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Liquid biopsy in microbial infection diagnosis: Sepsis detection and management

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ABSTRACT

Sepsis remains a leading cause of morbidity and mortality, with early and accurate diagnosis critical for improving patient outcomes. Traditional diagnostic methods, such as blood cultures and PCR, are limited by long turnaround times, low sensitivity, and contamination risks. Liquid biopsy, a non-invasive diagnostic approach, has emerged as a promising alternative, leveraging the detection of microbial cell-free DNA (cfDNA) in blood samples. This review explores the principles of liquid biopsy in the context of sepsis diagnosis, highlighting its advantages over conventional methods, such as enhanced sensitivity, specificity, and faster time-to-result. We examine the clinical applications of liquid biopsy in early detection, pathogen identification, and antimicrobial resistance profiling. Moreover, we discuss challenges, including technical limitations, cost barriers, and issues related to data interpretation and contamination. Looking to the future, we envision the integration of liquid biopsy with AI, electronic health records, and point-of-care platforms to revolutionize sepsis management. Despite hurdles, liquid biopsy offers great promise for improving diagnostic accuracy and clinical decision-making in sepsis care.

KEYWORDS

Sepsis diagnosis; Microbial DNA; Pathogen detection; Liquid biopsy

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Introduction

Sepsis is a critical condition that results from the body's uncontrolled reaction to infection, which can cause organ failure and potentially lead to death if not treated quickly. Each year, it impacts around 49 million people worldwide, causing roughly 11 million deaths, which represents nearly 20% of all deaths globally. Even with improvements in healthcare, detecting sepsis in its early stages is still a major hurdle due to its varied symptoms and the absence of precise testing methods. Conventional diagnostic approaches, like blood cultures, are regarded as the primary method for detecting infections in the bloodstream. Nevertheless, these techniques have significant drawbacks, including lengthy processing times (usually taking 24 to 72 hours), limited sensitivity, and a considerable chance of contamination. Such diagnostic delays can result in inappropriate or postponed treatment with antibiotics, heightening the risk of septic shock and death. Additionally, in areas with limited resources, the absence of sophisticated lab facilities further complicates the quick diagnosis and treatment of sepsis [1].

The urgent demand for quick, precise, and non-invasive diagnostic methods has sparked the investigation of new strategies. Among these, liquid biopsy has surfaced as an encouraging technique. Initially created for cancer-related uses, liquid biopsy focuses on examining cell-free DNA (cfDNA) found in the blood to identify disease-related genetic information. When applied to infectious diseases, this technique facilitates the detection of cfDNA from pathogens, allowing for the identification of the agents causing illness without needing invasive techniques [2]. Recent research has highlighted liquid biopsy's effectiveness in diagnosing severe infections like sepsis. For example, next-generation sequencing (NGS) technologies can assess cfDNA to find various pathogens, such as bacteria, viruses, and fungi, directly from plasma samples. This approach provides numerous benefits compared to traditional diagnostics: it is quicker, more sensitive, and can recognize hard-to-culture pathogens. Furthermore, combining artificial intelligence with data from liquid biopsy has shown potential in improving diagnostic precision and forecasting patient outcomes [3].

In summary, liquid biopsy signifies a groundbreaking progress in diagnosing and treating sepsis. By enabling swift, precise, and non-invasive pathogen identification, this technology has the capacity to address the shortcomings of conventional diagnostics, resulting in prompt and targeted therapeutic actions, ultimately enhancing patient survival rates [4].

Current Diagnostic in Sepsis

Sepsis is a critical condition characterized by organ failure stemming from an unregulated response to infection, which requires quick and precise diagnosis to start treatment without delay. Historically, blood cultures have been fundamental in detecting infections in the bloodstream. However, they have several drawbacks that can hinder effective management of sepsis [5].

Blood cultures need living microorganisms to grow, and their effectiveness can be diminished by previous antibiotic treatment or low levels of bacteria in the blood. Research has shown that nearly half of the patients showing symptoms of sepsis may have negative results from blood cultures.

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Furthermore, obtaining reliable results usually takes between 24 to 72 hours, postponing focused antimicrobial treatment. These delays may result in continued use of broad-spectrum antibiotics, which heightens the risk of developing resistance to these medications and experiencing adverse drug reactions. Diagnostics based on Polymerase Chain Reaction (PCR) have surfaced as quick alternatives, allowing for the detection of microbial DNA in blood samples. Techniques such as real-time PCR and multiplex PCR tests provide quicker results, often in just a few hours. Nonetheless, their sensitivity can differ, with some tests identifying only 37% to 65% of bloodstream infections. Additionally, PCR tests might not be able to distinguish between living and dead organisms, which could result in overdiagnosis or misunderstanding of the findings [6,7].

Numerous factors can contribute to false negatives in both blood cultures and PCR tests, such as low levels of bacteria, sporadic bacteremia, or errors in sample collection and processing. On the other hand, false positives, particularly in blood cultures, often emerge from contamination with skin bacteria or environmental microbes during the collection process. The rates of contamination in blood cultures can vary from 0. 6% to 12. 5%, with higher occurrences reported in emergency settings. These false positives can lead to unnecessary antibiotic treatments, extended hospitalizations, and increased healthcare expenses [8].

To address these challenges, it is crucial to implement strict aseptic techniques during sample collection, ensure adequate training for staff, and follow standardized protocols. Moreover, combining rapid diagnostic methods with clinical evaluations and antimicrobial stewardship initiatives can improve the precision of sepsis diagnoses and enhance patient outcomes [9].

Principles of Liquid Biopsy for Infectious Diseases

Liquid biopsy has become a groundbreaking method for diagnosing infectious diseases, allowing for the identification of pathogens through the examination of circulating microbial cell-free DNA (mcfDNA) found in bodily fluids. This non-invasive approach provides quick and thorough insight into the microbial environment of a patient, supporting timely and focused treatment options [10].

Circulating cell-free DNA (cfDNA) consists of short DNA fragments released into the bloodstream and other bodily fluids, usually measuring between 50 and 200 base pairs. These fragments come from cells that are dying or undergoing apoptosis, as well as from active secretion. In the realm of infectious diseases, mcfDNA is released by pathogens like bacteria, viruses, and fungi that shed their genetic material into the host's blood during the infection process. The identification of mcfDNA offers a glimpse into the infectious organisms present, making it a useful tool for diagnosis, particularly in situations where conventional culture techniques fall short or prove ineffective [11,12].

Cutting-edge molecular methods have played a key role in utilizing liquid biopsy for diagnosing infectious diseases. Next-generation sequencing (NGS) enables thorough analysis of cfDNA, allowing for the detection of a wide variety of pathogens without needing prior knowledge of the infectious agent. Digital polymerase chain reaction (dPCR), including droplet digital PCR (ddPCR), provides high levels of sensitivity and specificity by dividing the sample into many separate reactions, enabling accurate measurement of specific DNA sequences. Metagenomic sequencing enhances the ability to detect pathogens by evaluating the combined genome of all microorganisms in a sample, assisting in finding rare or previously unknown pathogens [13].

The effectiveness of liquid biopsy relies heavily on careful handling and processing of samples. Factors before analysis, such as the type of anticoagulant used, the duration until plasma separation, and storage conditions, can greatly affect cfDNA quality and quantity. Aspects of analytical sensitivity are impacted by elements like the efficiency of cfDNA extraction, the methods used for library preparation, and the depth of sequencing. It is critical to standardize procedures and implement quality control practices to reduce variability and guarantee dependable outcomes. Ongoing research seeks to enhance these methods, improving the clinical relevance of liquid biopsy in the diagnosis of infectious diseases [13,14].

Clinical Applications of Liquid Biopsy in Sepsis

Liquid biopsy, especially via the examination of microbial cell-free DNA (mcfDNA), has become a revolutionary instrument in the clinical handling of sepsis. This non-invasive method provides quick and thorough information about the existence of pathogens, allowing for prompt and focused treatment strategies [15].

Early detection of bloodstream infections

Conventional blood cultures are regarded as the standard method, but they frequently face long processing times and have restricted sensitivity, particularly in individuals who have previously been treated with antibiotics. On the other hand, mcfDNA sequencing enables the identification of pathogens directly from plasma specimens without requiring culture. Research has indicated that mcfDNA sequencing can reveal the causes of sepsis in about 30 hours, which is much quicker compared to traditional techniques. Additionally, this method has demonstrated improved detection rates for pathogens, especially in situations where blood cultures yield negative results because of low levels of microbes or earlier use of antimicrobial treatments [16].

Identification and antimicrobial susceptibility profiling

Beyond simple detection, liquid biopsy enables accurate recognition of pathogens at the species level. Cutting-edge sequencing methods, like next-generation sequencing (NGS), can reveal a wide variety of microorganisms, such as bacteria, viruses, and fungi. In addition, examining genetic material makes it possible to identify antimicrobial resistance genes, which sheds light on possible resistance trends. This knowledge is essential for directing suitable antimicrobial treatment, minimizing the dependence on broad-spectrum antibiotics, and addressing the growth of antimicrobial resistance [17].

Monitoring treatment response and disease progression

Liquid biopsy has the ability to allow for ongoing observation of how well treatments are working and how the disease is advancing. By measuring levels of mcfDNA over a period,

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doctors can evaluate the amount of microbial presence and gauge how the patient is reacting to the treatment. A decrease in mcfDNA levels may suggest that the treatment is working effectively, whereas consistent or increasing levels may indicate that the treatment is not successful or there are complications. This type of ongoing monitoring allows for swift changes to treatment plans, which might enhance patient results [17,18].

To conclude, incorporating liquid biopsy into medical routines shows promise for boosting the diagnosis, management, and observation of sepsis. Its quick, precise, and all-encompassing features can overcome the challenges associated with standard diagnostic methods, ultimately helping to improve patient care and outcomes [18,19].

Liquid Biopsy vs. Conventional Diagnostics: A Comparative View

Sepsis is a critical situation that arises from an uncontrolled response of the body to an infection, making it essential to diagnose it quickly and correctly to start treatment without delay. Conventional diagnostic techniques, including blood cultures and tests based on polymerase chain reaction (PCR), have been the primary tools for identifying bloodstream infections. Nevertheless, these techniques have shortcomings in their sensitivity, accuracy, and the time it takes to get results, which can slow down urgent clinical decisions [20].

Sensitivity and specificity metrics

Blood cultures, regarded as the best method for finding pathogens, exhibit a sensitivity of 30% to 50%, especially in patients who have previously undergone antibiotic treatment. PCR-based diagnostic methods provide enhanced sensitivity, identifying pathogens in about 60% to 80% of instances; however, they may still overlook infections caused by low levels of microorganisms or the emergence of new pathogens [21].

In comparison, liquid biopsy methods that examine microbial cell-free DNA (mcfDNA) present in the blood have shown greater sensitivity and specificity. Research has indicated sensitivities reaching 90% and specificities surpassing 95% for mcfDNA sequencing in detecting bloodstream infections. This improved precision enables the identification of a wider variety of pathogens, encompassing those that are difficult to grow, grow slowly, or cannot be cultured [22].

Time-to-result comparison

The typical timeframe for receiving blood culture results is between 24 to 72 hours, which may postpone the start of specific antimicrobial treatment. PCR tests provide quicker outcomes, typically in 4 to 6 hours, but often necessitate prior awareness of the potential pathogens [21,22].

Liquid biopsy techniques, especially those employing next-generation sequencing (NGS), are capable of delivering thorough identification of pathogens within a time frame of 24 to 48 hours. Certain sophisticated platforms have decreased this duration even more, providing outcomes in as few as 6 hours. This quick response enables earlier identification and prompt commencement of suitable treatment [23].

Clinical utility and decision-making impact

The inclusion of liquid biopsy in clinical practice provides numerous benefits compared to traditional diagnostic methods. The elevated sensitivity and specificity of mcfDNA analysis allow for precise identification of pathogens, even in situations where standard methods do not succeed. The quick processing time facilitates timely clinical decisions, enabling the swift start of specific antimicrobial treatment, which is vital for enhancing patient results. Additionally, liquid biopsy has the ability to identify genes associated with antimicrobial resistance, offering information about possible resistance trends and assisting in the choice of appropriate therapies. This ability is especially important in light of increasing antimicrobial resistance, as it aids antimicrobial stewardship initiatives by decreasing the usage of broad-spectrum antibiotics [24].

So, liquid biopsy is an important improvement in the diagnosis and treatment of sepsis. Its enhanced sensitivity, specificity, and swift processing time increase its usefulness in a clinical setting and assist with quick, informed decisions, thereby ultimately enhancing patient care and results [15,20].

Challenges and Limitations of Sepsis Diagnostics

Although liquid biopsy, specifically using microbial cell-free DNA (mcfDNA) analysis, shows potential improvements in diagnosing sepsis, various obstacles impede its broad clinical implementation.

The use of mcfDNA sequencing in regular clinical practice encounters notable technical and financial challenges. High-throughput sequencing systems, like Illumina's HiSeq or NextSeq, are crucial for analyzing mcfDNA. However, they require a significant financial investment, often more than $500,000, along with extra expenses for reagents and upkeep. Furthermore, the typical expense for each test can exceed $2,000, creating challenges in terms of affordability, particularly in settings with limited resources. The intricate nature of the process, which includes gathering samples, extracting DNA, preparing libraries, conducting sequencing, and performing bioinformatics analysis, requires skilled staff and appropriate facilities, thereby increasing operational expenses [18,24].

Interpretation of low-level microbial DNA

Identifying and understanding small amounts of microbial DNA fragments found in plasma is naturally difficult. The broken structure of cfDNA, which is typically shorter than 200 base pairs, makes it difficult to identify pathogens accurately. Furthermore, differentiating between harmful DNA and the DNA from non-harmful microbes or environmental origins necessitates strong analytical methods. The lack of standard benchmarks for determining clinically important microbial levels makes it harder to interpret results, which could result in incorrect positive or negative diagnoses [20,26].

Risk of contamination and over-interpretation

The high sensitivity of mcfDNA sequencing makes it vulnerable to contamination from different sources, such as skin bacteria during sample collection, lab materials, and germs present in the environment. Such pollutants can result in incorrect identification of pathogens, thereby misguiding clinical choices. It is essential to apply strict contamination control measures, including the use of DNA-free reagents, the inclusion of negative controls, and compliance with standardized protocols,

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in order to reduce the occurrence of false-positive results. Moreover, finding microbial DNA does not automatically mean there is an ongoing infection; it could represent temporary bacteria in the blood or dead organisms. Therefore, careful interpretation should be done alongside clinical observations. although liquid biopsy has considerable promise for improving sepsis diagnosis, it is essential to tackle the technical, interpretative, and contamination-related issues to ensure its effective incorporation into clinical practice [27].

Future Perspectives and Technologies in Liquid Biopsy for Sepsis

The incorporation of cutting-edge technologies into liquid biopsy techniques shows considerable potential for improving sepsis diagnosis. Major advancements in artificial intelligence, electronic health records, and point-of-care testing are ready to transform how sepsis is identified and treated. Artificial intelligence, especially through machine learning models, is capable of examining intricate patterns found in microbial cell-free DNA data, thereby enhancing both the precision and quickness of pathogen detection. Recent research has indicated that AI systems can forecast the likelihood of septic shock and organ failure by scrutinizing proteomic data from plasma samples. This integration can support quicker diagnostics and tailored treatment options [26,28],

Combining liquid biopsy findings with electronic health data allows for continuous monitoring and alert systems to be established. For example, the Targeted Real-time Early Warning System created by Johns Hopkins University employs health records to identify initial sepsis indicators, ultimately lowering death rates by 20%. Incorporating cfDNA analysis in these frameworks can improve the accuracy and timing of sepsis identification, facilitating timely clinical responses [25,28].

Innovations in biosensor technologies are creating pathways for portable, fast, and affordable point-of-care liquid biopsy solutions. New sensing technologies, such as colorimetric, fluorescent, and electrochemical sensors, provide low detection thresholds and greater specificity, which allows for on-site identification of sepsis biomarkers. The addition of artificial intelligence to these technologies can further boost their diagnostic functions, making them essential instruments in emergency situations and settings with limited resources.In conclusion, the merging of AI, electronic health record integration, and point-of-care testing technologies is on the verge of revolutionizing liquid biopsy uses in sepsis diagnosis, resulting in prompt, precise, and customized patient care [28,29].

Conclusions

Liquid biopsy signifies a significant improvement in the diagnosis and treatment of sepsis, providing several important benefits compared to conventional methods. By allowing for the quick and non-invasive identification of microbial cell-free DNA (cfDNA), it tackles significant drawbacks of blood cultures and PCR, such as extended processing times, low sensitivity levels, and risks of contamination. Advancements like next-generation sequencing, digital PCR, and AI-based interpretation tools have greatly improved the clinical application of liquid biopsy. These innovations facilitate earlier detection of pathogens, personalized antimicrobial treatment, and ongoing observation of treatment effectiveness.

Moving forward, incorporating liquid biopsy into standard clinical processes will necessitate addressing technical, regulatory, and ethical challenges. With increasing proof of its diagnostic precision and ability to lower sepsis-related illness and death rates, it is aptly positioned to be a fundamental component of targeted management in infectious diseases. The future of sepsis treatment depends on utilizing these advanced diagnostic tools to enable quicker, data-informed clinical decisions and enhance patient results.

Disclosure statement

No potential conflict of interest was reported by the authors.

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