ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Comparison of Blood Culture and Multiplex PCR Results in Patients Prediagnosed with Sepsis

Sepsis Ön Tanısı Alan Hastaların Kan Kültürü ve Multiplex PCR Sonuçlarının Karşılaştırılması

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ABSTRACT

Aim: *Sepsis is a life-threatening infection that affects multiple systems, leading to hemodynamic changes, shock, organ dysfunction, and potentially organ failure. Although blood culture is the gold standard for identifying the causative agent, the pathogen cannot be isolated in some cases, posing significant challenges in diagnosis and treatment, affecting mortality and morbidity rates. The aim of this study is to retrospectively and prospectively evaluate the results of blood cultures and the Multiplex PCR sepsis panel sent to Microbiology laboratory.*

Material and Method: *In this study, 100 samples sent to our laboratory for blood culture and sepsis panel between September 1, 2023, and August 31, 2024, were analyzed retrospectively and prospectively. All bottles with a positive signal were subjected to Gram staining, and simultaneous inoculations were made on 5% sheep blood agar, EMB, SDA, and Chocolate agar. After 24–48 hours of incubation at 37°C, the isolated strains were identified using conventional methods (colony morphology, Gram staining, etc.) and biochemical tests (catalase test, oxidase test, tube and slide coagulase tests). For the sepsis panel, nucleic acid extraction was performed on samples received in the laboratory using a total nucleic acid extraction kit based on magnetic bead technology, following the manufacturer's instructions.*

Results: *According to the PCR results of the 100 blood samples included in the study, Candida species were detected in 4 samples. Candida species were also identified in the blood culture. The distribution of strains in the sepsis panel included C.tropicalis, C.albicans, C.glabrata, and C.krusei. Among the blood culture samples, three demonstrated results that were consistent with the sepsis panel findings, while one sample was identified as C.glabrata through conventional methods, in contrast to the result from the sepsis panel. Among bacterial pathogens, Staphylococcus spp. was the most frequently identified (56 cases), followed by Escherichia coli.*

Conclusion: *The results of this study demonstrate that PCR is an effective method for diagnosing sepsis; however, some results need to be confirmed by blood culture. PCR testing provides rapid and accurate information, particularly in situations where quick results are essential, such as in intensive care units and emergency departments. However, it should be noted that PCR can amplify DNA from dead bacteria, so results should be interpreted with caution. In clinical practice, the combined use of both tests will contribute to more effective patient management and treatment.*

Key words: *sepsis; blood culture; multiplex PCR*

ÖZET

Amaç: *Sepsis, birçok sistemi tutan, özellikle hemodinamik değişikliklere yol açabilen, şok, organ fonksiyon bozukluğu ve yetmezliğine kadar gidebilen öldürücü bir enfeksiyondur. Kan kültürü altın standart yöntem olduğu halde bazı durumlarda etken izole edilememekte ve bu durum tanı ve tedavide ciddi zorluklara yol açarak mortalite ve morbidite oranlarına etki etmektedir. Bu çalışmanın amacı, rutin laboratuvarımıza gönderilen kan kültürü ve Multiplex PCR sepsis paneli sonuçlarının retrospektif ve prospektif olarak değerlendirilmesidir.*

Materyal ve Metod: *Bu çalışmada, 1 Eylül 2023 – 31 Ağustos 2024 tarihleri arasında laboratuvarımıza gönderilen kan kültürü ve sepsis panel istemi yapılan 100 örnek prospektif ve retrospektif olarak incelenmiştir. Kan kültür cihazında pozitif üreme sinyali veren tüm şişeler gram boyama yapılmış ve eş zamanlı olarak %5 koyun kanlı kanlı agar, EMB, SDA ve Çikolatamsı agar besiyerlerine ekimleri yapılmıştır. Tüm plaklar 37°C'de 24–48 saat inkübe edildikten sonra izole edilen suşlar konvansiyonel yöntemler (koloni morfolojisi, gram boyama vb.) ve biyokimyasal testler (katalaz testi, oksidaz testi, lam ve tüpte koagülaz) ile tanımlanmıştır. Sepsis paneli için örnekler laboratuvara geldiğinde örneklerin nükleik asit ekstraksiyonu, manyetik boncuk yöntemine dayanan toplam nükleik asit ekstraksiyon kiti kullanılarak, üretici firmanın talimatları doğrultusunda gerçekleştirilmiştir.*

Bulgular: *Çalışmaya dâhil edilen 100 sepsisli hasta örneğinin PCR sonuçlarına göre dört örnekte Candida türleri saptanmıştır. Aynı örneklerden yapılan kan kültürlerinde de Candida türleri saptanmıştır. Suşların dağılımı sepsis panelinde C.tropicalis, C.albicans, C.glabrata ve C.krusei olarak tespit edilmiştir. Kan kültür sonucunda üç örnek sepsis paneli ile aynı sonuçlanırken bir örnek sepsis sonucuna kıyasla konvansiyonel olarak C.glabrata olarak tanımlanmıştır. Bakteriyel etkenler arasında en sık sırasıyla Staphylococcus spp. (56), ikinci sıklıkta E.coli raporlanmıştır.*

Sonuç: *Çalışmanın sonucunda, PCR'nin sepsis tanısı koymada etkin bir yöntem olduğu, ancak bazı sonuçların kan kültürü ile doğrulanması gerektiği ortaya çıkmıştır. PCR testi ile elde edilen sonuçlar, özellikle hızlı ve doğru bilgi sağlanması gerektiği durumlarda (örneğin, yoğun bakım ve acil servisler gibi) faydalıdır. Ancak, testin ölü bakteri DNA'sını çoğaltma özelliği nedeniyle dikkatli bir şekilde yorumlanması gerektiği unutulmamalıdır. Klinik uygulamalarda her iki testin birlikte kullanılması, hastaların daha etkili bir şekilde tedavi edilmesini sağlayacaktır.*

Anahtar kelimeler: *sepsis; kan kültürü; multiplex PCR*

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Introduction

Sepsis is defined as organ dysfunction resulting from dysregulation of the host immune response to infections[1]. Bloodstream infections are significant causes of morbidity and mortality in hospitalized patients. Early diagnosis and the effective use of antibiotics are crucial for improving clinical outcomes in critical medical conditions such as sepsis and septic shock[2,3]. The rapid and accurate identification of bacterial pathogens isolated from blood cultures is important for initiating appropriate treatment at an early stage. This contributes to a reduction in morbidity and mortality, shorter hospital stays, lower healthcare costs, and the prevention of unnecessary antibiotic use[4,5]. Incorrect antibiotic therapy leads to difficulties in identifying the true pathogen, increases antimicrobial resistance, and facilitates the dominance of multidrug-resistant Gram-negative bacteria in the hospital environment[6].

Blood culture is considered the gold standard method for the diagnosis of sepsis. However, pathogens that are difficult or slow to grow may be overlooked in blood cultures from septic patients. Additionally, bacterial isolation from blood cultures may reflect asymptomatic bacteremia or contamination. Variables such as the type of microorganism, the microbial load in the sample, differences in the growth rates of microorganisms, and factors like the duration of sample storage at room temperature can also affect the results. Another disadvantage of blood cultures is their relatively low diagnostic sensitivity, particularly in patients receiving antibiotic treatment[7]. Molecular methods contribute to a reduction in hospital stay duration and mortality rates by enabling the detection of organisms that cannot be cultured, as well as shortening the time required for pathogen identification. Using PCR techniques, bacterial 16S rRNA genes are amplified through nucleic acid amplification. The identification of the pathogen on the same day and the molecular detection of major resistance patterns assist in the formulation of treatment policies[6]. This study aims to compare the results of blood cultures with the sepsis panel tested directly from the blood culture bottles using Multiplex PCR.

Materials and Methods

In this study, 100 samples of blood cultures and multiplex PCR, requested between September 1, 2023, and August 31, 2024, were prospectively and retrospectively analyzed. The blood culture bottles were incubated in an automated blood culture system (Becton Dickinson, BD BACTEC™ FX40). All bottles that showed a positive growth signal were Gram-stained, and simultaneously, they were cultured on 5% defibrinated sheep blood agar, Eosin Methylene Blue (EMB) agar, Sabouraud Dextrose Agar (SDA), and Chocolate agar. After incubating all samples at 37°C for 24–48 hours, the isolated strains were identified using conventional methods (colony morphology, Gram staining, etc.) and biochemical tests (catalase test, oxidase test, and coagulase test in both tube and slide methods). The antibiotic susceptibility of the strains was determined using the Kirby-Bauer disk diffusion method, and the results were evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint table. For coagulase-negative staphylococci, the organism was considered the causative agent if the same bacterium was isolated in at least two blood cultures. If bacterial growth occurred in only one of the two blood cultures but was clinically consistent, or if the same strain was isolated from different infection sites, it was also considered as causative agent.

When the samples for the sepsis panel arrived at the laboratory, nucleic acid extraction was performed using a total nucleic acid extraction kit based on the magnetic bead method (Bioeksen, Istanbul, Türkiye), following the manufacturer's instructions. The extraction was carried out using the Zybio EXM 3000 device (Zybio, Shenzhen, China). The sepsis panel identifies a total of 24 parameters, including *Candida tropicalis, C.albicans, C.parapsilosis, C.krusei, C.glabrata, S.aureus, Staphylococcus spp., E.faecium, E.faecalis, S.pneumoniae, Streptococcus spp., L.monocytogenes, P.aeruginosa, Pseudomonas spp., K.oxytoca, K.pneumoniae, A.baumannii, H.influenzae, Enterobacteriaceae, S.maltophilia, E.coli, N.meningitidis*, as well as Vancomycin-resistant Van and Carbapenem-resistant Oxa strains.

After nucleic acid extraction, the samples were processed for multiplex PCR according to the manufacturer's recommendations shortly as follows;

1. The Sepsis RT-qPCR MX-24L Panel "SY-1 Rxn and SY-2 Rxn" strips were placed on the cooling block, which had been removed from -22°C.
2. 10 µl sample of "Template nucleic acid" was added to each of the "SY-1 Rxn and SY-2 Rxn" strips.
3. The strips were carefully and securely sealed with their caps and placed in the Micro-PCR device for processing. The amplification steps were set according to the settings shown in Table 1.

Table 1. *Amplification steps for multiplex PCR*

Steps	Cycle	Temperature	Duration
Reverse transcriptase	1	52°C	3 min.
Holding	1	95°C	10 min.
Denaturation		95°C	1 sec.
Anneling/extension	12 Touchdown cycle	67°C–56°C	15 sec.
Denaturation	30	95°C	1 sec.
Anneling/extension		95°C	15 sec.
Read		(FAM-green) (HEX-yellow) (ROX-orange) (CYS-red)	

Table 2. *Interpretation of the PCR results*

Result	IC	Interpretation	
Positive	Positive or negative	Results valid, Pathogen detected	26<Cq <30 "Low positive" 16<Cq <26 "positive" Cq <16 "High positive"
Negative	Positive	Results valid, Pathogen not-detected	

IC: Internal control.

4. The shape of the obtained amplification curves was examined for each reaction well with Cq values. Sigmoidal curves above the threshold value were considered "positive," while non-sigmoidal curves were regarded as "negative."

Interpretation of the Results

For the *Candida krusei, C.glabrata, C.albicans, C.parapsilosis*, and *C.tropicalis* gene targets, a Cq value <26 was reported as positive, while a Cq value >26 was reported as negative. For all other gene targets, a Cq value <23 was reported as positive, and a Cq value >23 was reported as negative. In cases where multiple parameters yielded positive results, the outcome was reported following the evaluation process outlined below (Table 2).

The parameter with the lowest Cq value is identified=Min Cq.

If (the Cq value of the other parameter) –Min Cq <7, a positive result is reported for the other parameter.

If the Cq value of the other parameter –Min Cq >7, a negative result is reported for the other parameter.

Ethical Approval

The study protocol was reviewed and approved by the the non-interventional ethics committee of Kafkas University, with approval number 80576354-050-99/396. As the study involved retrospective and anonymized data and no interventions were performed, the requirement for individual informed consent was waived by the ethics committee.

Results

Of the blood culture and sepsis panel samples sent to our laboratory with a presumptive diagnosis of sepsis and showing positive growth, 60% came from the Anesthesia and Reanimation Intensive Care Unit, and 13% came from the Palliative Care Unit. The distribution of the samples included in our study according to the clinics is shown in Table 3.

Table 3. *Distribution of sepsis samples according to clinics*

Clinic	n	%
Anesthesia and reanimation intensive care unit	60	60
Palliative care unit	13	13
Internal medicine service	8	8
Cardiology service	7	7
Thoracic surgery service	5	5
Urology service	5	5
Neonatal intensive care unit	1	1
Emergency service	1	1
Total	100	100

The PCR results of 100 sepsis patients included in the study revealed the presence of Candida species in 4 samples. Candida species were also detected in the blood cultures of the same samples. The distribution of strains in the sepsis panel was identified as *C.tropicalis*, *C.albicans*, *C.glabrata*, and *C.krusei*. In the blood culture results, 3 samples matched the sepsis panel, while one sample was conventionally identified as *C.glabrata* compared to the sepsis result. Among bacterial pathogens, Staphylococcus spp. (56 cases) was the most frequently reported, followed by *E.coli* as the second most common. Of the 100 total samples evaluated, two showed no growth in blood culture but were positive on the Multiplex PCR panel. This accounts for the discrepancy between the total counts of blood culture (n=98) and PCR results (n=100). The distribution of

pathogens detected in the study according to species is shown in Table 4.

Table 4. *Microorganisms detected by blood culture and multiplex PCR sepsis panel*

Multiplex PCR	n	Blood culture		n
Staphylococcus aureus	4	*Staphylococcus aureus*	4	56
		MRKNS*	40	
Staphylococcus spp	52	MSKNS**	12	
		Escherichia coli		20
Enterocuccus faecium	5	*Klebsiella pneumoniae*		3
Enterocuccus faecalis	3	*Enterococcus spp*		11
Streptococcus pneumoniae	2	*Pseudomonas aeruginosa*		1
Streptococcus spp	2	*Acinetobacter spp*		3
Klebsiella pneumoniae	2	Viridans Streptococcus		2
Acinetobacter baumannii	5	*S.pneumoniae*		2
Escherichia coli	25			
Methicillin resistance mecA	60			
Total	100			98

* Methicillin resistant coagulase (-) Staphylococcus.
** Methicillin sensitive coagulase (-) Staphylococcus.
Of the 100 total samples evaluated, two showed no growth in blood culture but were positive on the Multiplex PCR panel. This accounts for the discrepancy between the total counts of blood culture (n=98) and PCR results (n=100).

In our study, a concordance rate of 88% was observed between blood culture and PCR results in patients with sepsis. The number of pathogens detected by PCR was found to be higher than that detected by blood culture. Given that the PCR method is capable of amplifying DNA from both viable and non-viable bacteria present in the environment, it was concluded that the interpretation of PCR results in conjunction with blood culture outcomes would yield a more accurate diagnostic approach for sepsis.

Discussion

Polymerase Chain Reaction (PCR) results provide faster outcomes than blood culture, making it particularly useful in intensive care units or for critically ill patients, where quicker and more accurate information is essential. Moreover, the administration of antimicrobial treatment before blood sampling reduces the sensitivity of blood culture[8]. In a study by Dinç et al, the pathogen detection rate in sepsis patients was found to be 32% with blood culture and 44.9% with PCR[9]. In other studies carried out with SeptiFast, it has been reported that the blood culture positivity ranged from 8–41%, while the PCR positivity ranged from 11–41%[10–12]. However, due to PCR's ability to amplify dead bacterial DNA, positive results must be carefully evaluated. The detection of dead bacterial DNA can lead to false-positive results and may produce outcomes that are not consistent with clinical findings[13]. In our study, when we compared blood culture and PCR results in sepsis patients, an 88% concordance rate was observed between the two methods. In other studies, the concordance between blood culture and PCR has been reported to range from 67–85%[8,10,11,14,15]. It can be concluded from these studies that the PCR method is more successful in pathogen detection. However, it is important to highlight that PCR results should be evaluated alongside blood culture results.

Fungal infections, particularly, have a high mortality rate[16]. In recent years, approximately 5% of sepsis cases are caused by fungi, primarily Candida species. Risk factors contributing to this condition include prolonged use of broad-spectrum antibiotics, parenteral hyperalimentation, the use of intravascular catheters, and corticosteroid therapy[17]. In hospital-acquired fungal infections, *C.albicans* is the most commonly identified pathogen. However, in recent years, the proportion of non-albicans Candida species, which are more difficult to treat with azole antifungals, has been increasing[18]. In a study by Dinç et al., despite the absence of fungal growth in blood cultures, PCR analysis identified two *C.parapsilosis* strains, one *C.albicans* strain, and one *A.fumigatus* strain as the presumed etiological agents[9]. In a study of Yertut et al., the fungal pathogens isolated from blood cultures were *C.albicans* in two samples, *C.krusei* in one sample, and a mold in another. However, using molecular methods, *C.albicans* and *C.krusei* were identified in two samples each[17]. In our study, when comparing the sepsis panel results obtained by PCR with blood culture results, Candida species were detected in four samples (4%). *C.tropicalis, C.albicans, C.glabrata*, and *C.krusei* were all included in the sepsis panel, while one of the strains isolated from the blood cultures was misidentified as *C.glabrata*. This finding suggests that the PCR method may offer an advantage in detecting microorganisms, particularly Candida species, which are difficult to identify using conventional methods.

The distribution of causative agents of sepsis varies between hospitals. Gram-negative bacteria are reported to account for 20–64% of cases, while Gram-positive bacteria are responsible for 27–74% of cases[19]. In other studies, the rate of Gram-positive bacterial growth in blood cultures ranges from 59–70%, while the rate of

Gram-negative bacterial growth ranges from 24–37%[20–22]. In these studies, the most commonly isolated bacteria were *E.coli* and coagulase-negative staphylococci, which are also the predominant pathogens in our study. The detection of these bacteria by blood culture and sepsis panel generally yielded similar results. However, the presence of resistant microorganisms, particularly MRS, is of significant importance for the management of patient treatment processes. The PCR method enables the rapid detection of such resistant organisms, facilitating the prompt initiation of appropriate treatment for patients. For instance, a systematic review and meta-analysis demonstrated that digital PCR offers high sensitivity (94%) and specificity (87%) for detecting pathogenic microorganisms in sepsis patients, outperforming traditional blood cultures in terms of detection time and accuracy[23]. Additionally, a retrospective study found that multiplex digital PCR kits identified a broader range of pathogens, including polymicrobial infections, with a quicker processing time compared to blood cultures[24].

Our study underscores the efficacy of PCR as a diagnostic tool for sepsis; however, it also highlights the necessity of confirming certain results with blood culture. PCR provides valuable insights, particularly in scenarios requiring rapid and accurate information, such as in intensive care units and emergency departments. Nonetheless, given the PCR method's propensity to amplify DNA from dead bacteria, results must be interpreted with caution. False positive results can have significant clinical implications, including unnecessary antibiotic prescriptions, which may contribute to antibiotic resistance. It is crucial for studies to address the potential for false positives in PCR testing and to discuss their impact on clinical decision-making and antibiotic stewardship strategies. The integration of blood culture findings with PCR data can lead to more precise and reliable identification of sepsis pathogens. In conclusion, while PCR offers substantial advantages in sepsis diagnosis, blood culture remains an indispensable diagnostic method. The concurrent application of both tests in clinical practice is likely to enhance the accuracy of diagnosis and improve patient management.

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