (mm/h)	5.7 (2.9)	32 (19.6)**	14.7 (9.5)#	<0.001
CRP (mg/L)	8 (6)	22.1 (32.1)	8.9 (8.4)	0.09
Neutrophil CR1	5.4 (1.4)	8.3 (2.6)*	5.7 (1.6)#	<0.01
Neutrophil CR3	53.7 (22.6)	86.9 (25.5)*#	62.1 (36.4)#	0.04
TNCR Index	3.1 (0.3)#	3.4 (0.5)^	2.9 (0.5)	<0.05
CIS	0.33 (0.7)#	2.5 (0.7)**	0.3 (0.5)	<0.001

*# p>0.05; ^p<0.05; *p<0.01; **p<0.001.*

When tested using One-Way ANOVA, ANC and CRP values were found to be comparable between the healthy controls, cases with CIS<2 and cases with CIS≥2 . While ESR, MFI of CR1 and CR3, TNCR index and CIS were observed to be statistically significantly different between the groups. However, the values of ESR, MFI of CR1, TNCR index and CIS were found to be significantly higher in patients with CIS≥ 2 when compared to patients with CIS<2 and healthy subjects. While MFI of CR3 was higher in patients with CIS≥ 2 than in patients with CIS<2, it was not statistically significant. In addition, it was observed that there was no significant difference in MFI of CR1, MFI of CR3, TNCR index and CIS between healthy subjects and patients with CIS<2. (Table 1)

Discussion

This exploratory study demonstrated the operational feasibility and acceptability of CIS estimation in a tertiary healthcare setting. CR1 and CR3 expression on granulocytes could be successfully measured by flow cytometry, CIS could be calculated within a clinically relevant turnaround time and in addition the findings provided preliminary evidence of clinical utility.

As the CIS is based on a blood sample, patient acceptability appeared favorable as only two patients declined consent. However, the requirement for transport at 2–4 °C and within 45–60 minutes of sample collection may limit operational flexibility and could present logistical challenges particularly when samples are analyzed at an external facility.

In this study, the MFI of CR1 was observed to be significantly higher in patients with CIS ≥ 2 than in patients with CIS< 2 and MFI of CR3 was found high in patients with CIS≥ 2 when compared to patients with CIS<2 though not statistically significant. (Table 1) These results agree with Lilius EM and Nuutila study, in which they reported that in neutrophils, CR1, and CR3 were upregulated in bacterial infections while CR1 was downregulated and CR3 was upregulated in viral infections [8]. A review by Kapasi et al. reported that among cell-surface biomarkers for differentiating bacterial from viral infections, CD64 (cutoff 1.64; up to 95.2% specificity) and CD35 (cutoff ≥1.5; up to 77% specificity) were the most reliable. The review also noted that combining markers improved diagnostic performance, including CD34/CD64; CD35+CD55 and CD35+CD32+CD88+MHC [7].

However, Nuutila reported that FcγRI (CD64) expression on neutrophils and monocytes increased significantly in both viral and bacterial febrile infections compared with healthy controls. Its sensitivity (73% and 52%) and specificity (65% and 52%) for distinguishing bacterial from viral infections were low, leading to the conclusion that CD64 is better suited as a marker of febrile infection rather than for differentiating infection aetiology [8]. This contrasts with findings reported by Kapasi et al [7].

A study from China by Lu et al. evaluated CD35 and CD64 expression on neutrophils, monocytes, and lymphocytes using flow cytometry to differentiate bacterial and viral infections in children. The NCD35/NCD64 ratio showed 90.0% sensitivity and 93.7% specificity for diagnosing viral infection at a cutoff <7.256. Individually, CD64 and CD35 had lower sensitivity and specificity than the ratio [9].

The CR1 and CR3 could be estimated in 1- 1.5 h after receiving samples and CIS can be provided to physicians within 1.75–2.25 hours of sample collection. Additionally, since samples must reach the laboratory within 1 hour, results can still be delivered within 2.25 hours even if testing is performed at an external facility.

In healthy subjects, the CIS was 0 in 9 of 12 participants, 1 in two participants, and 2 in one participant (Figure 1), consistent with values reported by Lilius E. M. et al., [8].

In the present study, the observed CIS ranged from 0 to 4, whereas Lilius EM and Nuutila reported a wider CIS range of 0 to 8 [8]. This difference may be attributed to variations in the severity of infections among the study populations. In the

current study, patients were recruited from outpatient services and general wards, with no patients from intensive care units. In contrast, in the study by Lilius EM et al., 36 out of 46 patients had severe infections such as sepsis or pyelonephritis [8].

Probably due to the inclusion of predominantly mild-to-moderate infections in the present study, the microbiological burden may have been low, resulting in a higher proportion of sterile cultures. However, it is in such patients with mild-to-moderate infections that empirical antimicrobial therapy is most commonly prescribed as culture confirmation is rarely possible, thereby further highlighting the clinical relevance and importance of such tests. Even in Lilius EM and Nuutila study, only in 84/492 (17%) of patients, infection could be confirmed microbiologically [8].

CIS ≥2 in 10 of 30 cases, suggest a likely bacterial infection (Figure 2) and CIS <2 in rest of the 20 cases suggest low likelihood of bacterial infection [8], as per the cutoff points proposed in Lilius EM and Nuutila study. However, these assumptions remain presumptive and require confirmation through appropriately designed diagnostic validation studies.

In the study of Lilius et al., 60 healthy controls and 292 hospitalized febrile patients were enrolled, of whom 46 were found to have microbiologically confirmed bacterial and 38 had microbiologically confirmed viral infection. It was reported that, in these patients at a cutoff point of >2, CIS differentiated bacterial from viral infections with 98% sensitivity and 97% specificity [8]. Whereas, procalcitonin, the most widely used marker for diagnosis of bacterial infections was reported to have a sensitivity of 76% and specificity of 69% at the commonly used cut-off of 0.5 ng/mL in a systematic review and meta-analysis assessing the diagnostic accuracy of procalcitonin for bacteraemia. The highest specificity (78%) was reported in immunocompromised/neutropenic patients, while the lowest (55%) in localized infections. The authors concluded that procalcitonin has fair diagnostic accuracy for bacteraemia in hospitalized adults with suspected infection or sepsis [10].

In a retrospective study involving 431 febrile patients with solid tumours and suspected infection, procalcitonin was estimated and culture samples were obtained before initiation of empirical antimicrobial therapy. Among 431 blood cultures, 181 were positive while the remainder were sterile. At a procalcitonin cut-off of 0.5 ng/dL, only 55% had positive blood cultures. Even using a higher cut-off of 1.52 ng/dL, procalcitonin demonstrated an AUC of 0.7 for diagnosing Gram-negative bacterial infections, with sensitivity and specificity of 72.1% and 70.1%, respectively. However, for Gram-positive/fungal infections, procalcitonin showed a statistically non-significant low AUC of 0.5, with sensitivity and specificity of 49.8% and 50.2%, respectively [11].

A cross-sectional study from Pakistan comparing the diagnostic accuracy of procalcitonin, C-reactive protein (CRP), total leukocyte count (TLC), and lactate for sepsis diagnosis included 126 adults with suspected sepsis. Using blood culture as the reference standard, ROC analysis showed that procalcitonin at a cut-off of >0.5 ng/mL had an AUC of 0.781, whereas CRP (>10 mg/L), TLC (>10 × 10^9/L), and lactate (>2.2 mmol/L) had AUCs of 0.568, 0.617, and 0.545, respectively. The study also reported a negative predictive value of 80.8% for procalcitonin at a cut-off of 0.15 ng/mL, suggesting its potential utility in ruling out sepsis when levels are <0.15 ng/mL [12].

In a similar retrospective study from China evaluating the utility of procalcitonin for diagnosing bacterial infections in patients with chronic gouty arthritis, 66 patient records were analyzed. Among these, 21 patients had microbiologically confirmed infections, while 43 had sterile cultures. Procalcitonin at a cut-off of 0.5 ng/mL showed an AUC of 0.526, with sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of 22.2%, 61.5%, 0.577, and 1.265, respectively. The AUCs for ESR (>20 mm/h), CRP (>8 mg/L), WBC count (>10 × 10^9/L), and neutrophil ratio (>70%) were 0.53, 0.635, 0.577, and 0.712, respectively. The authors concluded that procalcitonin may not be a reliable marker for diagnosing bacterial infection in febrile patients with chronic gouty arthritis [13].

As the CIS cut-off value of >2 has been reported to demonstrate a sensitivity of 98% and specificity of 97% for differentiating bacterial from viral infections [8], along with a rapid turnaround time of approximately 2 hours, it appears to be a promising tool in the current clinical scenario, particularly when compared with other acute phase reactants for which lower sensitivity and specificity have been reported in the above-mentioned studies. However, since estimation of complement receptor expression on neutrophils is not routinely performed in clinical practice, the present study was undertaken to explore the feasibility and acceptability of CIS estimation prior to conducting a validation study.

Another advantage of the CIS is its cost-effectiveness compared with rapid pathogen identification tests such as the BioFire Film Array. A single BioFire test costs about $200 (~₹18,150), whereas the CIS costs ₹2,000–2,500 per test—an approximately 80% cost reduction—making it a more affordable option [14].

The strengths of the study are that this is the first study that explored the feasibility and acceptability of estimating CIS, a promising tool in the current clinical scenario. In this study, the range of CIS was assessed both in healthy participants and patients with suspected bacterial and viral infections.

However, the limitations of the study are that though the samples where appropriate were sent for culture susceptibility tests and viral serology/antigen tests for confirmation of aetiological agent, as most of the patients had mild-moderate infection, the tests were reported sterile/negative except in 2 cases. Therefore, in this study, inflammatory conditions/ fungal causes could not be ascertained which could have resulted in similar clinical picture in the patients.

Conclusion

To our knowledge, this is the first study that explored the feasibility and acceptability of estimating CIS. It showed that measuring CR1 and CR3 expression on granulocytes and calculating the CIS is feasible operationally in healthcare settings. The CIS range in healthy controls and patients with suspected infection was consistent with findings reported by Nuutila. However randomized controlled studies are needed for validation of CIS as rapid diagnostic test and for assessment of its impact on reducing empirical antimicrobial therapy.

Conflict of interest

All the authors declare that they have no conflict of interest. The study is done only for academic interest.

Ethics Committee Approval

The study was initiated only after obtaining Institutional Ethics Committee Approval and participants both healthy subjects and patients were recruited into the study only after obtaining written informed consent.

Declaration

The corresponding author declares that all authors on this publication have met all of the following criteria of authorship.
All the authors have
(a) significant contributed to the concept and design/ data acquisition/ analysis and interpretation of data
(b) drafted or revised the article for scientific content
(c) approved the manuscript content
(d) agreed to be accountable for all aspects of the study and manuscript preparation.
Nobody who qualifies for authorship has been omitted from the list.

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Data Availability Statements

The data shall be shared upon request to corresponding author

Supplemental material

None.

Equipment used in study

Beckman Coulter Navios 3-laser, 10-color flow cytometer.

Supplier of reagents

IMMUNOTECH SAS a Beckman coulter company 13276 Marseille Cedex 9 France is the supplier for the three key reagents used in study, CD35 FITC, CD11b PE and CD45 Krome Orange.

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