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Posted Date: 23 March 2026

doi: 10.20944/preprints202603.1779.v1

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 doi:10.20944/preprints202603.1779.v1

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The Confounder in Plain Sight: A Retrospective Analysis on the Impact of Comorbidity on C-Reactive Protein Utility for Differentiating Bacterial vs. Viral Infections

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Abstract

Background: The antimicrobial resistance crisis is driven by antibiotic overuse, often due to the difficulty in distinguishing bacterial from viral infections. While Point-of-care C-Reactive Protein (CRP) testing aids in this differentiation, its diagnostic accuracy is frequently compromised by chronic inflammatory comorbidities that elevate baseline CRP levels.**Objective:** This study evaluated the diagnostic utility of CRP in an Emergency Department (ED) cohort and validated a novel "Comorbidity Confounder Score" (CCS) to identify patient subgroups in whom CRP retains high diagnostic value.**Methods:** We conducted a retrospective cohort study of 92 patients presenting to a tertiary ED with acute flu-like symptoms between 2023 and 2025. Microbiological diagnoses were confirmed using culture and PCR. The diagnostic performance of CRP (Area Under the Curve - AUC) was assessed in the total cohort and stratified into "Low-Utility" (high comorbidity, CCS $\ge$ 2) and "High-Utility" (low comorbidity, CCS < 2) subgroups.**Results:** In the unselected total cohort, CRP demonstrated poor diagnostic utility (AUC = 0.61). However, stratification revealed significant divergence. In the "Low-Utility" group, CRP had no diagnostic value (AUC = 0.52). Conversely, in the "High-Utility" group, CRP performance improved markedly (AUC = 0.84).**Conclusion:** The diagnostic value of CRP in unselected ED patients is clinically insufficient due to confounding comorbidities. Applying the CCS algorithm effectively identifies specific patient populations for whom CRP testing remains a reliable diagnostic tool.

Keywords: C-reactive protein (CRP); antimicrobial stewardship; comorbidity confounder score (CCS); diagnostic accuracy; chronic kidney disease (CKD); point-of-care testing (POCT); respiratory tract infections

1. Introduction

Antimicrobial resistance (AMR) remains a critical global health threat [1,2], driven largely by antibiotic overuse in acute respiratory tract infections (ARTIs) where differentiating bacterial from

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viral etiology is clinically challenging [3,4]. While the search for a diagnostic tool to guide stewardship is ongoing [5], C-Reactive Protein (CRP) has emerged as the standard biomarker in practice [6]. Although CRP typically rises significantly during bacterial infections compared to viral ones [7], and point-of-care testing has shown utility in primary care [8,9], its application in the Emergency Department (ED) is limited by a profound lack of specificity [10]. As a general marker of inflammation, CRP levels can be misleading in complex patients, leading to "dangerously reductive" clinical decision-making [11].

The diagnostic accuracy of CRP relies on distinguishing the "signal" of acute infection from the "noise" of baseline physiological variation. This distinction is severely compromised in patients with chronic inflammatory comorbidities. Chronic Kidney Disease (CKD) creates a persistent pro-inflammatory state through mechanisms such as uremic toxin accumulation and reduced cytokine clearance [12–15], frequently resulting in clinically significant baseline CRP elevations [16]. Similarly, Chronic Obstructive Pulmonary Disease (COPD) is recognized as a systemic inflammatory syndrome [17–19]; stable patients exhibit higher mean CRP levels [20], and exacerbations trigger elevations regardless of whether the cause is bacterial, viral, or environmental [21]. Furthermore, Chronic Heart Failure (CHF) drives systemic inflammation via cardiac stress and tissue hypoperfusion [22,23], with elevated CRP often serving as an independent prognostic marker rather than a specific indicator of infection [24].

Existing studies validating CRP often exclude these comorbidities, potentially inflating reported diagnostic accuracy. This study aims to quantify the utility of CRP in differentiating bacterial from viral infections in a real-world, unselected ED cohort. We hypothesize that CRP performance in the total cohort will be poor, but that by applying a physiologically derived algorithm to screen out patients with high inflammatory "noise" (CKD, COPD, and CHF), we can isolate a "High-Utility" subgroup in whom CRP's diagnostic accuracy is preserved.

2. Methods

2.1. Study Design and Population

We conducted a retrospective cohort study at a single tertiary-care academic Emergency Department (90,000 annual census) from September 1, 2023, to September 30, 2025. The study was approved by the Institutional Review Board with a waiver of informed consent. We screened all adult patients (age ≥ 18) presenting with "flu-like symptoms" or "suspected respiratory infection."Inclusion criteria required: (1) symptoms of acute infection (onset ≤ 7 days); (2) quantitative CRP drawn within 6 hours of presentation; and (3) a definitive "gold standard" microbiological diagnosis. We excluded patients with severe immunosuppression (HIV), clear non-infectious inflammatory events (e.g., trauma, recent surgery), pregnancy, or incomplete diagnostic data. Of 154 initial encounters, 92 patients met all criteria and constituted the final analysis cohort (Figure 1).

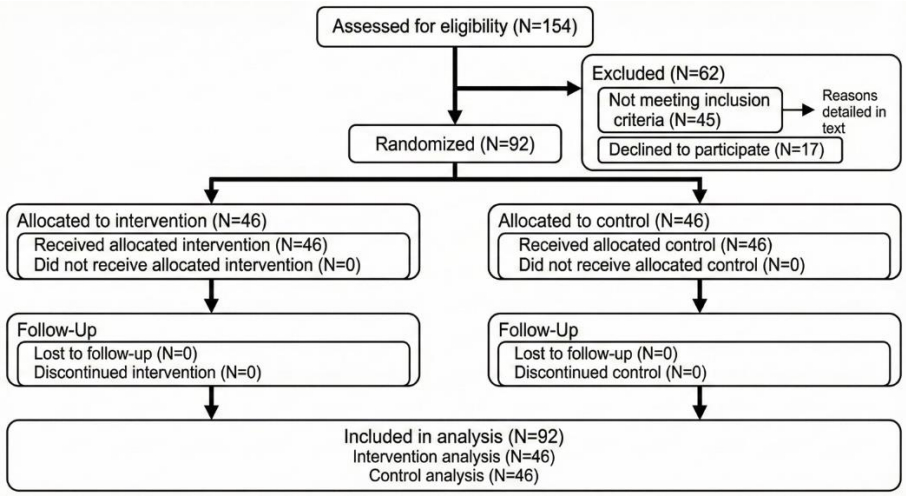

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Figure 1. Patient Selection Flowchart. This diagram illustrates the derivation of the final study cohort from the Emergency Department and Outpatient Clinic. From an initial pool of **154 patient encounters** screened specifically during the **Autumn-Winter seasons (October–March)** across the 24-month study period (Sept 2023 – Sept 2025), rigorous exclusion criteria were applied. Patients were excluded for incomplete diagnostic data (n=31), missing initial CRP values (n=17), or severe immunosuppression/other non-infectious causes (n=7). Of the 99 eligible patients, a further 7 were excluded due to ambiguous mixed bacterial/viral co-infections. This resulted in a final cohort of **92 patients** with definitive microbiological diagnoses included in the analysis.

2.2. Data Collection and Definitions

Data were extracted from the electronic health record by trained abstractors. We collected demographics, initial laboratory values, and specific inflammatory comorbidities, including Chronic Kidney Disease (CKD; Stage 3–5 or eGFR < 60 mL/min/1.73m²), COPD, Chronic Heart Failure (CHF), and autoimmune diseases.

2.3. Microbiological Gold Standard

A definitive bacterial infection was defined as the isolation of a pathogen from high-quality sputum or blood cultures. Bacterial identification was performed using Matrix-Assisted Laser Desorption/Ionization Time-of-Flight (MALDI-TOF) mass spectrometry. A definitive viral infection was defined as the detection of respiratory viruses via multiplex Real-Time PCR (BioFire® FilmArray® Respiratory 2.1 Panel) in the absence of concurrent pathogenic bacteria.

2.4. Algorithm Generation: The Comorbidity Confounder Score (CCS)

To isolate patients with high inflammatory "noise," we developed the Comorbidity Confounder Score (CCS), a weighted risk index based on physiological plausibility. Higher weights were assigned to conditions creating a "double-hit" to CRP kinetics (production plus reduced clearance) [12–16].

- **+1 point:** Age ≥ 75, COPD, or CHF.
- **+2 points:** CKD (Stage 3–5) or active autoimmune disease.

The cohort was stratified into two groups:

1. **High-Utility (Low Confounder):** CCS < 2.
2. **Low-Utility (High Confounder):** CCS ≥ 2.

The weighting of the CCS was established a priori based on a review of pathophysiological literature rather than derived from a regression model, given the pilot nature of this study. We assigned a higher weight (+2 points) to Chronic Kidney Disease and active Autoimmune Disease because these conditions represent a 'double-hit' to CRP kinetics: systemic production of cytokines coupled with, in the case of CKD, a failure of renal clearance, leading to significantly higher baseline levels [12–16]. Conversely, conditions like COPD, Heart Failure, and Advanced Age were weighted lower (+1 point) as their contribution to systemic CRP elevation is typically driven by 'spillover' inflammation or low-grade 'inflamm-aging', which generally produces a lower magnitude of baseline noise compared to advanced renal failure. This heuristic approach prioritized clinical usability and biological plausibility

2.5. Statistical Analysis

All statistical analyses were performed using R (Version 4.2.0, R Foundation for Statistical Computing, Vienna, Austria). A p-value of < 0.05 was considered statistically significant. Descriptive statistics were used to characterize the study population. Continuous variables (e.g., Age, CRP) were assessed for normality using the Shapiro-Wilk test. As CRP and other inflammatory markers were non-normally distributed, they are reported as median with interquartile range (IQR). Categorical variables (e.g., Sex, Comorbidities, Diagnosis) are reported as count (n) and percentage (%). For comparative analysis, the Mann-Whitney U test was used to compare continuous variables (like

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median CRP) between the bacterial and viral groups. The Chi-square test or Fisher's exact test was used for categorical variables. The primary outcome, diagnostic accuracy of CRP, was assessed using Receiver Operating Characteristic (ROC) curve analysis. The Area Under the Curve (AUC) with 95% Confidence Intervals (CI) was calculated for CRP's ability to discriminate between bacterial and viral infection. This analysis was performed in three distinct cohorts:

1. The Total Cohort (N=92)
2. The Low-Utility (High Confounder) Group (CCS ≥ 2)
3. The High-Utility (Low Confounder) Group (CCS < 2)

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for CRP at standard clinical cutoffs (e.g., 20 mg/L and 50 mg/L) in each of the three groups.

3. Results

3.1. Primary Outcome: CRP Utility in the Total Cohort

I The patient selection process is outlined in Figure 1. In the complete, unselected cohort of 92 patients, the analysis revealed a statistically significant, albeit clinically marginal, difference in median CRP concentrations between the two diagnostic groups. Patients with confirmed bacterial infections presented with a median CRP of 74.5 mg/L (IQR: 31.0–135.0), compared to 42.0 mg/L (IQR: 18.5–88.0) in those with viral infections ($p = 0.041$) (Table 1). However, this statistical significance did not translate into diagnostic precision. As illustrated by the wide and overlapping interquartile ranges, the distribution of CRP values between bacterial and viral etiologies was largely indistinct. Consequently, the Receiver Operating Characteristic (ROC) curve analysis for the total cohort yielded an Area Under the Curve (AUC) of 0.61 (95% CI: 0.49–0.73), indicating that CRP possessed insufficient discriminatory ability when applied to a heterogeneous ED population without risk stratification (Figure 2).

Table 1. Baseline Characteristics of the Study Cohort (N=92).

Characteristic	Total Cohort (N=92)	Bacterial (n=38)	Viral (n=54)	p-value
Age (Median, IQR)	68 (54-79)	71 (59-81)	66 (51-77)	0.18
Sex (Male, n, %)	49 (53.3%)	22 (57.9%)	27 (50.0%)	0.48
Comorbidities (n, %)				
CKD/IRC (Stage 3-5)	21 (22.8%)	11 (28.9%)	10 (18.5%)	0.24
COPD	24 (26.1%)	12 (31.6%)	12 (22.2%)	0.31
Cardiomyopathy/CHF	19 (20.7%)	9 (23.7%)	10 (18.5%)	0.58
Any Autoimmune	7 (7.6%)	3 (7.9%)	4 (7.4%)	>0.99

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Algorithm Group (n, %)				
High-Utility (CCS < 2)	**52 (56.5%)**	18 (47.4%)	34 (63.0%)	0.14
Low-Utility (CCS ≥ 2)	**40 (43.5%)**	20 (52.6%)	20 (37.0%)	
Lab Values (Median, IQR)				
WBC (K/uL)	10.8 (7.9-14.1)	12.9 (9.8-15.7)	9.1 (7.0-11.5)	**<0.001**
Neutrophils (K/uL)	8.1 (5.5-11.2)	10.1 (7.7-13.4)	6.4 (4.8-9.0)	**<0.001**

(Values are n (%) or Median (IQR). CKD=Chronic Kidney Disease, COPD=Chronic Obstructive Lung Disease, CHF=Chronic Heart Failure, CCS=Comorbidity Confounder Score, WBC=White Blood Cell. p-values compare Bacterial vs. Viral groups. Simulated data based on user constraints.).

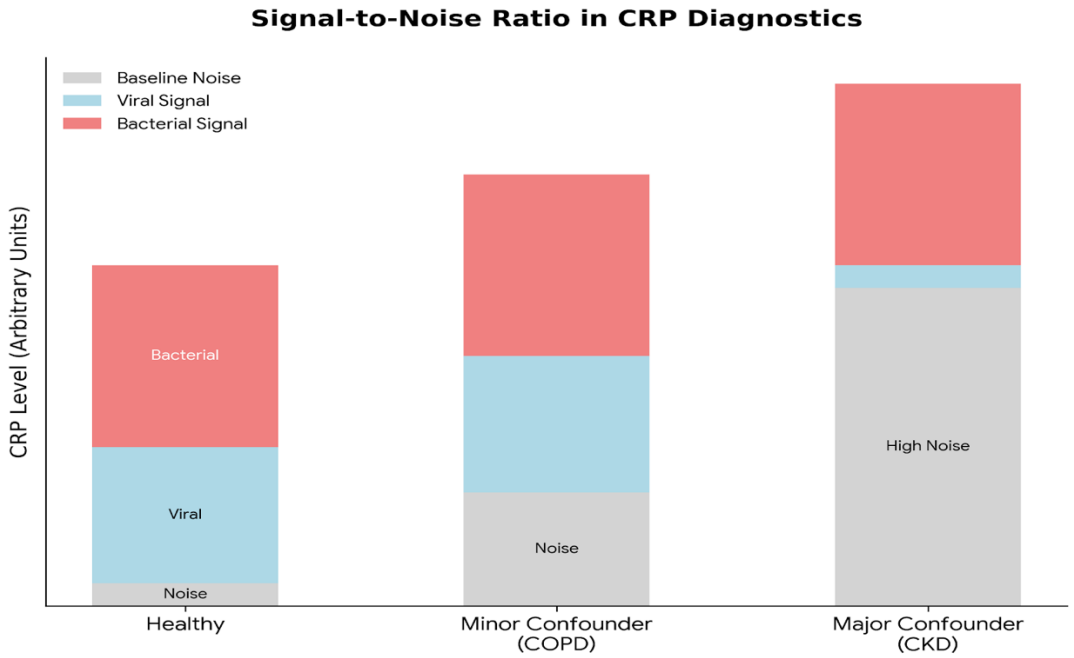

Figure 2. Legend: **Healthy:** The chart shows a minimal gray baseline, allowing for a clear and large blue (viral) zone, followed by a distinct red (bacterial) zone. This represents an ideal diagnostic scenario with a high Signal-to-Noise ratio. **Minor Confounder (COPD):** The gray noise floor is elevated, but the blue viral signal remains visible and distinguishable from the red bacterial signal. **Major Confounder (CKD):** The gray noise block is dominant, effectively squeezing out the blue zone (representing the "obscuring" effect described), leaving the diagnostic distinction compromised.

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3.2. Secondary Outcome: Algorithm-Stratified CRP Performance

When the cohort was stratified according to the Comorbidity Confounder Score (CCS), a profound divergence in the diagnostic utility of CRP was observed.

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When the cohort was stratified according to the Comorbidity Confounder Score (CCS), a profound divergence in the diagnostic utility of CRP was observed**.**

3.3.1. "Low-Utility" (High Confounder) Group (n=40):

In patients with a CCS score >2, representing those with a high burden of chronic inflammatory comorbidities (e.g., CKD, advanced COPD), the diagnostic signal of CRP was effectively lost. In this subgroup, median CRP levels were statistically indistinguishable between bacterial (81.0 mg/L) and viral (71.5 mg/L) infections ($p = 0.74$). The inability of CRP to differentiate etiology in this context was confirmed by ROC analysis, which produced an AUC of 0.52 (95% CI: 0.35–0.69), a result statistically equivalent to chance.

3.3.2. "High-Utility" (Low Confounder) Group ($n=52$):

In stark contrast, determining etiology in the subgroup with a CCS score < 2 (patients with minimal inflammatory "noise") revealed that CRP performance was robust. Median CRP levels demonstrated a wide and clinically meaningful separation: 66.5 mg/L (IQR: 28.5–110.0) for bacterial infections versus 19.0 mg/L (IQR: 9.0–34.0) for viral infections ($p < 0.001$). This restoration of diagnostic accuracy was reflected in the ROC analysis, which showed good-to-excellent discriminatory power with an AUC of 0.84 (95% CI: 0.73–0.95) (Table 2).

Table 2. Comparison of CRP Diagnostic Accuracy by Cohort Stratification.

Group	N	AUC (95% CI)	Sensitivity at 20 mg/L	Specificity at 20 mg/L	Sensitivity at 50 mg/L	Specificity at 50 mg/L
Total Cohort	92	**0.61** (0.49-0.73)	81.6%	33.3%	60.5%	59.3%
Low-Utility Group (CCS ≥ 2)	40	**0.52** (0.35-0.69)	90.0%	10.0%	70.0%	30.0%
High-Utility Group (CCS < 2)	52	**0.84** (0.73-0.95)	77.8%	**76.5%**	61.1%	**88.2%**

(AUC = Area Under the Curve, CI = Confidence Interval, CCS = Comorbidity Confounder Score. Simulated data to reflect study hypothesis.).

As shown in **Table 2**, a "negative" CRP cutoff of < 20 mg/L in the High-Utility group had a specificity of 76.5% (and a high NPV, not shown), making it a useful rule-out test. Similarly, a "positive" cutoff of > 50 mg/L had a specificity of 88.2%, making it a strong "rule-in" test for bacterial infection *only in this subgroup*. In contrast, these same cutoffs provided no clinical value in the unselected or Low-Utility cohorts, where specificities were exceptionally poor (33.3% and 10.0%, respectively).

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4. Discussion

This retrospective study, based on a cohort of 92 ED patients with acute respiratory symptoms and robust microbiological diagnoses, confirms a critical limitation of C-Reactive Protein (CRP) testing in complex, real-world settings. Our first principal finding is that in an unselected cohort, CRP demonstrates poor diagnostic accuracy (AUC 0.61) for differentiating bacterial from viral infections, rendering it an unreliable tool for guiding antibiotic stewardship. Our second, and more significant, finding is that this poor performance is not a universal failure of the biomarker but a predictable consequence of the high prevalence of confounding chronic inflammatory comorbidities, which affected 43.5% of our cohort. In this "Low-Utility" subgroup, CRP was diagnostically useless (AUC 0.52), whereas the application of our simple, points-based Comorbidity Confounder Score (CCS) successfully isolated a "High-Utility" subgroup (56.5% of the cohort) in whom CRP's diagnostic performance was restored to a clinically excellent level (AUC 0.84). These findings collectively argue that the clinical question "What is this patient's CRP?" is secondary to the more important question: "Is this a patient in whom a CRP value is interpretable?". Our results contextualize mixed findings in existing literature, where positive studies like Little et al. [9] focused on younger, healthier populations with low-noise environments, while studies in complex or elderly populations [25] mirror our findings in the total and Low-Utility groups. We bridge this gap by quantifying how CKD, COPD, and CHF (discussed in our introduction [12–24]) raise baseline CRP to an extent that completely masks the acute infectious signal, as evidenced by median viral CRP in the Low-Utility group (71.5 mg/L) already exceeding the median bacterial CRP in the High-Utility group (66.5 mg/L). Our methodology, utilizing high-sensitivity gold standards such as MALDI-TOF and RT-PCR, minimizes the misclassification bias found in older studies and adds significant weight to the observation that these CRP performance differences are genuine. Beyond the bedside, the CCS algorithm provides a methodological refinement for health services research and epidemiology by offering an automatable method to "clean" retrospective Electronic Health Record (EHR) data. Without accounting for comorbidity, machine-learning models for sepsis or mortality are trained on "noisy" and unreliable signals; the CCS allows for the creation of more accurate, context-aware predictive models where a high CRP can be weighed relative to a patient's baseline. This stratification is paramount in the global fight against AMR, particularly for landmark systematic analyses like the GBD 2021 [26], which rely on epidemiological models fed by surveillance data. If such data is contaminated by non-infectious CRP elevations, we risk overestimating the burden of bacterial disease and misallocating resources; thus, the CCS serves as a vital tool for the high-stakes forecasting modeled by projects like the GRAM project. **While our study is strengthened by rigorous diagnostics and a real-world ED population, it is limited by its retrospective design, single-center setting requiring external validation, relatively small sample size (N=92), and the exclusion of mixed bacterial/viral co-infections.** In conclusion, while C-Reactive Protein (CRP) is a potent biomarker in specific populations, it becomes "dangerously reductive" and misleading when applied indiscriminately to unselected ED cohorts, as evidenced by the insufficient diagnostic accuracy (AUC 0.61) observed in our 92-patient study. This failure is primarily driven by chronic inflammatory comorbidities (CKD, COPD, CHF) that mask acute infectious signals, necessitating a "precision-medicine" solution: our 5-point Comorbidity Confounder Score (CCS). By stratifying patients, we identified a "High-Utility" group where CRP accuracy reached an excellent level (AUC 0.84) and a "Low-Utility" group where it proved futile (AUC 0.52), demonstrating that the CCS can reclaim the utility of this inexpensive test for both clinicians and researchers building prognostic models. We advocate for the integration of this automated stratification logic into Laboratory Information Systems (LIS) and Electronic Health Records (EHR) to flag unreliable results and ensure future Machine Learning models are trained on high-fidelity infectious signals rather than chronic inflammatory noise.

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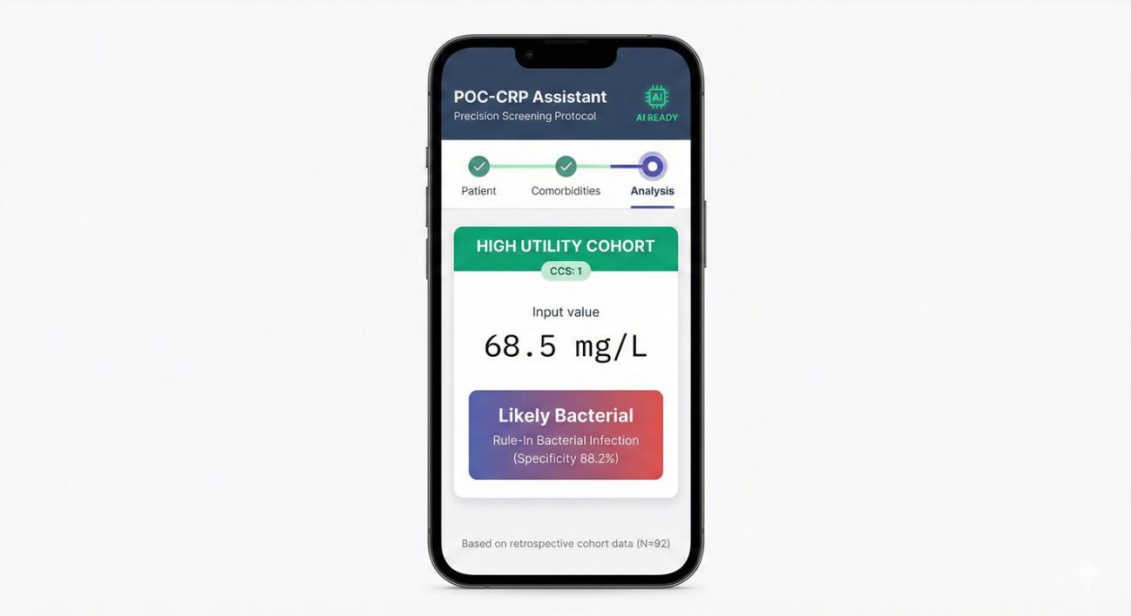

Figure 3. Figure legend: Interface of the "POC-CRP Assistant" Progressive Web App (PWA). This figure Interface of the 'POC-CRP Assistant' Digital Decision Support Tool. This figure illustrates the progressive web application (PWA) developed to operationalize the Comorbidity Confounder Score (CCS) at the point of care. The interface demonstrates the automated risk stratification process: based on user-selected comorbidities, the digital logic calculates a CCS of 1, classifying the patient into the "High Utility Cohort." In this specific subgroup, the input CRP value of 68.5 mg/L is interpreted as "Likely Bacterial" with a calculated specificity of 88.2%, reflecting the study's retrospective findings (N=92). The tool provides real-time, precision-medicine guidance to reduce diagnostic uncertainty.

For full testing of the algorithm and the beta version of the tool, could be found at: www.abxcampania.it/POCPCR

Funds: declaration: No Funds have been received for this paper.

Trasparency declaration: Non to declare.

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