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RESEARCH

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Non-cancer febrile neutropenia in children: pathogens, antimicrobial susceptibilities, and outcomes

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Abstract

Background Febrile neutropenia is a medical emergency and remains a significant cause of morbidity and mortality, it is defined as a temperature > 38.3 °C (101 °F), or a sustained temperature > 38.0 °C (100.4 °F) for more than 1 h in a neutropenic patient. Neutropenia is defined as a decrease in the absolute number of neutrophils in the blood < 1500 cells/ mm^3 in children.

Aim of the study To identify the specific pathogens causing infections, determine antimicrobial susceptibility, and identify factors associated with morbidity and mortality in febrile neutropenic children.

Methods A prospective cohort study, 38 non-cancerous pediatric patients admitted with 61 febrile episodes, was conducted. Sepsis screen, pan-cultures, and tests to identify the causative pathogens and antimicrobial sensitivity were collected.

Results Coagulase-negative staphylococci (CONS) infection accounted for 38.4% of all positive cultures, while Klebsiella infection represented 23%. SARS-CoV2 (severe acute respiratory syndrome coronavirus 2) virus infection accounted for 23% of febrile episodes that lead to COVID-19 (coronavirus disease of 2019) sickness; however, it did not significantly impact patients' outcomes. Unfavorable outcomes were associated with higher C-reactive protein (CRP) levels, positive blood cultures, and gram-negative organisms ($p = < 0.001$, 0.013, 0.038 respectively). Prolonged duration of fever and elevated CRP levels were significant predictors of poor outcomes in febrile neutropenia, with a sensitivity of 88.9% and 100% and specificity of 70.6% and 62.3%, respectively.

Conclusion Among febrile neutropenic patients, CONS is the most common pathogen, while Klebsiella is the most common gram-negative infection. Gram-positive organisms predominate in bloodstream infections. Prolonged duration of fever and elevated CRP levels can significantly predict poor outcomes.

Keywords Blood culture, COVID-19, C-reactive protein, CRP, Febrile neutropenia

Background

Neutropenia in children refers to a decrease in the ANC (absolute neutrophil count) in the blood, typically below 1500 cells/mm^3, which is further classified as mild (ANC, 1000–1500/mm^3), moderate (ANC, 500–1000/mm^3), severe (ANC < 500/mm^3), and very severe (ANC < 100/mm^3). Patients with ANC < 500/mm^3 are at highest risk for invasive bacterial infection. It can be categorized as congenital or acquired, as well as transient or chronic [1].

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In febrile neutropenic patients, fever is defined as a temperature exceeding 38.3 °C (101 °F) or a sustained temperature above 38.0 °C (100.4 °F) for more than 1 h [2]. The majority of febrile neutropenia cases are caused by infectious agents, although the responsible organism is only identified in about 30% of episodes [3]. Bacteremia is the most common type of infection, occurring in approximately 25% of patients [3]. Prompt initiation of broad-spectrum empiric antimicrobial therapy has become the standard approach for managing most febrile neutropenic patients [4].

The local pattern of bacterial infections in these patients has changed over time, thus treatment regimens should consider local infection epidemiology and susceptibility/resistance patterns, as geographical and institutional variations can occur. Regular surveillance studies are essential to monitor changes in infection epidemiology, as well as susceptibility and resistance patterns [5]. This study aimed to identify specific pathogens responsible for infections, determine antimicrobial susceptibility, and identify factors associated with morbidity and mortality in non-cancerous febrile neutropenic children.

Methods

We conducted a prospective cohort study involving 38 infants and children with non-cancerous febrile neutropenia (61 hospital admissions with febrile episodes), who were receiving regular follow-up care in the pediatrics hematology and bone marrow transplantation (BMT) units of Cairo University Hospitals from December 2020 to January 2022.

Patients with febrile neutropenia, i.e., known cases of neutropenia resulting from bone marrow failure and presenting with fever (temperature equal to or above 38 °C), in the age range from 2 months to 18 years, both genders were included in the study.

Patients with neutropenia associated with hematological or non-hematological malignancies or transient neutropenia (e.g., due to transient viral infections) were excluded. The degree of neutropenia was classified as either severe, very severe, or non-severe (mild or moderate) based on ANC, as mentioned earlier.

The study participants underwent a thorough clinical assessment, including history and physical examination. Demographic data were collected, and the present illness was explored, focusing on symptoms, recent infections, and antimicrobial use. Physical examination covered vital signs, skin assessment, head and neck examination, central nervous system evaluation, cardiovascular examination, chest examination, gastrointestinal and renal evaluation. Anthropometric measurements were also recorded. This comprehensive approach provided a detailed overview of the participants' medical history and physical health status.

The diagnostic tests included in the study were initially performed and subsequently repeated during the patients' admission period based on their clinical course progression.

The tests included the following:

1. General laboratory tests: complete blood picture (CBC) with differential counts were done for hematological assessment, in addition to C-reactive protein (CRP) for sepsis screening. Also, liver function tests (alanine transaminase (ALT), aspartate transaminase (AST), total serum bilirubin level, and direct serum bilirubin level) and kidney function tests (urea and creatinine) were done.
2. Microbiological tests for pathogen isolation: blood and urine specimens were sent for culture for each patient, other body site cultures such as wound swabs and hematoma aspirate according to patient presentation and clinical findings

For blood culture, two sets were sent for each patient; each set is composed of one aerobic and one anaerobic blood culture bottles for detection of bacterial and fungal infections (blood samples were withdrawn following strict aseptic precautions in pediatric), BacT/ALERT FA Plus and BacT/ALERT are standard anaerobic bottles. Bottles were labeled and sent immediately to the lab to be inoculated for incubation within the BacT/ALERT continuous monitoring blood culture system (BacT/ALERT 3D, bioMerieux Inc., Durham, NC, USA). The machine gives a positive signal in case of growth, prompt sub-culture, gram staining, and further processing was done.

Blood, Chocolate, and MaCconkey agar media (Oxoid, UK) were used for the culture of all specimens and Cled (Oxoid, UK) was used for urine. Incubation of culture plates, primary identification of growth by gram staining to gram-positive and gram-negative organisms, and further identification by biochemical reactions and interpretation were done following standard microbiological procedures according to the manual of clinical microbiology.

3. Antimicrobial susceptibility testing: susceptibility testing for penicillins, combined penicillins, 3rd generation cephalosporins, 4th generation cephalosporins, aminoglycosides, vancomycin, macrolides, quinolones, linezolid, and lincosamides was done with gram-positive organisms, and for penicillins, combined penicillins, 3rd generation cephalosporins, 4th generation cephalosporins, carbapenems, aminoglycosides, quinolones, trimethoprim-sulphameth-

oxazole and colistin with gram-negative organisms. Antimicrobial discs used (Oxoid, UK) Antimicrobial susceptibility testing was done by Kirby disc diffusion methods for all antibiotics used except for vancomycin (vancomycin screen agar was used) and colistin, (colistin dilution agar was used). Interpretative criteria were done according to Clinical Laboratory Standard Institute performance standards for antimicrobial susceptibility testing (CLSI, 2023).

4. Other microbiological testing: Galactomannan test was done for fungal infection detection. Respiratory viral screen by nasal swab for SARS-CoV2 (severe acute respiratory syndrome coronavirus 2) PCR testing was conducted during the pandemic period (December 2020 to January 2022) for 53 patients' febrile episodes.

Regarding the management of the admitted cases, in uncomplicated febrile episodes, our unit protocol was initiated "empirical monotherapy with piperacillin-tazobactam, cefepime, or meropenem". For complicated cases or those exhibiting hemodynamic instability, a combination of vancomycin with one of the previously mentioned agents is employed. Additional considerations include Metronidazole for gastrointestinal symptoms and, for persistent fever beyond 4–7 days despite broad-spectrum antibiotics, antifungal therapy. Should patients fail to respond clinically, or exhibit sustained high CRP levels, the protocol advocates transitioning to culture-based therapy guided by positive blood cultures or other positive cultures, such as urine or wound cultures.

Analysis methods

Data were analyzed using IBM SPSS advanced statistics (Statistical Package for Social Sciences), version 24 (SPSS Inc., Chicago, IL, USA). Numerical data were presented as medians and interquartile range (IQR), while categorical data were expressed as numbers and percentages. Comparison between multiple groups were compared using the Kruskal-Wallis test, and the Mann-Whitney *U* test was employed for pairwise group comparisons. The chi-square test was utilized to compare categorical variables.

Additionally, a receiver operating characteristic (ROC) curve analysis was conducted to identify predictors of mortality during hospital admissions. In all analyses, statistical significance was defined as a p value of ≤ 0.05, and all tests were two-tailed.

Results

Among our study participants, 29 were aplastic anemia patients admitted with 41 febrile episodes, 6 patients with Fanconi anemia admitted with 14 febrile episodes and 3 neutropenia patients admitted with 6 febrile episodes not following aplastic anemia or Fanconi anemia diagnosis. Study participants' mean age was 7.6 (± 3) years, with male to female ratio of 3:2. Regarding severity of neutropenia, 57.4% of our study participants had very severe neutropenia, 26.2% had severe neutropenia and 16.4% had non-severe neutropenia (Table 1).

Table 1 Epidemiological data of study populations

Variable		*N* (%)
Sex ($n=38$)	Male	23 (60.5%)
	Female	15 (39.5%)
Age by years ($n=38$)		7.6 (± 3)[a]
Diagnosis ($n=38$)	Aplastic anemia	29 (76.3%)
	Fanconi anemia	6 (15.8%)
	Other neutropenia	3 (7.9%)
Positive consanguinity ($n=38$)		16 (42%)
Severity of neutropenia ($n=61$)	Non-severe	10 (16.4%)
	Severe	16 (26.20%)
	Very severe	35 (57.4%)

[a] Mean ± SD); *N* number of patients, *SD* standard deviation

Table 2 Treatment protocols and outcome

Variable		*N*/total (%)
Ongoing treatment	Immunosuppression	9/29 (31%)
	Androgen therapy	4/6 (66.6%)
Antibiotics regimen during admission	Empirical only	43/61 (70.5%)
	Culture-based	18/61 (29.5%)
Patients' outcome	Discharged	52/61 (85.2%)
	Died	9/61 (14.8%)

N number of patients

Regarding their ongoing treatment, immunosuppression therapy (IST) was used in 9 out of 29 aplastic anemia patients, while androgen therapy was used in 4 out of 6 Fanconi anemia patients (66.6%) patients. The IST included cyclosporine or cyclophosphamide (Table 2).

Blood and urine cultures were done on all study participants, 15 blood cultures showed positive results, 9/15 of them were gram-positive (CONS (coagulase-negative staphylococci) is the most common blood isolate as 7 out of 15 positive blood culture) while the others were gram-negative isolates. Other cultures (wound swabs, hematoma aspirate) were done for only 10 patients' febrile episodes according to each infection site. SARS-CoV2 PCR test was done for only 53 patients' febrile episodes but was not done in the 8 patients with febrile episodes who were admitted before the COVID (coronavirus disease of 2019) sickness pandemic, 39 out of 53 SARS-CoV2 PCR (64%) were negative (Table 3).

Table 3 Results of infection screen in study patients

Cultures/test	Positive *N* (%)	Negative *N* (%)
Blood culture (*n* = 61)	15 (24.6%)	46 (75.4%)
Urine culture (*n* = 61)	2 (3.3%)	59 (96.7%)
Other cultures (*n* = 10)	9 (90%)	1 (10%)
Galactomannan test (*n* = 61)	2 (3.3%)	59 (96.7%)
COVID PCR (*n* = 53)	14 (23%)	39 (64%)
CRP (mg/L)	81.6 (34–96)[a]	

[a] Median (IQR); *COVID* corona virus disease of 2019, *CRP* C-reactive protein, *IQR* interquartile range, *N* number of patients underwent the mentions test, *PCR* polymerase chain reaction

In Table 4, positive cultures were reported in total in 26 (42.6%) febrile episodes, with 15 being blood cultures and 11 from other culture types (urine and wound swabs). Regarding the pan-culture pathogens profile, CONS infection represents the most common infection (38.4% of all positive cultures) while Klebsiella spp. came next as the most common gram-negative infection (23% of all positive cultures). Aspergillus flavus was isolated in only one culture representing (3.8% of all positive cultures), which may be considered as a colonizer but on a clinical basis, it is a respectable result due to the immunocompromised state of the studied patients. Antimicrobial

Table 4 Pathogen profile of pan-cultures isolates

Total positive cultures: 26 (100%)					
Gram-positive bacteria: 13 (50%)		**Gram-negative bacteria: 12 (46.2%)**		**Fungal: 1 (3.8%)**	
Organism: *N* (%)	**Culture site: (*N*)**	**Organism: *N* (%)**	**Culture site:(*N*)**	**Organism: *N* (%)**	**Culture site: (*N*)**
CONS: 10 (38.4%)	Blood cultures: (7) wound swabs: (3)	Klebsiella Spp.: 6 (23%)	Blood culture (3) wound swab culture (2) oral swab culture (1)	Aspergillus flavus: 1 (3.8%)	Oral swab culture: (1)
MRSA: 3 (11.6%)	Blood cultures: (2) hematoma aspirate culture: (1)	Acinetobacter MDR: 1 (3.8)	Blood culture (1)		
		Neisseria mucosa sicca: 1 (3.8)	Blood culture (1)		
		Pseudomonas MDR: 1 (3.8)	Blood culture (1)		
		Enterobacter MDR: 1 (3.8)	Urine culture (1)		
		E.coli: 1 (3.8)	Urine culture (1)		
		Pseudomonas aeruginosa: 1 (3.8)	Wound swab culture (1)		

CONS coagulase-negative staphylococcus aureus, *E. coli* Escherichia coli, *ESBL* extended-spectrum beta-lactamase, *MDR* multi-drug resistant, *MRSA* methicillin-resistant staphylococcus aureus, *N* number of pan-cultures isolates

Table 5 Antimicrobial susceptibility of pathogen profile

Antibiotic tested	Gram-positive		Gram-negative	
	Sensitive	Resistant	Sensitive	Resistant
Penicillins	0 (0)	12 (100)	2 (15.4)	11 (84.6)
Combined penicillins	0 (0)	12 (100)	3 (23)	10 (77)
3rd generation cephalosporins	0 (0)	12 (100)	2 (15.4)	11 (84.6)
4th generation cephalosporins	0 (0)	12 (100)	1 (7.7)	12 (92.3)
Carbapenems	–	–	6 (46)	7 (54)
Aminoglycosides	1 (8.3)	11 (91.7)	8 (61.5)	5 (38.5)
Vancomycin	11 (91.6)	1 (8.3)	–	–
Macrolides	2 (16.6)	10 (83.3)	–	–
Quinolones	8 (66.6)	4 (33.3)	3 (23)	10 (77)
Trimethoprim-sulphamethoxazole	–	–	2 (15.4)	11 (84.6)
Linezolid	11 (91.6)	1 (8.3)	–	–
Colistin	–	–	5 (38.5)	8 (61.5)
Lincosamides	7 (58.3)	5 (41.6)	–	–

susceptibility for those pathogens profiles is shown in Table 5.

Among all clinical and laboratory data, culture-positive infections and those caused by gram-negative organisms were strongly linked to prolonged fever duration (p values 0.008, < 0.001, respectively). The correlation between fever duration and CRP was assessed using the non-parametric method (Spearman's rho), revealing a significantly positive result (correlation coefficient (r) = 0.513, significant level < 0.001). Additionally, culture-positive infections, gram-negative organism infections, and higher CRP levels upon admission were associated with a higher incidence of patient mortality (p values 0.013, 0.038, < 0.001, respectively) (Table 6).

Using the ROC curve, we found that, a CRP level with a cutoff value of 92 mg/L is able to predict patients' mortality with a sensitivity of 100% and specificity of 62.3%, also the duration of fever with a cutoff value of 8.5 days is able to predict patients mortality with sensitivity 88.9% and specificity 70.6% (Fig. 1, Table 7).

Table 6 Clinical and laboratory variables affecting the duration of fever and patients' mortality

Variable		Duration of fever		Patients' mortality		
		Median (IQR)	*P* value	Discharged *N* (%)	Died *N* (%)	*P* value
Severity of neutropenia	Non-severe	6 (2–14)	0.457	10 (100%)	0 (0%)	0.107
	Severe	4.5 (2.5–6)		15 (93.8%)	1 (6.3%)	
	Very severe	7 (2–15)		27 (77.1%)	8 (22.9%)	
Antibiotics regimen during admission	Empirical only	4 (2–7)	0.001	41 (95.3%)	2 (4.7%)	0.001
	Culture-based	14 (7–32)		11 (61.1%)	7 (38.9%)	
Culture results	Positive	14 (7–32)	< 0.001	13 (68.4%)	6 (31.6%)	0.013
	Negative	4 (2–7)		39 (92.9%)	3 (7.1%)	
Organism type	Gram + ve	7 (4.5–12)	0.008	8 (100%)	0 (0%)	0.038
	Gram – ve	15 (13–38)		4 (57.1%)	3 (42.9%)	
COVID PCR	Positive	2.5 (18.75)	0.042	11 (78.8%)	3 (21.2%)	0.725
	Negative	5 (3–13.5)		34 (87.2%)	5 (12.8%)	
CRP (mg/L)				48 (24–96)[a]	192 (96–196) [a]	< 0.001

[a] Median (IQR), *CRP* C reactive protein, *IQR* inter quartile range, *N* number of patients (%)

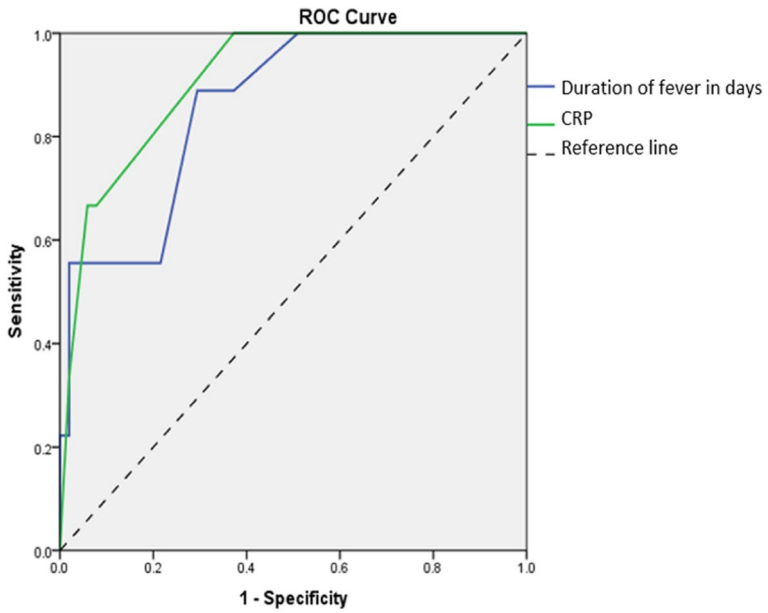

Fig. 1 ROC curve for patient's outcome predictors

Table 7 ROC curve analysis for predictors of patients' outcome

Variables	AUC	*P* value	Cutoff	Sensitivity	Specificity	95% confidence interval	
						Lower bound	Upper bound
Duration of fever in days	.859	0.001	8.5	88.9%	70.6%	.743	.976
CRP	.908	< 0.001	92	100%	62.3%	.822	.995

AUC area under the curve, *CRP* C-reactive protein

Discussion

Febrile neutropenia is considered a medical emergency and remains the most common and serious complication in bone marrow failure patients. Most febrile episodes are caused by infectious agents; however, the causative agent is only identified in about 30% of episodes [3].

This study aimed to identify specific pathogens responsible for infections, determine antimicrobial susceptibility, and identify factors associated with morbidity and mortality in non-cancerous febrile neutropenic children.

Upon our study participants' admission, the blood culture positivity rate was 24.6%, and gram-positive organisms predominated with CONS being the most common isolates (7 out of 15 positive blood cultures) (Table 4).

Aslan and colleagues reported almost similar results as CONS was the most common blood isolate (72 out of 128 positive blood cultures), with a blood culture positivity rate of (27.5%) [6]. In contrast, Samanta et al. reported a blood culture positivity rate of 34.2%, with gram-negative bacteria comprising a larger proportion (68.2%) than gram-positive bacteria (31.8%) and fungi (13.6%), (Klebsiella pneumoniae were the most common blood isolate (6 out of 13 positive blood cultures) [7]. Figure 2 demonstrates a comparison between blood culture our work and other studies regarding blood culture positivity rate and the commonest blood isolate. The causes of this difference in the epidemiology of the infection have not been clearly identified, but they may include the local bacteriology change with its epidemiologic trends and susceptibility/resistance patterns [5], more profound and prolonged neutropenia, increased usage of intravenous catheters, and selective use of antibiotics [8].

In the current study, antimicrobial susceptibility analysis revealed that gram-positive strains were most sensitive to vancomycin, quinolones, linezolid, and licosamides, but were resistant to aminoglycosides, macrolides, penicillins, cephalosporins, and carbapenems. Conversely, gram-negative strains were most sensitive to carbapenems, aminoglycosides, and colistin but resistant to cephalosporins and penicillins, vancomycin, macrolides, quinolones, trimethoprim-sulfamethoxazole, linezolid, and lincosamides (Table 5). These results are consistent with another study [7]. On the contrary, Salama and colleagues reported that gram-positive organisms were

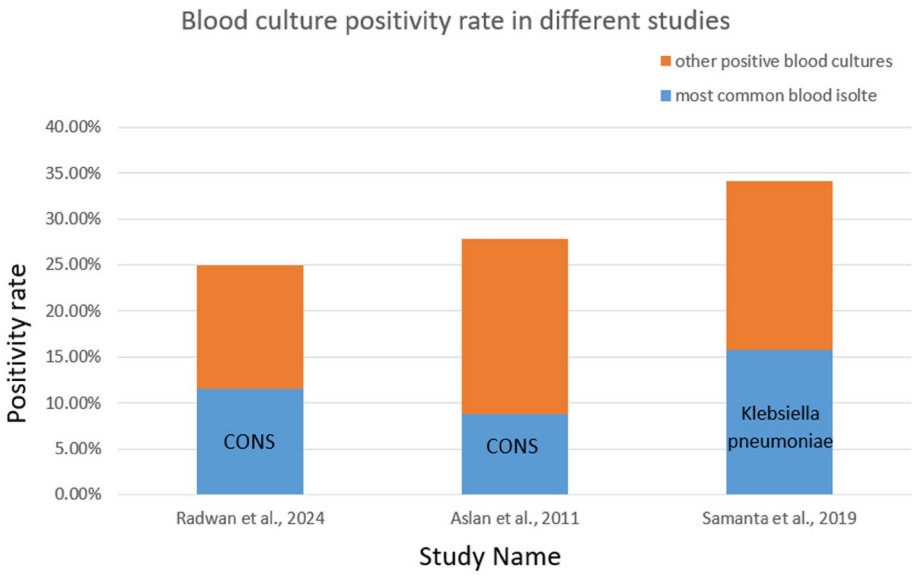

Fig. 2 Blood culture positivity rate in different studies

most sensitive to vancomycin, rifampicin, gentamycin, erythromycin, clindamycin, and ciprofloxacin [9]. These contradictory results could be explained by the increased prevalence of drug-resistant bacteria due to the overuse of antimicrobials [10].

Of implication, we observed that a longer duration of fever was significantly associated with patients' mortality ($p = 0.001$). ROC curve analysis indicated that fever duration (> 8.5 days) served as a specific predictor for these adverse outcomes with high sensitivity and specificity (Table 7, Fig. 1). The association between prolonged fever and poor outcome could be explained as prolonged fever may adversely affect immune function, perpetuating pro-inflammatory responses and compromising immune cell apoptosis [11, 12].

Regarding other risk factors, the current study showed that high CRP levels were significantly associated with patients' mortality. A specific cutoff (> 92 mg/L) of CRP level served as a sensitive predictor (100%) for these adverse outcomes with relatively high specificity (62.3%). In agreement, a recent meta-analysis by Haeusler and colleagues found that CRP can strongly predict adverse events using a cutoff > 50 mg/L, with a sensitivity of 66% and specificity of 73% [13], while in disagreement with our findings, another study demonstrated that CRP level was not associated with development of complications among patients with febrile neutropenia, they also stated that CRP could not predict bacteremia among patients with FN and also it has no association with patients' outcome [14]. These discordant results highlighted the need for further multi-center studies into the role of CRP as a predictor of complications in non-malignant febrile neutropenia patients since the previous studies investigated malignant febrile neutropenic patients.

Our study also revealed a significant association between culture-positive febrile episodes and the duration of fever and patients' mortality (Table 6). These findings align with a previous study which reported that the isolation of organisms from blood cultures correlated with poor patient outcomes [15]. The previous finding could be explained as the isolation of certain aggressive organisms can affect tissue viability in addition to the aggressive use of the antibiotics, while patients with culture-negative febrile episodes tended to have a milder infection with minimal use of antibiotics with less side effects.

The prevalence of SARS-CoV2 PCR positivity among our patients during the pandemic period was 23%, but it did not significantly affect the clinical outcomes (Table 6). Febrile neutropenic patients who were admitted with causes other than COVID-19 sickness tended to have a prolonged duration of fever ($p = 0.042$). In agreement with us, other authors believed that aplastic anemia patients will have a milder COVID sickness, as the severity of COVID-19 sickness is mostly related to the hyper-inflammatory condition, which they may not be able to have due to their immunocompromised state [16]. Because these patients are immunocompromised, it is unknown whether they are more likely to get SARS-CoV-2 infection or are more sensitive to severe COVID-19 sickness [17]. Further research is needed to understand the impact of COVID-19 sickness on immunocompromised pediatric patients.

Neutropenia severity emerged as a significant feature in our study, with 57.4% of patients presenting with very severe neutropenia, while 26.2% were admitted with severe neutropenia compared to 16.4% with non-severe neutropenia (Table 1). These findings are in line with Salama and colleagues who also reported a similar distribution of patients based on the degree of neutropenia [9]. This seems to be a logical observation as severely neutropenic patients are more vulnerable to community-acquired infection and usually necessitate hospital admission.

Conclusions

In conclusion, our study provides insight into non-cancerous febrile neutropenia management among pediatric patients. CONS and multidrug-resistant Klebsiella were the most common infections encountered, gram-positive organisms predominated in bloodstream infections. Prolonged fever and elevated CRP levels emerged as significant predictors of poor outcomes.

Based on the paucity of local data about non-cancer febrile neutropenia in pediatrics, the current study expands the existing data, regarding antimicrobial patterns and susceptibility in febrile episodes in non-cancerous neutropenic children and factors that affect their outcomes.

Limitations

Limited numbers of studied patients, although our center is a tertiary care center, we could only assess 38 patients during 61 febrile episodes over a year. The lack of studies on febrile neutropenia among children with non-malignant hematological diseases made the discussion of the current results more challenging.

Abbreviations

ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
BMT	Bone marrow transplantation
CBC	Complete blood picture
CONS	Coagulase-negative staphylococci
COVID-19	Coronavirus disease of 2019
CRP	C-reactive protein
IST	Immunosuppression therapy
ROC	Receiver operating characteristic
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SPSS	Statistical Package for Social Sciences

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Authors' contributions
RR contributed to the design of the work, idea of study, and data acquisition, and drafted the manuscript. IY contributed to the design of the work and idea of the study, revised the manuscript, and approved it with its revision. RA contributed to the design of the work and the idea of the study, revised the manuscript, and approved it with its revision. AB revised the manuscript. MB helped in laboratory work and revised the manuscript. EAM contributed to the design of the work, the idea of the study, interpretation of data, revised the manuscript, and approved it with its revision. All authors read and approved the final manuscript.

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Availability of data and materials
All data used during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki for studies including human participants and was approved by the institutional research ethics committees at the Faculty of Medicine, Cairo University (Approval code: MD-183–2020). Written informed consent was obtained from the parents. Participants' data have been anonymized.

Consent for publication
Written informed consent was obtained from the parents. Participants' data have been anonymized.

Competing interests
The authors declare that they have no competing interests.

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