Original Article

A diagnostic test of real-time PCR detection in the diagnosis of clinical bloodstream infection

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Background: Blood culture remains the standard for diagnosing bloodstream infections, but it is difficult to identify bacteria directly and timeliness. The real-time polymerase chain reaction (PCR) has the potential to fill this diagnostic gap. This study intends to explore the sensitivity and specificity of PCR in detecting bloodstream infection pathogens and to compare it with routine blood culture to explore its clinical application value.

Methods: A total of 126 patients with bloodstream infections collected from various clinical departments of The First Hospital of Hebei Medical University. The patient's sample was divided into two parts. The one for multiplex PCR detection was performed using the Pathogeno Elite Multiplex PCR kit. Another blood culture was a fully automatic blood culture system from Autobio company.

Results: Among the 126 patients, a total of 17 pathogens were detected by PCR and blood culture both methods. PCR detected a total of 43 positive samples and 83 negative samples. Five samples were positive with blood culture, and 81 were negative. The negative predictive value of PCR was 0.98, with a sensitivity of 0.71 and a specificity of 0.68. A total of 38 specimens were positive for PCR but negative for blood culture, and 2 samples were positive for blood culture but negative for PCR. The top 5 pathogens with PCR detection were Epstein-Barr virus (27 cases), *Human herpes virus 5* (9 cases), *Klebsiella pneumoniae* (5 cases), *Staphylococcus* (5 cases), and *Stenotrophomonas maltophilia* (4 cases).

Conclusions: PCR detection can rapidly identify more pathogens and even multi-pathogen infections. Therefore, PCR testing may improve pathogen detection in patients with suspected bloodstream infections, enabling targeted treatment of patients.

Keywords: Real-time polymerase chain reaction; blood culture; bloodstream infection

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Introduction

Bloodstream infection is a common clinical emergency. If the diagnosis and treatment are not timely, it can seriously threaten the life of patients, and the fatality rate is extremely high (1). In recent years, the incidence of bloodstream infections has shown a significant upward trend due to the application of various antibiotics, immunosuppressants, surgical operations, and other invasive procedures and interventional treatment methods

(2,3). Currently, the diagnosis of bloodstream infection mainly relies on traditional blood culture identification results. However, it takes 2–3 days or even longer from the positive blood culture of the specimen to the identification of the pathogenic bacteria in the laboratory, which seriously lags behind clinical needs (4). Furthermore, because the pathogenic bacteria cannot be identified, doctors can only use broad-spectrum antibiotics covering gram-positive cocci and gram-negative bacilli for treatment in advance, which dramatically increases the physical and economic burden of patients but also leads to bacterial resistance. In addition, an increasing number of multi-drug-resistant and pan-drug-resistant strains continue to emerge. Therefore, obtaining laboratory diagnostic results as soon as possible is particularly important for the treatment and prognosis of patients. At the same time, it can shorten the use time of clinical broad-spectrum antibiotics as soon as possible and reduce the generation of drug-resistant strains.

In recent years, real-time polymerase chain reaction (PCR) has been widely used in various molecular experiments. With the continuous development and innovation of current medical technology, real-time PCR is rapidly replacing traditional microbial detection methods (5). Real-time PCR can complete the PCR reaction and product analysis process in a reaction tube at one time. It can automatically conduct dynamic monitoring and data analysis, significantly reducing cross-infection incidence. In addition, the operation method of real-time PCR is relatively simple, the operation speed is fast, the quantification is reasonably accurate, the sensitivity is high, the operation can be repeated, and the application value is relatively high (6). Multiplex PCR is based on single real-time PCR, adding 2 or more pairs of primers to the same reaction system to amplify multiple product fragments simultaneously, fully reflecting the advantages of multiplex PCR with high efficiency and low cost (7). Multiplex PCR also has the high sensitivity and high specificity of single PCR. These advantages demonstrate that multiplex PCR is suitable for application in clinical experiments, simplifying and shortening the procedure and the time of detection processes, and providing a reference for clinical diagnosis and treatment (8,9).

In recent years, with molecular detection technology, PCR has been developed to detect DNA in the bloodstream. With the PCR detection, Selva *et al.* found that the sensitivity and specificity of *Streptococcus pneumoniae* were 94.0% and 98.4% in 128 blood culture vials (10). Arabestani *et al.* used multiplex PCR to identify *Staphylococcus aureus*, *coagulase-negative Staphylococcus*, *Enterococcus*, *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in blood culture-positive specimens, which took significantly less time than traditional blood culture identification (11). However, Kang *et al.* showed that the overall sensitivity of multiplex PCR in detecting BSI pathogens could be as high as 94.6%, and the sensitivity in multiplex infection is reduced to 78.6%. Therefore, this technology is considered prone to false positive results in the mecA gene detection of Staphylococcus aureus and coagulase-negative *Staphylococcus* (12). Therefore, more samples are needed to study the clinical application value of PCR detection in bloodstream infection pathogens.

In this study, multiplex PCR was performed to detect pathogens in patients with bloodstream infections. This method was compared with conventional blood culture to evaluate its clinical application value. We present the following article in accordance with the STARD reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1071/rc).

Methods

Study cohort and patients

The study included 126 cases suspected of infection detected by the microbiology laboratory of The First Hospital of Hebei Medical University laboratory department from April 2022 to June 2022 (Figure S1). There were 77 males and 49 females, with ages ranging from 18 to 98 (median age =60.5) (Table S1). The collection of all blood samples was carried out under strict relevant standards. Adults used double sets of bottles, and each set included aerobic and anaerobic bottles to ensure that the blood collection volume of each bottle was 8–10 mL. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the First Hospital of Hebei Medical University (No. 20220816), and the patients and their families knew and gave informed consent.

Sample pathogen detection

The patient's sample was divided into 2 parts; one for blood culture and the other for multiplex PCR detection. The fully automatic blood culture system from Autobio company was used for blood culture (product model/item number: BC120). All samples were homogenized for nucleic

Table 1 Comparison of pathogen detection by PCR and blood culture

Pathogen	PCR		Blood culture	
	No.	%	No.	%
Negative	83	65.9%	119	94.4%
Epstein-Barr virus	27	21.4%	0	3.2%
Klebsiella pneumoniae	5	4.0%	4	3.2%
Escherichia coli	2	1.6%	1	0.8%
Acinetobacter baumannii	1	0.8%	2	1.6%
Stenotrophomonas maltophilia	4	3.2%	0	0.0%
Pseudomonas aeruginosa	2	1.6%	0	0.0%
herpesvirus 1	1	0.8%	0	0.0%
Klebsiella oxytoca	1	0.8%	0	0.0%
Staphylococcus	5	4.0%	0	0.0%
Human herpesvirus 5	9	7.1%	0	0.0%
VIM	1	0.8%	0	0.0%
Rickettsia felis	1	0.8%	0	0.0%
Enterococcus faecium	1	0.8%	0	0.0%
ampC	1	0.8%	0	0.0%
Mycobacterium tuberculosis complex	2	1.6%	0	0.0%
KPC	1	0.8%	0	0.0%
Human metapneumovirus	1	0.8%	0	0.0%

PCR, polymerase chain reaction.

acid extraction using the Zymo BIOMICS DNA/RNA Miniprep kit (Zymo R2002) according to the manufacturer's instructions. Then, PCR was performed using the Pathogeno Elite Multiplex PCR kit (SJ0101, Shanghai Pathogeno Medical Technology Co., Ltd.) and the reaction system was configured strictly following the operating test instructions. The operation method of PCR amplification was as follows: 95 ℃ ×5 min, 1 cycle; 95 ℃ × 10 s, 35 cycles; fluorescence detection was controlled at 60 ℃, 30 s. The selected fluorescence channels were FAM, VIC, Cy5, and T0exas Red. The reaction volume was 10 μL. The final reaction system was detected using the ABI7500 instrument from Life Tech Company (Applied Biosystems). All blood culture bottles were under routine procedures.

Statistical analysis

Using blood culture as the gold standard reference method, PCR detection was used for diagnostic tests. The cases were counted as the number of cases or percentage. The number of positive results for each test in paired samples was compared in a 2-by-2 contingency table. The data were statistically analyzed using SPSS 22.0 (IBM Corp., USA) or Microsoft Excel to calculate the detection rate, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Results

Distribution of pathogenic bacteria in patient specimens detected by PCR

Blood samples from 126 patients (age: 18–98) were collected, including 63 samples from patients under 60 years and 63 samples from patients over 60 years. Among the pathogens detected by PCR, the overall number of pathogen-positive items was 65, and the top 5 pathogens with a higher positive rate were Epstein-Barr virus (27 cases), *Human herpes virus 5* (9 cases), *Klebsiella pneumoniae* (5 cases), *Staphylococcus* (5 cases), and *Stenotrophomonas maltophilia* (4 cases). Among the pathogens detected by blood culture, the total number of pathogen-positive items was 7, including *Klebsiella pneumoniae* (4 cases), *Acinetobacter baumannii* (2 cases), and *Escherichia coli* (1 case) (*Table 1*). Among patients aged 60 and below, the top 3 detected items

Table 2 Numbers of individual pathogens detected by PCR and blood culture

Pathogen	No. of positive			
	Age 18–60	Age >60	Total	Percent
Epstein-Barr virus	10	17	27	41.54%
Klebsiella pneumoniae	1	4	5	7.69%
Escherichia coli	1	1	2	3.08%
Acinetobacter baumannii	1	0	1	1.54%
Stenotrophomonas maltophilia	2	2	4	6.15%
Pseudomonas aeruginosa	0	2	2	3.08%
herpesvirus 1	0	1	1	1.54%
Klebsiella oxytoca	0	1	1	1.54%
Staphylococcus	4	1	5	7.69%
Human herpes virus 5	4	5	9	13.85%
VIM	1	0	1	1.54%
Rickettsia felis	1	0	1	1.54%
Enterococcus faecium	1	0	1	1.54%
ampC	0	1	1	1.54%
Mycobacterium tuberculosis complex	1	1	2	3.08%
KPC	0	1	1	1.54%
Human metapneumo virus	1	0	1	1.54%
Total	28	37	65	

PCR, polymerase chain reaction.

were Epstein-Barr virus (10 cases), *Staphylococcus* (4 cases), and *Human herpes virus 5* (4 cases). Among patients over 60 years old, the top 3 detected items were Epstein-Barr virus (17 cases), *Human herpes virus 5* (5 cases), and *Klebsiella pneumoniae* (4 cases) (*Table 2*).

PCR detection of mixed infection of pathogens in patients

Of the 126 samples tested by PCR, 83 were positive, with a positive detection rate of 65.9% (83/126). Among them, 30 cases were infected with 1 pathogen, 8 were infected with 2 pathogens, 5 were infected with 3 pathogens, and 1 was infected with 4 pathogens. Among the patients with double and multiple infections, the proportion of co-infection with Epstein-Barr virus was higher, accounting for 75% (6/8) of patients with double infection and 60% (3/5) of patients with triple infection. One case of quadruple infection was also co-infected with Epstein-Barr virus (*Table 3*).

Differences in pathogen detection performance between PCR and blood culture

Of the 126 blood samples, both methods tested negative in 81 cases and positive in 5 cases. Two specimens were positive for blood culture but negative for PCR. A total of 38 specimens were negative for blood culture and positive for PCR. The NPV of PCR and blood culture was 97.6% (81/83), the PPV was 11.6% (5/43), the sensitivity was 71.4% (5/7), the specificity was 68.1% (81/119), and the accuracy result was 68.3% (86/126). Among the 30.2% (38/126) of samples with positive PCR and negative blood culture, 66 items were specifically detected (*Table 4*).

Discussion

Blood culture is a classic method for detecting pathogenic microorganisms in blood, and it is still the gold standard for isolating and identifying pathogenic microorganisms in bloodstream infections (13). However, blood culture also has some shortcomings determined by the characteristics of the method itself, which restrict the speed and sensitivity of its detection (14). For example, it takes a certain amount of time for bacteria to divide and multiply to detectable levels. This speed is related to the bacterial species. Some bacteria grow slowly, and fastidious bacteria do not even grow, making blood cultures slow. The sensitivity for detecting neonatal bloodstream infections is low due to the small amount of blood used for detection and the low bacterial counts in the blood. In addition, blood culture has certain challenges including that the positive rate of blood cultures decreases significantly after antibiotic treatment, blood cultures can only detect viable microorganisms, and antibiotic treatment kills bacteria and reduces the detection rate (15,16). The above factors considerably reduce the speed and sensitivity of blood culture in diagnosing bloodstream infections. Therefore, clinical diagnosis and treatment urgently need a sensitive method to quickly and accurately identify pathogenic microorganisms in bloodstream infections.

PCR is a molecular biology technique used to amplify a specific DNA fragment, which can be regarded as DNA replication outside the organism. With the continuous development and innovation of current medical technology, PCR is rapidly replacing traditional microbial detection

Table 3 Mixed infection of pathogens detected by PCR

Pathogen	Patients number of Infection species			
	Single species (n=30)	Double species (n=8)	Triple species (n=5)	Quadruple species (n=1)
Epstein-Barr virus	19	4	3	1
Klebsiella_pneumoniae	1	2	2	0
Escherichia coli	1	0	1	0
Acinetobacter baumannii	0	0	1	0
Stenotrophomonas maltophilia	1	0	2	1
Pseudomonas aeruginosa	1	0	1	0
herpesvirus 1	0	1	0	0
Klebsiella oxytoca	0	1	0	0
Staphylococcus	3	2	0	0
Human herpes virus 5	1	4	3	1
VIM	1	0	0	0
Rickettsia felis	1	0	0	0
Enterococcus faecium	0	0	0	1
ampC	0	0	1	0
Mycobacterium tuberculosis complex	0	1	1	0
KPC	0	1	0	0
Human metapneumo virus	1	0	0	0

PCR, polymerase chain reaction.

Table 4 Sensitivity, specificity, PPV, and NPV of PCR detection

		Blood culture			Sensitivity	Specificity	Accuracy	PPV	NPV
		Positive	Negative	Total					
PCR	Positive	5	38	43	0.71	0.68	0.68		
	Negative	2	81	83				0.12	0.98
	Total	7	119	126					

PPV, positive prediction value; NPV, negative prediction value; PCR, polymerase chain reaction.

methods (17,18). This technology can complete the PCR reaction and product analysis process in one reaction tube. Conducting dynamic monitoring and analysis of corresponding data reduces the incidence of cross-infection. In addition, the operation method of fluorescent PCR technology is relatively simple, the operation speed is fast, the quantification is reasonably accurate, the sensitivity is high, the operation can be repeated, and the application value is high (19). Selva *et al.* used PCR to detect Streptococcus pneumoniae in 128 blood culture flasks and obtained 94.0% specificity and 98.4% specificity (10). Arabestani *et al.* used multiplex PCR to identify Staphylococcus aureus, coagulase-negative staphylococcus, Enterococcus, Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacter baumannii in blood culture-positive specimens, and the time spent was significantly less than traditional blood culture identification (11). In another study of 285 patients with pyrexia, the positive rate of PCR

detection was 17.2%, which was higher than the positive rate of ordinary blood culture. In this study, of the 126 samples, the positive detection rate of PCR detection was 65.9% (83/126) (20).

This study compared blood culture with PCR to detect pathogenic microorganisms in bloodstream infections. The PCR detection was positive, while blood culture-negative samples accounted for 30.2%. Similar detection by Lucignano *et al.* showed that the rate of *SeptiFast* detection was 36.3% (21). A study showed that the detection rate was only 19.4% (22). The results of previous study showed that the sensitivity range of PCR was 66–85%, and the specificity was 87–93% compared to blood culture (21,22). This study's sensitivity is 71.4%, but the specificity is relatively low (68.1%). This study is a single-center observational study, which may limit the generalizability of the findings.

The PCR is positive when the corresponding pathogen is also detected in other body parts. At the same time, a negative blood culture specimen reflects the accurate result to a certain extent. Whether there is an association between bacterial DNA in the blood and the development of systemic inflammatory response syndrome and sepsis remains controversial. Some studies have found that the appearance of cell-free DNA in the blood is a risk factor for evaluating multiple organ failure in intensive care unit (ICU) patients (23,24). Therefore, PCR can not only be used to detect unknown pathogens or their DNA, but also provide valuable clinical information. This is difficult to achieve with conventional blood cultures.

Conclusions

In summary, PCR detection can rapidly and sensitively detect pathogens in patients with bloodstream infections, even if the patient has been on antibiotics. However, unlike blood cultures, PCR assays do not provide information on the resistance of infectious pathogens. Therefore, the extensive use of PCR detection combined with blood culture detection can offer an immediate treatment plan for clinical patients, reduce the generation of drug-resistant bacteria, and facilitate the recovery of patients.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1071/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1071/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1071/coif). YZ and RB are from Bingyuan Medical Technology Co., LTD., Shanghai, China. They performed the data analysis and interpretation in this study, and have no financial support from their company. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the First Hospital of Hebei Medical University (No. 20220816), and the patients and their families knew and gave informed consent.

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Supplementary

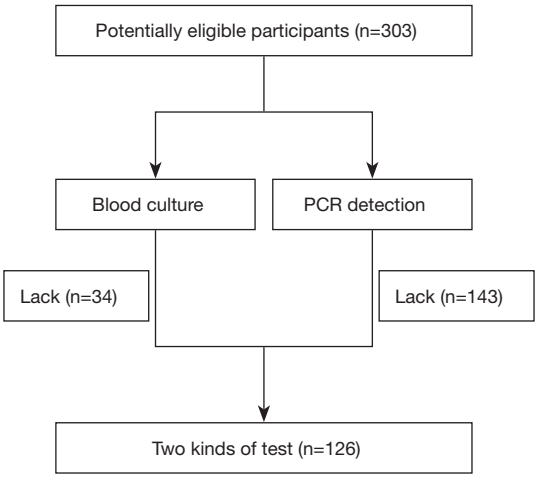

Figure S1 Flow of participants. The potential eligible participants were 303. However, 143 patients lacked the real-time polymerase chain reaction (PCR) detection, and 34 lacked blood cultures, including patients not tested by either method. In the end, 126 patients underwent both tests.

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Table S1 Characteristics of the patients

Patients No.	Gender	Age	PCR detection	Blood culture
P1	Male	71	Negative	Negative
P2	Male	61	Positive	Positive
P3	Female	49	Positive	Positive
P4	Female	71	Negative	Negative
P5	Female	95	Positive	Negative
P6	Male	31	Positive	Negative
P7	Male	61	Negative	Positive
P8	Female	71	Negative	Negative
P9	Male	56	Negative	Negative
P10	Male	76	Positive	Negative
P11	Male	56	Positive	Negative
P12	Female	49	Negative	Negative
P13	Male	35	Negative	Negative
P14	Male	66	Positive	Negative
P15	Male	56	Negative	Negative
P16	Male	61	Positive	Positive
P17	Female	67	Negative	Negative
P18	Male	66	Negative	Negative
P19	Male	50	Positive	Negative
P20	Female	53	Negative	Negative
P21	Male	83	Negative	Negative
P22	Male	46	Negative	Negative
P23	Female	34	Negative	Negative
P24	Male	84	Negative	Negative
P25	Male	31	Negative	Negative
P26	Male	18	Negative	Negative
P27	Male	66	Positive	Positive
P28	Female	84	Positive	Positive
P29	Female	70	Positive	Negative
P30	Male	67	Positive	Negative
P31	Female	84	Positive	Negative
P32	Female	98	Negative	Negative
P33	Male	86	Negative	Negative
P34	Male	88	Negative	Positive
P35	Male	35	Negative	Negative
P36	Male	66	Negative	Negative
P37	Female	65	Negative	Negative
P38	Female	84	Positive	Negative
P39	Male	48	Negative	Negative
P40	Male	57	Negative	Negative
P41	Female	84	Negative	Negative
P42	Male	30	Negative	Negative
P43	Male	67	Negative	Negative
P44	Female	36	Negative	Negative
P45	Male	35	Negative	Negative
P46	Male	82	Negative	Negative
P47	Male	54	Negative	Negative
P48	Female	66	Negative	Negative
P49	Male	56	Negative	Negative
P50	Female	51	Negative	Negative
P51	Male	90	Negative	Negative
P52	Male	42	Negative	Negative
P53	Male	38	Negative	Negative
P54	Male	82	Negative	Negative
P55	Male	38	Negative	Negative
P56	Female	60	Positive	Negative
P57	Male	74	Negative	Negative
P58	Male	53	Negative	Negative
P59	Male	52	Positive	Negative
P60	Male	66	Negative	Negative
P61	Female	32	Positive	Negative
P62	Female	51	Negative	Negative
P63	Female	62	Negative	Negative
P64	Male	38	Negative	Negative
P65	Female	62	Negative	Negative
P66	Male	75	Positive	Negative
P67	Female	79	Positive	Negative
P68	Female	61	Positive	Negative
P69	Female	55	Negative	Negative
P70	Male	49	Positive	Negative
P71	Female	57	Negative	Negative
P72	Male	38	Negative	Negative
P73	Female	79	Negative	Negative
P74	Female	55	Negative	Negative
P75	Male	49	Negative	Negative
P76	Male	32	Positive	Negative
P77	Female	62	Negative	Negative
P78	Male	79	Positive	Negative
P79	Male	82	Positive	Negative
P80	Female	57	Positive	Negative
P81	Male	52	Positive	Negative
P82	Male	62	Positive	Negative
P83	Male	80	Positive	Negative
P84	Male	60	Positive	Negative
P85	Female	54	Positive	Negative
P86	Male	31	Negative	Negative
P87	Male	43	Negative	Negative
P88	Male	49	Negative	Negative
P89	Male	64	Positive	Negative
P90	Male	80	Negative	Negative
P91	Male	43	Positive	Negative
P92	Female	76	Positive	Negative
P93	Male	43	Negative	Negative
P94	Female	65	Negative	Negative
P95	Female	51	Positive	Negative
P96	Male	44	Positive	Negative
P97	Female	30	Negative	Negative
P98	Female	48	Negative	Negative
P99	Male	46	Negative	Negative
P100	Female	71	Positive	Negative
P101	Female	65	Negative	Negative
P102	Male	67	Negative	Negative
P103	Female	64	Negative	Negative
P104	Male	71	Negative	Negative
P105	Male	73	Negative	Negative
P106	Female	65	Negative	Negative
P107	Male	68	Negative	Negative
P108	Male	73	Negative	Negative
P109	Female	64	Negative	Negative
P110	Male	52	Negative	Negative
P111	Male	56	Negative	Negative
P112	Female	73	Negative	Negative
P113	Female	64	Negative	Negative
P114	Male	60	Negative	Negative
P115	Male	73	Negative	Negative
P116	Female	62	Positive	Negative
P117	Female	56	Negative	Negative
P118	Male	85	Negative	Negative
P119	Male	54	Positive	Negative
P120	Female	56	Negative	Negative
P121	Female	62	Positive	Negative
P122	Male	42	Negative	Negative
P123	Male	60	Positive	Negative
P124	Male	42	Negative	Negative
P125	Male	55	Positive	Negative
P126	Female	54	Positive	Negative

PCR, the real-time polymerase chain reaction.

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