RESEARCH ARTICLE

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# Impact of Rapid Molecular Diagnostic Technique on Time to Optimal Antimicrobial Therapy and Hospital Outcomes in Pediatric Cancer Patients with Sepsis

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## Abstract

**Background:** sepsis is a leading cause of morbidity and mortality in pediatric cancer patients. We sought to assess the impact of using rapid molecular diagnostic techniques on time to pathogen identification, early administration of targeted antimicrobial treatment, and hospital outcomes. **Patients and methods:** This prospective study was conducted at the Egyptian National Cancer Institute (1/2018-1/2019) on pediatric cancer patients with suspected sepsis. The cohort was divided into two groups. In one group, blood samples were sent for rapid molecular detection [multiplex-Polymerase Chain Reaction (PCR)] and blood cultures (PCR-group). While only blood cultures were collected for the second group (BC-group). **Results:** In the entire cohort (n=120), the most common bacteria identified on blood cultures was Escherichia Coli (n=33,27.5%) followed by Klebsiella (n=31,25.8%). Multidrug-resistant bacteria were identified in 63 patients (52.5%). The median turnaround time to initial results was 5 hours in PCR-group (n=60), and 120 hours in BC-group (n=60)(P<0.001). For PCR-group, agreement in pathogen identification between the rapid molecular detection kit (PCR) and blood cultures was noted in 56 patients (93.3%). While the remaining four patients had no bacterial growth on blood cultures. The empirical antibiotic treatment for the PCR-group was modified based on the result of the PCR test. Antibiotic shift, based on blood culture sensitivity results, was done in 29 patients (48%) in PCR-group, compared to 45 patients (75%) in BC-group (P=0.003). Median sepsis episode duration [8-days vs. 10-days,P=0.361), and hospital mortality (42% vs. 50%, P=0.360) were slightly lower in PCR-group. However, this did not reach statistical significance. **Conclusion:** There was a substantial agreement in pathogen identification between the rapid molecular detection method (PCR) and blood culture results. PCR had a much shorter turnaround time, which allows for earlier start of optimal antimicrobial treatment, and might potentially improve hospital outcomes, which in turn will reduce associated health care costs.

**Keywords:** Molecular- PCR- sepsis- children- pediatric- oncology- cancer

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## Introduction

Despite the recent advances in antibiotic therapies and medical care of critically ill patients, sepsis continues to be one of the leading causes of morbidity and mortality in pediatric cancer patients (Verroken et al., 2016). Current aggressive systemic therapy regimens leads to significant immunosuppression and subsequent major infections (Adamsky et al., 2008). Unfortunately, conventional blood cultures results may take up to 7 days to be available, a significantly lengthy time given the gravity of those patients' condition and expected poor prognosis. In addition, conventional blood cultures were not able to identify causative micro-organisms in about half of the patients with suspected sepsis and in up to three quarters of those with febrile neutropenia (Dutka-Malen et al., 1995). Therefore, adequate prevention, rapid accurate diagnosis, and early administration of proper antibiotic treatment are of paramount importance to improve patients' outcome. There has been an ongoing need to develop techniques that can provide accurate diagnostic information in a timely fashion. Which will, in turn, allow for a more informed use of antibiotic therapy at an early stage of the infectious process (Warhurst et al., 2015).

The development of novel molecular assays has allowed for the rapid detection and identification of causative bacteria. Those tests use PCR techniques to identify bacterial-specific DNA within a few hours of suspected sepsis, compared to 3-7 days for the conventional blood culture technique (Guido et al., 2016). By reducing time to pathogen identification and potentially detecting organisms that may get missed by conventional

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blood cultures, those molecular diagnostic methods can have a huge impact on improving patients' outcomes and reducing hospital and Intensive Care Unit (ICU) stays. In addition, prompt switch to narrower-spectrum antibiotics allows for judicious use of antibiotics and helps reduce the development of antibiotics resistance (Liesenfeld et al., 2014; Greco et al., 2018).

The primary objective of this study was to assess the impact of rapid molecular diagnostic technique (multiplex PCR) on reducing the turnaround time of pathogen identification and the early administration of targeted antimicrobial treatment. Secondary outcomes included assessing whether the use of rapid molecular diagnostic technique (multiplex PCR) would have an effect on patients' outcomes and hospital stay.

## Materials and Methods

The National Cancer Institute Ethical Committee's approval was granted for this study.

*Study design and patients' population*

This prospective study was conducted at the Egyptian National Cancer Institute between January 2018 and January 2019. The study included 120 pediatric cancer patients who were clinically suspected to have sepsis according to SIRS criteria (Singer et al., 2016). The study cohort was divided into two groups, each of 60 patients. In the first group, blood samples were sent for rapid molecular detection (multiplex-PCR) and blood cultures (PCR group). While only blood cultures were collected for the second group (BC group). Inclusion in study groups was done on an intention to treat basis.

*Microbiological methods:*

*Conventional blood cultures and Antibiotic Susceptibility*

Blood cultures were done using Bactec 9120 and Bact/Alert systems (bioMérieux, Marcy l'Etoile, France), incubated for up to 7 days; and susceptibility test were done using manual disc diffusion method and automated method using Vitek 2 system (bioMérieux, Marcy l'Etoile, France).

According to the standard method established by the Clinical and Laboratory Standard institute 2016; susceptibility of the bacterial isolates to Amoxicillin/clavulanic acid (AMC), Ampicillin/sulbactam (SAM), Piperacillin/tazobactam (TZP), Trimethoprim/sulphamethoxazole (SXT), Aztreonam (ATM), Cefotaxime (CTX), Cefotriaxone (CRO), Ceftazidime (CAZ), Cefuroxime (CXM), Cefoxitin (FOX), Cefipime (FEP), Amikacin (AK), Gentamycin (GN), Tobramycin (TOB), Ciprofloxacin (CIP), Levofloxacin (LEVO), Imipenem (IPM), Meropenem (MEM), Etrapenem (ETP), Tigecycline (TGC), Colistin (CT) and Vancomycin (VA) were determined by standard Kirby-Bauer disc diffusion method. According to the Centers for Disease Control and Prevention (CDC); the isolates that showed resistance to three or more antibacterial agents from different classes were regarded as multi-drug resistant (MDR) (Alqasim et al., 2018).

The Vitek 2 Compact system (30 card capacity) uses a fluorogenic methodology for organism identification and a turbidimetric method for susceptibility. Available test kits included gram negative bacilli identification (ID-GN), gram positive cocci identification (ID-GP), gram-negative susceptibility (AST-GN) and gram-positive susceptibility (AST-GP).

*Rapid molecular detection test (PCR)*

Rapid molecular detection test (PCR) was done using the Light Cycler SeptiFast Test M Grade (Roche Molecular Systems). It is an in-vitro nucleic acid amplification test to detect and identify a wide range of Gram-negative bacteria [Escherichia Coli (E. Coli), Klebsiella (Pneumoniae/Oxytoca), Serratia Marcescens, Enterobacter (Cloacae/Aerogenes), Proteus Mirabilis, Acinetobacter Baumannii, Pseudomonas Aeruginosa and Stenotrophomonas Maltophilia], Gram-positive Bacteria (Staphylococcus Aureus, coagulase-negative Staphylococci, Streptococcus Pneumonia, Streptococcus Saprophyticus, Enterococcus Faecium and Enterococcus Faecalis) and fungal pathogens (Candida Albicans, Candida Tropicalis, Candida Parapsilosis, Candida Glabrata, Candida Krusei and Aspergillus Fumigatus). The assay uses dual fluorescence resonance energy transfer probes targeting the species-specific internal transcribed spacer (ITS) regions. These regions are multicopy non-coding sequences interspaced among highly conserved bacterial and fungal rDNA that have already been used as target for the identification of microbial pathogens.

*Statistical Analysis*

Numerical variables were expressed as median [Interquartile range (IQR)] and were compared across the groups using Mann-Whitney U test. Categorical variables were expressed as numbers (percentage) and were compared across the study groups using Chi square test or Fisher's exact test. The correlation and agreement between the PCR and blood culture results were estimated by Pearson's R correlation coefficient and Kappa statistics. Logistic-regression analysis was used to study factors associated with in-hospital mortality in the entire cohort. Variables included in the univariable analysis were age, gender, ICU admission, diagnosis, time from admission to infection, episode duration, invasive procedures, study groups, organism type, presence of mixed infection, antimicrobial resistance, neutrophil count, temperature, fever at day 7, tachycardia, tachypnea, and hypotension. Variables with P-value <0.1 were included in the multivariable model.

For all statistical analyses, a two-tail P-value <0.05 was considered statistically significant. Data analyses were performed using IBM SPSS software (version 25.0; SPSS, Inc., Chicago, IL).

## Results

This study prospectively enrolled 120 pediatric cancer patients suspected to have sepsis according to the revised consensus conference definition criteria in 2001 (Sepsis 2). The majority of the patients were males (n=69, 57.5%), and the median patients' age was 7 years (IQR 4-13) (Table

1). Patients' primary diagnosis included Acute Lymphoid Leukemia (ALL, 44%), Acute Myeloid Leukemia (AML, 27%), solid tumor (18%), and Non-Hodgkin Lymphoma (NHL, 11%). The majority of patients (75%) had their sepsis episode during the induction phase of systemic treatment, and 84% of the patients were neutropenic at the time of sepsis diagnosis (Table 1).

*Microbiological results by conventional blood culture technique*

The most common bacteria identified by blood cultures were E. coli (n=33/120, 27.5%) followed by Klebsiella (n=31/120, 25.8%), and Acinetobacter (n=11/120, 9.2%) (Table 2). More than half of the patients (n= 63, 52.5%) had multidrug resistant bacteria, including 84.9% of E. coli isolates and 71% of Klebsiella isolates.

Only one patient had a gram-positive bacteria [Methicillin Resistant Staph Aureus (MRSA)]. In patients with gram negative bacteria, the maximum resistance was noted against Cephalosporins (i.e., Cefuroxime, 94%), followed by Augmentin (93%). Minimum resistance was noted against Tigecycline (20%) and Colistin (9%). Resistance against Aminoglycosides such as Amikacin and Gentamycin was (59%) and (61%), respectively (Figure 1).

Enterobacteriaceae like E. coli showed maximum resistance against Cephalosporins such as Ceftriaxone and Cefuroxime (100%), followed by Augmentin (94%). It also showed a high resistance level against Carbapenems [Imipenem (81.9%) and Meropenem (84.9%)]. While it showed a moderate resistance to Amikacin (41.4%) and Gentamycin (53.8%). Klebsiella isolates were highly resistant to Cephalosporins such as Ceftazidime and Cefotaxime (87.1%), and to Augmentin (86.1%). While it showed moderate level of resistance against GN (53.3%), AK (61.3%). Resistance against IPM, MEM and Ciprofloxacin was 71% for each.

The Non-fermenters (i.e., Acinetobacter) also showed a higher resistance level against Cephalosporins such as Ceftriaxone and Cefuroxime (100% for each), as well as

Table 1. Patients' Demographic and Clinical Characteristics of the Entire Cohort (n=120).

| Variable | No. (%) |
|---|---|
| Age, in years (median, IQR) | 7 (4-13) |
| Gender | |
| Male | 69 (57.5) |
| Female | 51 (42.5) |
| Primary Diagnosis | |
| ALL | 53 (44.2) |
| AML | 32 (26.7) |
| Solid Tumor | 22 (18.3) |
| NHL | 13 (10.8) |
| State of the Disease | |
| Induction | 90 (75) |
| Maintenance | 17 (14.2) |
| Relapse | 13 (10.8) |
| ICU Admission | 30 (25) |
| From admission to infection | |
| ≤7 days | 11 (9.2) |
| 8-30 days | 42 (35) |
| >30 days | 67 (55.8) |
| Neutropenia | 101 (84.2) |
| Fever at 7th day of infection | 83 (69.2) |

ALL, Acute Lymphocytic Leukemia; AML, Acute Myeloid Leukemia; ICU, Intensive Care Unit; IQR, Interquartile Range; NHL, Non-Hodgkin Lymphoma

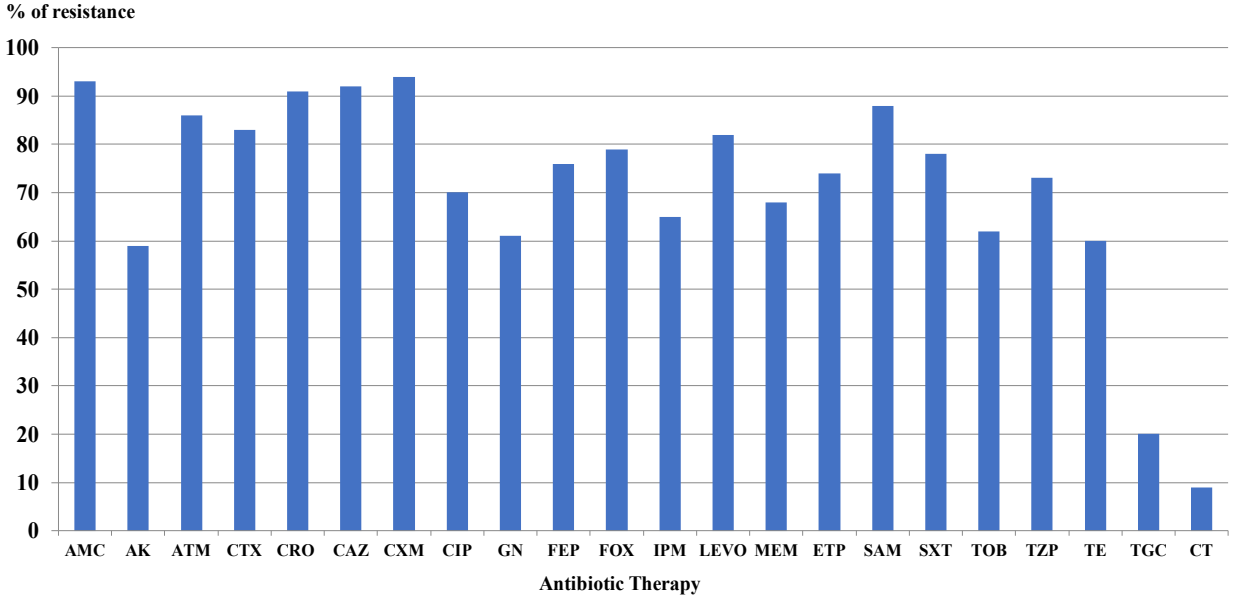


Figure 1. Antibiotic Resistance Pattern of the Study Cohort Isolates. AK, Amikacin; AMC, Ampicillin-Clavulanic acid; ATM, Aztreonam; CAZ, Ceftazidime; CIP, Ciprofloxacin; CRO , Ceftriaxone; CT, Colistin; CTX, Cefotaxime; CXM, Cefixime; ETP, Etrapenem; FEP, Cefepime; FOX, Cefoxitin; GN, Gentamycin; IPM, Imipenem; LEVO, Levofloxacin; MEM, Meropenem; SAM, Ampicillin-Sulbactam; SXT, Sulfamethoxazole /Trimethoprim; TE, Tetracycline; TGC, Tigecycline; TOB, Tobramycin; TZP, Piperacillin-Tazobactam

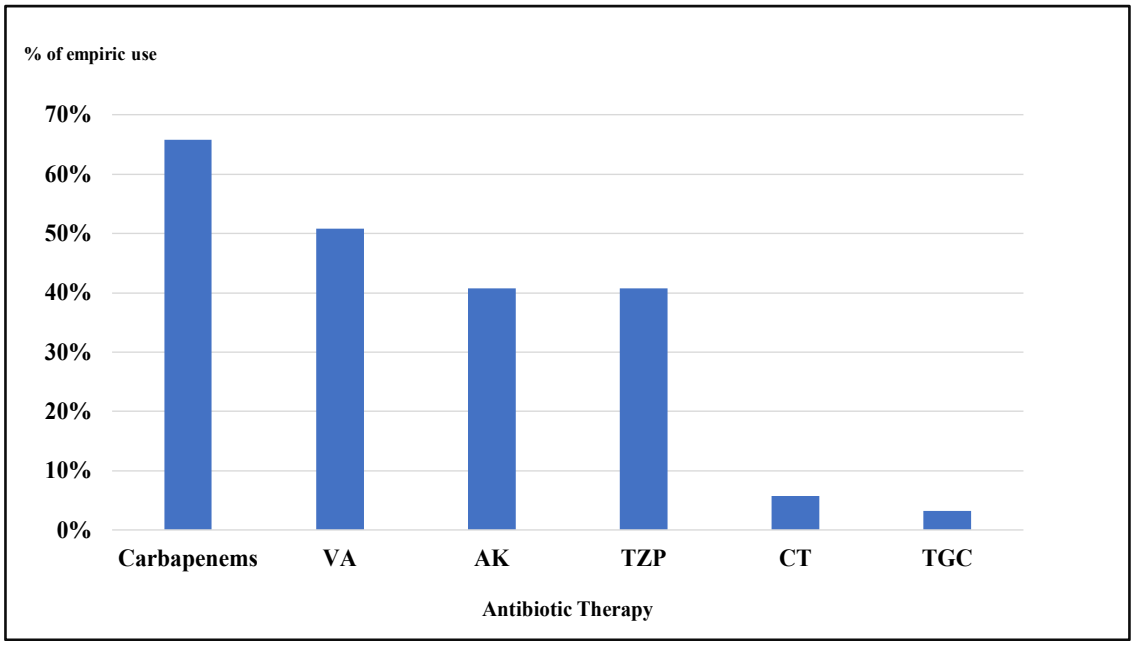


Figure 2. Empirical Antibiotic Treatment. AK, Amikacin; CT, Colistin; TGC, Tigecycline; TZP, Piperacillin-Tazobactam; VA, Vancomycin

Table 2. Microbiological Characteristics of the Entire Cohort (n=120).

| Blood culture organism | No. (%) | MDR isolates No. (%) |
|---|---|---|
| E Coli | 33 (27.5) | 28 (84.9) |
| Klebsiella | 31 (25.8) | 22 (71) |
| Acinetobacter | 11 (9.2) | 8 (72.7) |
| Pseudomonas | 9 (7.5) | 3 (33.3) |
| Enterobacter | 2 (1.7) | 1 (50) |
| Serratia | 7 (5.8) | 1 (14.3) |
| Staph Aureus | 1 (0.8) | - |
| NBG | 26 (21.7) | - |

MDR, Multi-Drug Resistant; NBG, No Bacterial Growth

Cefotaxime and Cefipime (72.7% for each). While it was less resistant to IPM (55.5%) and Amikacin 60%.

*Results of rapid diagnostic technique (Multiplex PCR)*

Out of the 60 isolates that were detected by the rapid molecular detection kit method; 13 isolates (22%) were E. coli, 13 isolates (22%) were Klebsiella, 8 isolates (13%) were Acinetobacter Baumanii, 2 isolates (3%) were Pseudomonas Aeruginosa, 1 isolate (2%) was Enterobacter Cloacae, and 1 isolate (2%) was Staphylococcus Aureus. While no bacteria were identified in the remaining 22 isolates (36%). There was a high agreement between the results of the rapid molecular detection kit method (PCR) and conventional blood cultures results (56 cases, 93.3%). Pearson's R correlation coefficient between PCR and Blood culture results was 0.898 (SE 0.052). While in the remaining four samples, bacterial isolates were detected by PCR method and no bacterial growth was noted on blood culture; this may be due to collection of blood culture samples after starting antibiotic therapy (Table. 3). Pearson's R correlation coefficient between PCR and Blood culture results was 0.898 (SE 0.052).

*Antibiotic therapy and hospital outcomes*

Empirical antibiotic therapy was given according

Table 3. Agreement between Rapid Molecular Detection and Blood Culture Results in the PCR Group (n=60)

| Blood Culture | PCR | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | E Coli No. (%) | Klebsiella No. (%) | Acinetobacter No. (%) | Pseudomonas No. (%) | Staph A No. (%) | NBG No. (%) | Enterobacter No. (%) | Total No. (%) |
| E Coli | 12 (92) | | | | | | | 12 (20) |
| Klebsiella | | 12 (92) | | | | | | 12 (20) |
| Acinetobacter | | | 6 (75) | | | | | 6 (10) |
| Pseudomonas | | | | 2 (100) | | | | 2 (3) |
| Staph A | | | | | 1 (100) | | | 1 (2) |
| NBG | 1 (8) | 1 (8) | 2 (25) | | | 22 (100) | | 26 (43) |
| Enterobacter | | | | | | | 1 (100) | 1 (2) |
| Total | 13 (100) | 13 (100) | 8 (100) | 2 (100) | 1 (100) | 22 (100) | 1 (100) | 60 (100) |

Orange color, agreement between PCR and blood culture; Blue color, disagreement between PCR and blood culture. NBG, No Bacterial Growth; PCR, Polymerase W

Table 4. Antibiotic Shift and Mortality of the Study Groups Patients

| Parameter | PCR group (n=60) No. (%) | BC group (n=60) No. (%) | P value |
|---|---|---|---|
| Antibiotic shift | | | |
| Yes | 29 (48) | 45 (75) | 0.003 |
| No | 31 (52) | 15 (25) | |
| Antibiotic shifted to | | | |
| Carbapenem | 4 (14) | 12 (27) | 0.252 |
| AK | 1 (3) | 18 (40) | <0.001 |
| VA | 2 (7) | 2 (4) | 0.642 |
| TZP | 3 (10) | 0 (0) | 0.056 |
| CT | 21 (72) | 21 (47) | 0.029 |
| TGC | 8 (28) | 17 (38) | 0.336 |
| Hospital mortality | 25 (42) | 30 (50) | 0.36 |

AK, Amikacin; BC, Blood Culture; CT, Colistin; TGC, Tigecycline; PCR, Polymerase Chain Reaction; TZP, Tazobactam Piperacillin; VA, Vancomycin

to our local institutional guidelines which were adopted according to the Infectious Disease Society of America (IDSA) and the National Comprehensive Cancer Network (NCCN) guidelines.

For the entire study cohort (120 patients), Carbapenems were the most commonly used empirical antibiotic treatment (n=79,65.8%) followed by VA (61, 50.8%). AK and TZP were used in 49 patients (40.8%). CT was used in 7 patients (5.8%) and TGC was used in 4 patients (3.3%) (Figure 2).

The empirical antibiotic treatment for the PCR group was modified based on the result of the PCR test. After the blood cultures results, antibiotic treatment was shifted in 29 patients (48%). While in the BC group, antibiotic shift was done in 45 patients (75%), (P. value 0.003). The median turnaround time from blood sample collection to initial pathogen identification was 5 hours (IQR 4-6 hours) for the PCR group, and 120 hours (IQR 96-144 hours) for BC group, (P value <0.001). The median sepsis episode duration (8-days vs. 10-days, P=0.361), and in-hospital mortality (42% vs. 50%, P=0.360) were slightly lower in PCR Group patients. However, this did not reach statistical significance level (Table 4).

Factors associated with in-hospital mortality were explored in the entire cohort (n=120) using logistic regression analysis. On univariable analysis, factors associated with higher in-hospital mortality were ICU admission (OR: 3.84, 95% CI: 1.58-9.36, P=0.003), onset of infection within 7 days from admission (OR: 4.78, 95% CI: 1.16-19.72, P=0.031), type of organism [no bacterial growth (NBG): reference, Lactose fermenters (OR: 13, 95% CI: 2.82-60.01, P = 0.001), and non- lactose fermenters (OR: 9.33, 95% CI: 1.84-47.44, P=0.007)], MDR / Carbapenems resistance [OR: 7.28, 95% CI: 2.64-20.08, P <0.001), and high grade fever / hypothermia (OR: 2.39, 95% CI: 1.06-5.37, P = 0.035). In the multivariable model, the only factor that was associated with higher in-hospital mortality was ICU admission (OR: 3.49, 95% CI: 1.15-10.66, P=0.028) (Table 5).

## Discussion

This study included 120 critically ill pediatric cancer patients with sepsis, divided into two groups [PCR + blood culture (PC group) vs. blood culture alone (BC group)]. We found a significantly high agreement in pathogen identification between PCR results and conventional blood culture results, yet with a significantly shorter turnaround time, a lower rate of antibiotic shifts following final blood cultures sensitivity results, and favorable patients' outcomes (i.e., sepsis duration and hospital mortality).

We performed a thorough literature search in PubMed and Google Scholar databases using the key words (pediatric, children, cancer, oncology, molecular, PCR, sepsis, bacteria). There is a paucity of data on the role of molecular diagnostic techniques in pediatric cancer patients, with only few studies reporting on its diagnostic accuracy. To the best of our knowledge, this is the first study to report on the association of using PCR diagnostic techniques with pediatric cancer patients' outcomes, compared with the sole use of conventional blood culture.

Quiles et al., (2015) explored the potential role of rapid molecular PCR diagnostic technique in a single arm study that included 137 pediatric cancer patients with clinically suspected sepsis. The mean age of their patients was 9 years old, which is slightly older than our patients (7-years old), and male gender comprised 54% of their study population which is comparable to the 57% reported in our study. In Quiles et al., (2015) study, only 49% of blood cultures were positive for bacterial growth, compared to 64% in our PCR group. Unlike our results which showed a significant predominance of gram-negative organisms, Quiles et al., (2015) study reported that gram negative organisms were detected in only one third of their patients. Similar to our findings, PCR results showed excellent sensitivity and specificity (90% and 88%) in reference to the gold standard conventional blood cultures results. Unfortunately, Quiles et al., (2015) study did not report patients' clinical outcomes.

Shachor-Meyouhas et al., (2013) explored the diagnostic accuracy of PCR molecular techniques in 148 blood cultures drawn from 70 pediatric hematology / oncology patients with central venous catheters who developed fever. Blood cultures were positive for bacterial growth in only 18%, and the sensitivity and specificity of PCR was found to be 46% and 98%, respectively. PCR identified bacteria in 2 patients with negative blood culture.

In a pilot study by Ammann et al. (2007), the authors explored the diagnostic accuracy of PCR in 45 blood samples from pediatric oncology patients with neutropenic fever. They reported that PCR assay was able to identify bacterial isolates in three out of ten blood samples with positive blood culture, and in 10 out of 25 blood culture negative samples.

Given the paucity of data on the role of PCR in pediatric cancer patients, we expanded our literature review to include studies reporting on adults and non-cancer patients. We then compared predominant bacterial isolates and antibiotic sensitivity in our patients' culture samples to those reported in other studies.

Table 5. Logistic Regression Analysis of Factors associated with Hospital Mortality

| Variables | Univariable analysis | | Multivariable analysis* | |
|---|---|---|---|---|
| | Odds ratio (95% CI) | P value | Odds ratio (95% CI) | P value |
| Age | 1.05 (0.98-1.12) | 0.154 | | |
| Gender (Male) | 1.21 (0.58-2.50) | 0.61 | | |
| ICU admission | 3.84 (1.58-9.36) | 0.003 | 3.49 (1.15-10.66) | 0.028 |
| Diagnosis | | | | |
| Solid tumors | Reference | | | |
| Lymphoma | 1.84 (0.45-7.54) | 0.399 | | |
| Leukemia | 2.09 (0.78-5.65) | 0.145 | | |
| From admission to infection | | | | |
| >30 days | Reference | | | |
| 8-30 days | 2.17 (0.99-4.76) | 0.054 | 1.44 (0.58-3.55) | 0.433 |
| =<7 days | 4.78 (1.16-19.72) | 0.031 | 4.26 (0.76-23.95) | 0.1 |
| Episode duration (days) | 1.07 (0.97-1.18) | 0.156 | | |
| Invasive procedure | | | | |
| Study group | | | | |
| PCR group | Reference | | | |
| BC group | 1.40 (0.68-2.88) | 0.36 | | |
| Organism | | | | |
| NBG | Reference | | Reference | |
| LF | 13.00 (2.82-60.01) | 0.001 | 4.16 (0.52-33.39) | 0.18 |
| Non-LF | 9.33 (1.84-47.44) | 0.007 | 2.97 (0.34-25.90) | 0.325 |
| Mixed infection | 1.81 (0.77-4.26) | 0.173 | | |
| Resistance | | | | |
| No resistance | Reference | | Reference | |
| ESBL / MRSA | 3.89 (0.89-17.06) | 0.072 | 2.22 (0.33-14.91) | 0.412 |
| MDR / Carbapenem | 7.28 (2.64-20.08) | <0.001 | 3.22 (0.70-14.78) | 0.133 |
| CT / TGC | 3.89 (0.89-17.06) | 0.072 | 1.38 (0.17-11.56) | 0.767 |
| Neutrophils count | | | | |
| Normal/Neutrophilia | Reference | | | |
| Neutropenia | 1.20 (0.44-3.22) | 0.722 | | |
| Temperature | | | | |
| Low grade fever | Reference | | Reference | |
| High grade fever / Hypothermia | 2.39 (1.06-5.37) | 0.035 | 2.48 (0.95-6.44) | 0.062 |
| Fever at day 7 | 1.89 (0.85-4.21) | 0.119 | | |
| Heart Rate (tachycardia) | 0.99 (0.31-3.13) | 0.98 | | |
| Resp. Rate (tachypenia) | 2.05 (0.60-7.06) | 0.256 | | |
| Blood pressure (hypotension) | 1.21 (0.36-4.04) | 0.76 | | |

* Variables with P-Value <0.1 were included in the multivariable model. BC, Blood Culture; CT, Colistin; ESBL, Extended Spectrum Beta Lactamase; ICU, Intensive Care Unit; LF, Lactose Fermenter; MDR, Multidrug Resistant; MRSA, Methicillin Resistant Staph A; NBG, No Bacterial Growth; PCR, Polymerase Chain Reaction; TGC, Tigecycline

In the current study, over three quarters of the patients had gram-negative organisms, mainly Enterobacteriaceae and Klebsiella. Similar findings of gram-negative predominance in septic patients were reported by several studies. Babu et al., (2018) studied 293 bacterial isolated from patients with severe sepsis / septic shock presenting to the ED of a tertiary hospital. They found that the most common isolates were E. coli (20.8%), followed by Klebsiella pneumonia (18.8%) and Pseudomonas aeruginosa (7.8%). Zboromyrska et al., (2019) studied 809 blood samples from 636 adult patients with suspected sepsis using both molecular testing and conventional blood cultures. They reported a high agreement between PCR and blood cultures results in 87% of the samples. Also, similar to our findings, there was a predominancy of gram negative bacterial isolated, particularly Enterobacteriaceae (E. coli, 33.6%).

MDR bacteria are one of the most important public health problems. The prevalence of MDR bacteria is closely related to the use of broad-spectrum antibiotics,

both for empiric and definitive therapy. This increased use, in turn, leads to even higher rates of MDR bacteria, thus creating a vicious cycle that leads to bad outcomes compared to that of patients who infected with susceptible organisms (Van Duin, 2016).

More than half of our patients (52.5%) were infected by multidrug resistant bacteria, particularly those with E. coli (84.9%) and Klebsiella isolates (71%). Patel et al., (2012) studied antibiotic resistance in 583 culture samples from critically ill patients in the intensive care unit. The authors found a high level of MDR among gram negative isolates, particularly E. coli / Klebsiella (80%), Pseudomonas species (79%), and Acintobacter (77%). In another study done in Saudi Arabia by Alqasim et al., (2008), out of 100 urine samples positive for E. coli, 67% had MDR isolates.

This study is limited by the relatively small number of patients included and the lack of randomization and blinding. Also, the lack of data on the differences in hospital stay cost between the PCR group and BC group slightly limits the study conclusion.

In conclusion, in the Egyptian National Cancer Institute's pediatric cancer patients who had a predominance of multidrug resistant, gram-negative bacilli, there was a high agreement between the results of the rapid molecular detection kit method (PCR) and those of the conventional blood cultures. The PCR group had a significantly shorter turnaround time and a lower rate of antibiotics shift following final sensitivity results. To our knowledge, this is the first study to report on the potential association of using PCR diagnostic techniques on pediatric cancer patients' hospital outcome. Although we noted a shorter duration of sepsis episode and slightly lower mortality rate, those findings did not reach statistical significance level. Future studies with larger sample sizes should further evaluate the effect of using PCR techniques on patients' outcomes, and on reducing bacterial antibiotic resistance and health care cost.

## Author Contribution Statement

Design and methodology of the study: All authors. Data collection and interpretation: FM, HM, SH. Manuscript draft: FM, HM, SH. Revision and approval of final manuscript: All authors.

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The study was internally funded by the Egyptian National Cancer Institute. The study was approved by the Institutional Review Board. None of the authors has any disclosure / conflict of interest regarding this study. No ethical concerns were raised by the Institutional Review Board. Patients' consents were obtained prior to inclusion in the study. De-identified data are available to be shared upon request.

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