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Microbial Biomarkers in Clinical Chemistry, Diagnostic and Prognostic Application: A Review

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Abstract

Background

These biomarkers assisted medical professionals in predicting clinical outcomes, guiding antibiotic stewardship, and differentiating between infectious and non-infectious inflammatory illnesses. However, the limitations of traditional biomarkers such as poor specificity, inter-patient variability, and overlap with non-infectious diseases led to the development of more sophisticated diagnostic instruments. Real-time PCR, multiplex pathogen detection panels, and next-generation sequencing NGS. are examples of significant advancements in molecular diagnostics that have expanded the biomarker spectrum beyond host derived analytes to include direct microbial fingerprints. Even in complex or culture-negative disorders, accurate organism identification was made possible by metagenomic sequencing, microbial cell free DNA, and pathogen-specific proteins. Precision medicine initiatives were encouraged, diagnostic accuracy was enhanced, and early detection was made possible when these molecular approaches were integrated with traditional clinical chemistry processes. Emerging multi-omics tools, such as proteomics, metabolomics, transcriptomics, and microbiome profiling, have enabled the discovery of novel biomarkers that captured dynamic host-pathogen interactions at previously un heard of resolution. In order to maximize patient survival and reduce unnecessary drug exposure, timely and correct diagnosis was essential. Infectious illnesses continued to be a major worldwide health burden. Because it provided an overview of current research on host response, biomarkers and pathogen, directed molecular technologies and demonstrated how their combination improved clinical decision making, antibiotic stewardship, and individualized patient care, The goal of this study. The goal of this study is to provide a thorough evaluation of both traditional biochemical biomarkers and advanced molecular diagnostic methods, highlighting their combined diagnostic and prognostic significance in infectious diseases. This review also aims to highlight current problems, clinical applications, and possible future directions to improve the accuracy of pathogen detection and patient treatment.

المؤشرات الحيوية الماكوبية في الكيمياء السريرية، التطبيقات التشخيصية والتنبؤية: مراجعة

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الخلاصة

المقدمة

ساعدت هذه المؤشرات الحيوية الأطباء في التنبؤ بالنتائج السريرية، وتوجيه الاستخدام الأمثل للمضادات الحيوية، والتمييز بين الأمراض الالتهابية المعدية وغير المعدية. مع ذلك، أدت محدودية المؤشرات الحيوية التقليدية، كضعف دقتها، واختلافها بين المرضى، وتداخلها مع الأمراض غير المعدية، إلى تطوير أدوات تشخيصية أكثر تطورًا. يُعد تفاعل البوليميراز المتسلسل في الوقت الحقيقي (PCR)، ولوحات الكشف عن مسببات الأمراض المتعددة، وتقنية التسلسل الجيني من الجيل التالي (NGS)، أمثلةً على التطورات الهامة في التشخيص الجزيئي التي وسّعت نطاق المؤشرات الحيوية ليشمل، بالإضافة إلى التحليلات المشتقة من المضيف، البصمات الميكروبية المباشرة. حتى في الحالات المعقدة أو التي لا تظهر نتائج إيجابية في الزرع، أصبح تحديد الكائن الحي بدقة ممكنًا بفضل التسلسل الميتاجينومي، والحمض النووي الخالي من الخلايا الميكروبية، والبروتينات الخاصة بمسببات الأمراض. شُجّعت مبادرات الطب الدقيق، وتحسّنت دقة التشخيص، وأصبح الكشف المبكر ممكنًا عند دمج هذه الأساليب الجزيئية مع عمليات الكيمياء السريرية التقليدية. أتاحت أدوات علم الجينوم المتعدد الناشئة، مثل علم البروتينات، وعلم الأيض، وعلم النسخ، وتحليل الميكرو بيوم، اكتشاف مؤشرات حيوية جديدة رصدت التفاعلات الديناميكية بين المضيف والممرض بدقة غير مسبوقة. لتحقيق أقصى قدر من فرص نجاة المرضى وتقليل التعرض غير الضروري للأدوية، كان التشخيص الصحيح وفي الوقت المناسب أمرًا بالغ الأهمية. ولا تزال الأمراض المعدية تشكل عبئًا صحيًا عالميًا كبيرًا. ولأن هذه المراجعة قدمت نظرة عامة على الأبحاث الحالية حول استجابة المضيف، والمؤشرات الحيوية، والتقنيات الجزيئية الموجهة للممرض، وأوضحت كيف ساهم دمجها في تحسين عملية اتخاذ القرارات السريرية، والاستخدام الرشيد للمضادات الحيوية، والرعاية الصحية الفردية للمرضى، فقد كان هدف هذه الدراسة تهدف هذه المراجعة إلى تقديم تقييم شامل لكل من المؤشرات الحيوية الكيميائية الحيوية التقليدية وأساليب التشخيص الجزيئي المتقدمة، مع تسليط الضوء على أهميتها التشخيصية والتنبؤية المشتركة في الأمراض المعدية. كما تهدف هذه المراجعة إلى إبراز المشكلات الحالية، والتطبيقات السريرية، والاتجاهات المستقبلية الممكنة لتحسين دقة.

1.Introduction

Clinical chemistry labs provided rapid and quantitative biomarkers that reflected host responses to microbial invasion. These tests were crucial for emergency medicine, critical care, and antimicrobial stewardship, because they were scalable and readily accessible. However, effective interpretation required understanding the kinetics, specificity, and other noninfectious confounders of each biomarker. Patient outcomes and diagnostic accuracy were enhanced when direct pathogen detection and host biomarkers were combined (Norman-Bruce et al., 2024).

Recent developments in molecular immunology have shown that patients' inflammatory responses differed greatly based on their age, comorbidities, and genetic background. This highlighted the need to increase accuracy by using a multi-marker diagnostic method. Additionally, because of their speed, mobility, and suitability for point-of-care applications, the integration of traditional biochemical assays with contemporary biosensing technologies gained significant clinical interest(Woodhouse et al., 2024). Procalcitonin and CRP are two traditional acute-phase biomarkers. CRP is a broadly responsive acute-phase reactant that the liver produces in response to IL-6; it increases quickly with inflammation but is not specific to infection. Procalcitonin (PCT) has been approved as a tool to direct the start and stop of antibiotics in sepsis and lower respiratory infections, and it has a higher specificity for systemic bacterial infections. Although efficacy varies by clinical setting (e.g., COVID-19, immunocompromised patients), numerous systematic reviews and trials show PCT-guided algorithms can reduce antibiotic exposure without affecting results in specific populations (Reinhart et al., 2012). According to recent research, in emergency and critical-care settings, PCT-guided clinical algorithms can cut the length of antibiotic therapy by 30–45%. Furthermore, research has demonstrated that kinetic modeling of CRP and PCT during the first 48–72 hours has greater diagnostic value than single measures because dynamic changes more accurately represent the host inflammatory response and the course of treatment (Mantovani & Garlanda, 2023). Lactate, ferritin, and other biochemical markers Ferritin, an iron-storing protein, has been utilized as a severity indicator in viral syndromes (such COVID-19) and macrophage activation syndromes. It also rises during numerous infections and inflammatory conditions. Elevated serum lactate correlates with mortality and directs resuscitation; it is still a key prognostic indicator in sepsis, reflecting tissue hypoperfusion and metabolic stress. Integration with other laboratory data and the clinical context is necessary for the interpretation of these markers (Yameny, 2021). Hyperferritinemia, or extremely high ferritin, has been linked to hyper-inflammatory diseases, such as cytokine storm syndromes, and may be a precursor to consequences such acute respiratory distress syndrome (ARDS). However, because of its high association with early mortality and its function in assessing tissue hypoperfusion and directing resuscitation methods, serum lactate continues to be a key component of the Surviving Sepsis Campaign (Chrostek et al., 2024). Differentiating between bacterial and viral infections: In order to direct treatment, clinicians frequently need to distinguish between bacterial and viral etiologies. as biomarkers (such low PCT and moderate CRP) are combined, discrimination is improved as compared to individual tests. However, no one biomarker is completely specific; concentrations can change according to age, comorbidities, localized infections, and recent surgery. In pooled diagnostic accuracy investigations, multi-marker panels and algorithmic techniques perform better than single analytes (Mayne et al., 2023). More than 90% accuracy in distinguishing between bacterial and viral illnesses has been shown by composite biomarker profiles, such as those that combine transcriptomic immunological markers with PCT/CRP. Diagnostic accuracy has been further enhanced by the use of machine-learning algorithms in biomarker interpretation, particularly in pediatric and emergency-care populations with fever

(Jackson et al., 2023).Biomarkers for prognosis and severity stratification: Serial measures of CRP, PCT, and lactate provide prognostic information in illnesses like sepsis; rising or consistently elevated values predict worse outcomes, but lowering levels frequently suggest therapeutic response. In the emergency room and intensive care unit, biomarker trajectories combined with scoring systems (SOFA, qSOFA) can improve risk categorization and triage choices. Biomarker-guided care packages have also been studied in randomized trials, with varying effects based on adherence and setting (Karakikeetal.,2019). When PCT, CRP, and delta-SOFA (the change in SOFA score over time) are combined, mortality prediction is much better than when standard scoring is used alone. Furthermore, when evaluated in conjunction with lactate levels, inflammatory cytokines like IL-6 and IL-10 offer a multifaceted prognostic framework that improves early risk classification in sepsis (Zhou et al., 2024). Molecular and pathogen-specific biomarkers: nucleic acid testing and mNGS PCR panels and metagenomic next-generation sequencing (mNGS) are molecular techniques that directly detect microbial nucleic acids and identify pathogens that are slow or difficult to cultivate. Clinical mNGS can significantly change diagnosis and treatment in difficult patients and provides comprehensive, hypothesis-free pathogen detection from sterile fluids and tissue. Cost, turnaround time, bioinformatic interpretation, contamination risk, and varying sensitivity based on sample type and pathogen burden are some of the difficulties with mNGS. Clinical significance is increased when mNGS data are integrated with host biochemical markers (Willmann & Moita, 2024). Metagenomic next-generation sequencing (mNGS) has revolutionized the diagnostic process in situations of unusual or inexplicable diseases by enabling the objective detection of hundreds of pathogens in a single test. A useful addition to infection monitoring is quantitative microbial cell-free DNA (cfDNA) analysis, which has also shown promise in evaluating microbial load and forecasting treatment response(Zhao et al., 2025). Indirect pathogen signals and microbial metabolites Microbial metabolites, such as endotoxin levels, specific short-chain fatty acids, and pathogen-associated molecular patterns, are being investigated as diagnostic or prognostic biomarkers in addition to host acute-phase proteins. Many metabolite assays are attractive in research, but they lack clinical validation and standardization. However, they could be useful when paired with molecular pathogen detection and recognized clinical chemistry indicators (Moniz et al., 2021).The potential of novel biomarkers including lipopolysaccharide (LPS), β-glucan, and pathogen-associated microRNAs to detect bacterial and fungal sepsis early is drawing interest. Many are still in the research stage, but when combined with proven clinical chemistry indicators and molecular testing, they provide additional diagnostic value (Cui et al., 2025). Applications in clinical pathways and antimicrobial stewardship: Biomarker-guided antibiotic stewardship limits needless antibiotic exposure and encourages early de-escalation using PCT and integrated biomarker algorithms. There is evidence that following PCT-based procedures reduces antibiotic days in a number of settings; nonetheless, successful implementation necessitates local pathways, clinician education, and consideration of populations where PCT performs less well. A potent stewardship toolset is produced by combining host biomarkers with quick pathogen identification (molecular assays)(Gu et al., 2019).PCT guided stewardship practices can lower antimicrobial resistance at the institutional level by up to 15% over a three-year period, mainly by reducing needless antibiotic exposure, according to meta-analyses. Additionally, it has been demonstrated that biomarker-based strategies optimize ICU admissions and reduce hospital stays, which improves resource use(Schuetz et al., 2019). Practical considerations, confounders, and limitations The impact of comorbidities (renal failure, immunosuppression), assay variability, false-positive elevations in

noninfectious inflammation (trauma, autoimmune illness), and false-negative results in early or localized infections are significant limits. In various health systems, test selection is influenced by factors such as cost, availability, and turnaround time. To minimize false discoveries and guarantee clinical actionability for mNGS, strict laboratory processes and bioinformatics pipelines are crucial (Selvarajan et al., 2021). Inter-laboratory test variability, the absence of global standards for inflammatory biomarkers, and the possibility of false increases due to autoimmune disorders, trauma, or cancer are some of the current issues. One of the main challenges for mNGS is differentiating between colonization or contamination and actual illness, which highlights the necessity of stringent analytical procedures and clinical correlation(Elbehiry & Abalkhail, 2025). Future directions: (1) multimarket panels that combine pathogen detection with host response signatures; (2) standardization and prospective validation of metabolite biomarkers; (3) clinical trials testing integrated diagnostic–therapeutic pathways; and (4) scalable mNGS bioinformatics and reporting frameworks that provide actionable results within clinically useful turnaround times should be the top priorities for future research. More accurate, quick, and customized infection diagnosis and treatment are promised by this integration (Norman-Bruce et al., 2024).

1.2 Electrical Biosensors for PCT Detection

In order to detect PCT and immobilize antibodies, Shesadri et al. created an electrolyte-gated organic field-effect transistor (EGOFET) using poly-3-hexylthiophene as the transducing channel material Fig.1. It was the first electronic-based EGOFET biosensor created for PCT detection, with a LOD as low as 2.2 pM and a fabrication time of about 45 minutes. Clinical importance for sepsis diagnosis was demonstrated by the detection range (Seshadri et al., 2018).

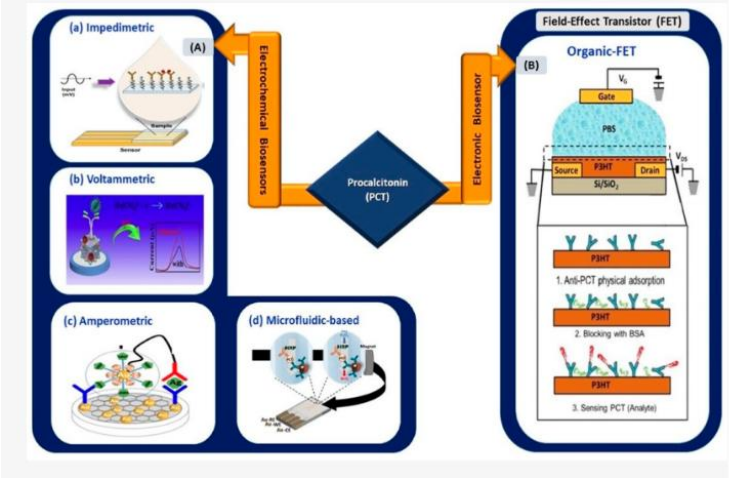

Figure1: (**A**) Electrochemical biosensors: (**a**) impedimetric sensing of PCT using gold-interdigitated electrodes, (**b**) nano cube-based voltametric sensor, (**c**) nanocomposite-based amperometry PCT sensor and (**d**) magneto immunoassay-based microfluidic PCT sensor (**B**) Organic FET-based electronic biosensor for the detection of PCT (reprinted with permission from (Selvarajan et al., 2021).

Even with the widespread availability of traditional biochemical indicators like ferritin, lactate, procalcitonin (PCT), and C-reactive protein (CRP), differentiating between infectious and non-infectious inflammatory diseases is still a significant clinical problem. Many of these biomarkers have poor specificity, function differently in different patient populations, and overlap with autoimmune and postoperative disorders. Although pathogen detection has improved with the advent of modern molecular diagnostics, such as PCR panels, microbial cell-free DNA testing, and metagenomic next-generation sequencing (mNGS), their routine use is still limited by problems with cost, turnaround time, and interpretation. In order to improve patient outcomes, guide antimicrobial stewardship, and increase diagnostic accuracy, it is imperative to assess and use both host-response biomarkers and pathogen-direct molecular techniques (Evans et al., 2024). The current understanding of microbial biomarkers used in clinical chemistry is summarized in this article using a narrative review method (Lehnert & Gijs, 2024).

1.3. Studies That Satisfied the Following Requirements Were Included

2. The reported diagnostic or prognostic efficacy of molecular pathogen-direct biomarkers or traditional biochemical biomarkers.
3. Consisted of experimental, clinical, or meta-analytic data.
4. Offered quantitative or qualitative information pertinent to the diagnosis of infectious diseases. Included were review articles, clinical trials, systematic reviews, and studies with a technical focus. Excluded were studies unrelated to infectious illness biomarkers, non-English literature, and duplicate data. In order to assess diagnostic performance, draw attention to limits, and determine future research directions, the extracted findings were combined (Hu et al., 2017).

1.4. Criteria for Inclusion

Research assessing the predictive or diagnostic efficacy of host-response or microbial biomarkers. experimental research, systematic reviews, meta-analyses, and clinical trials. Articles that present quantitative or qualitative information pertinent to the diagnosis of infectious diseases.

1.5. Criteria for Exclusion

Studies in languages other than English Studies on non-infectious biomarkers. Duplicate information Case studies lacking analytical value

1.6. Integrating Host Biomarkers and Molecular Diagnostics for Improved Infection and Cancer-Related Clinical Decision-Making

One of the most important things to consider is the contextual performance of classical biomarkers. CRP, for instance, is a good indicator of inflammation but lacks pathogen specificity and often rises in autoimmune, malignant, and postoperative conditions. Increased levels can also result after trauma, surgery, and certain forms of cancer, even though PCT is more specific for bacterial infections. These limitations made it evident that clinical chemistry data must be linked with clinical assessment, imaging modalities, and microbiological evidence rather than relying only on one biomarker (Yang et al., 2025). The field underwent a radical transformation as a result of developments in molecular diagnostics, which enabled pathogen, specific identification. However, there were certain drawbacks to molecular diagnostics, including high cost, limited availability, contamination risk, and challenges distinguishing between colonization and active infection. Large datasets generated by mNGS systems also required highly qualified personnel and advanced bioinformatics knowledge, raising concerns regarding uniformity and practicality in

conventional clinical laboratory settings (Gu et al., 2019). Microbial biomarkers evaluated in clinical chemistry labs remain crucial for prompt diagnosis and prognosis. The best diagnostic and prognostic outcomes were obtained by combining host biomarkers (CRP- PCT- ferritin-lactate) with contemporary molecular pathogen-detection techniques (PCR- mNGS). To translate biomarker results into improved clinical outcomes, careful interpretation, understanding of inherent limitations, and structured clinical decision-maker processes were required(Woodhouse et al., 2024). We address both prognostic and predictive microbial associate indicators founded in colorectal cancer in this review, Microflora associated diagnostic, preventative and predictive strategies for colorectal cancer was supported by the dynamic relationship between the faucal associated microbiota and colon cancer. To enhanced the diagnostic and treatment management of colorectal cancer, it is evident that more clinical research is required to validate these parameters, as summarized in Table1, Table2 and Table3.

Table1: Comparison CRP vs PCT

	CRP	**PCT**
Full Name	**C-Reactive Protein**	**Procalcitonin**
Site of Production	Produced by the liver in response to general inflammation	Produced by body cells mainly in response to bacterial infection
When It Rises	Rises in any inflammation (bacterial, viral, immune, rheumatologic)	Rises mainly in bacterial infections
Begins rising in	6–8 hours; peaks in 48 hours	in 2–4 hours; peaks in 12–24 hours
Normal Values	< 10 mg/L	< 0.05 ng/mL
Levels Become Very High	Severe inflammation, shock, autoimmune diseases	Sepsis and severe bacterial infections
Clinical Uses	Assess inflammation severity; monitor treatment response	Diagnose sepsis; guide antibiotic decisions
Effect of Non-Infectious Conditions	Strongly affected by non-infectious factors (e.g., obesity, chronic inflammation)	Less affected; more specific to bacterial infection
Cost	Low	High

Table2: Comparison of Typical Biochemical Biomarkers

Biomarker	**Specificity**	**Sensitivity**	**Typical Uses**	**Limitations**
CRP	Low	High	General inflammation, pneumonia	Elevated in autoimmune & postoperative cases
PCT	Moderate–High	High	Bacterial infection, sepsis	Expensive; affected by trauma, surgery
Ferritin	Low	Moderate	Viral infections, hyperinflammation	Very non-specific
Lactate	High (prognosis)	Moderate	Sepsis severity & mortality	Reflects hypoperfusion, not cause

Table3: Molecular Diagnostic Platform Comparison

Method	**Turnaround Time**	**Cost**	**Advantages**	**Limitations**
PCR panels	1–4 hours	Moderate	High sensitivity; rapid	Limited pathogen spectrum
Mngs	24–72 hours	High	Broad detection; culture-independent	Expensive; contamination risk
Microbial cfDNA	6–24 hours	High	Detects low burden infections	Emerging technology; not standard

1.7. Obstacles and Restrictions

Despite the notable advancements in molecular and biomarker-based diagnostic techniques, certain obstacles still exist, Conventional biomarkers, particularly ferritin and CRP, have low specificity. False-positive increases brought on by trauma, cancer, and autoimmune diseases. The requirement for microbial marker-based diagnostic methods is made extremely difficult by the complexity of the microbiome. There is currently no universal microbial marker specified for CRC detection, despite numerous research reporting links between microbial markers, such as F. nucleate or colibactin-producing E. coli, and CRC. Future test development should take into account a number of restrictions. First, it is nearly hard to find a universal microbial marker due to the extremely high heterogeneity of the microbiota composition between individuals related to sex, age, nutrition, lifestyle, genetic background, medication use, ethnicity, or geographic location. The use of microbial markers is severely restricted by antibiotic therapy, which also significantly affects the expression of microbial markers(Villéger et al., 2018).

2. Conclusion

Clinical chemistry biomarkers remain indispensable tools for the rapid assessment, prognosis, and management of infectious and inflammation-related diseases. Traditional host-response markers such as CRP, procalcitonin, ferritin, and lactate provide valuable insights into inflammatory burden, disease severity, and therapeutic response; however, their diagnostic specificity is limited by biological variability, comorbid conditions, and overlap between infectious and non-infectious inflammation. Evidence consistently demonstrates that reliance on single biomarkers is insufficient for accurate etiological discrimination or risk stratification. The integration of host biomarkers with molecular pathogen-direct diagnostics—including PCR-based panels, microbial cell-free DNA assays, and metagenomic next-generation sequencing—represents a significant advancement in precision diagnostics. Combined diagnostic approaches improve pathogen identification, guide antimicrobial stewardship, reduce unnecessary antibiotic exposure, and enhance clinical decision-making, particularly in complex or critically ill patients. Nevertheless, molecular technologies face important challenges, including high cost, limited availability, bioinformatics complexity, contamination risk, and difficulties distinguishing colonization from active infection, underscoring the need for careful clinical correlation. Emerging diagnostic strategies, such as multi-marker panels, kinetic biomarker modeling, biosensor-based point-of-care platforms, and machine-learning–assisted interpretation, offer promising avenues to overcome current limitations. In parallel, growing evidence highlights the potential role of microbial-associated biomarkers and microbiota signatures in cancer—particularly colorectal cancer—where host–microbiome interactions may support diagnostic, prognostic, and predictive applications. However, substantial heterogeneity in microbiome composition and the lack of standardized microbial markers necessitate further validation through large-scale, prospective clinical studies. In conclusion, optimal diagnostic and prognostic accuracy is achieved through an integrated framework that combines clinical assessment, host-response biomarkers, and molecular pathogen detection. Future research should prioritize standardized biomarker validation, scalable molecular diagnostics, and clinically actionable reporting systems to translate laboratory advances into improved patient outcomes across infectious and oncologic settings.

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