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Fever of unknown origin in pediatrics: causes and clinical characteristics in a single centre experience

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Abstract

Background Fever of unknown origin (FUO) is a common condition worldwide in children that remains a diagnostic challenge. The causes of FUO vary depending on the patient's age, residency, and the time of study. Therefore, this study aimed to identify the common aetiologies of FUO at Alexandria University Children's Hospital under the current diagnostic abilities and newly emerging diseases.

Methods The current prospective observational study included all children fulfilling the definition of FUO admitted at Alexandria University Children's Hospital from January 2020 to December 2021 using a steps approach for investigations.

Results A total of 110 children with fever of unknown origin (FUO) were included in this study; the average duration of fever was 36.76 ± 31.73 days. In most of the enrolled cases 105/110 (95.4%) the definite etiology of FUO was identified. The common causes were collagen vascular diseases (30.9%), infectious diseases (28.2%), miscellaneous conditions (19.1%), and malignancy (17.3%). Among collagen vascular diseases, systemic lupus erythematosus (SLE) (47.1%) and systemic onset juvenile idiopathic arthritis (sJIA) (38.2%) were the most common. In the infectious category, Katayama fever (16.1%), brucellosis (12.9%), and urinary tract infection (UTI) (12.9%) were the most frequently observed. Post-Covid MIS-C (52.4%) was the most common in the miscellaneous category. Children in the infectious category had significantly higher neutrophil [5.76 (2.28–7.92) × 10^3/μl] and lymphocytic counts [4.2 (2.04–5.91) × 10^3/μl]; ($P < 0.001$ and < 0.010 respectively). Moreover, in the collagen category the median lymphocytic count was lower [1.95 (1.47–2.73) × 10^3/μl] with a significantly ($P < 0.010$) higher neutrophil/ lymphocyte ratio [2.30 (1.53–3.91)].

Conclusion Collagen vascular diseases, infectious diseases, miscellaneous, and malignancy were the most common causes of FUO. Katayama fever, urinary tract infections (UTI), and brucellosis were the most common causes in the infectious category. Post-Covid MIS-C and hemophagocytic lymphohistiocytosis were the most common diagnoses in the miscellaneous category.

Keywords Fever of unknown origin, Children, Post-covid MIS

A prospective observational study included all children fulfilling the definition of FUO admitted at Alexandria University Children's Hospital from January 2020- December 2021.

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Background

Fever in children presents a challenging diagnostic dilemma. In most cases, self-limited viral infections are the most common cause [1] fever of unknown origin (FUO) is defined as a temperature of 38°C or higher, that cannot be explained after eight days of inpatient evaluation or three weeks of outpatient evaluation [1, 2]. In children, the major causes of FUO can be grouped into four categories: infections, inflammatory diseases, malignancies, and other miscellaneous conditions [3]. Infectious causes are the most common reasons for FUO, although non-infectious inflammatory diseases have become more common in recent years due to improved diagnostic methods [1, 2]. The etiology of FUO differs between different geographic areas, and different healthcare systems, and can be affected by emerging new infections or newly identified diseases such as post-COVID- Multisystem inflammatory syndrome in children (MIS-C) [4]. Despite this, there are still a significant number of undiagnosed cases in the most recently published series, despite the development of rapid laboratory tests and powerful diagnostic instruments [5–7].

Methods

The study was conducted following the approval of the ethical committee of the Faculty of Medicine, Alexandria University. Children aged one month to 18 years, who met the criteria for fever of unknown origin (FUO), were included in the study. FUO was defined as an axillary temperature of 38°C or higher without any apparent cause after three weeks of outpatient evaluation or one week of inpatient evaluation.

The included children were subjected to a three-stage evaluation: -

1. First stage evaluation: included detailed history taking (pattern and duration of fever, other symptoms, vaccination status, history of sick contact, animal contact, and medication history). History taking followed by a complete physical examination and daily assessment of children for new clinical signs. The first-step investigations were done on all cases including a complete blood count with peripheral blood smear, C-reactive protein, Erythrocyte Sedimentation Rate (ESR), routine biochemical analysis, urine culture, aerobic, anaerobic blood culture, stool examination for common parasites by stool analysis, and chest radiographic examination.
2. The second-stage investigations as needed based on clinical presentation and the first-stage investigations included serological tests for viral and parasitic infections. Other tests such as the Widal test, tuberculin test, antinuclear antibody testing (ANA), complement 3 and 4 levels, testing for cytoplasmic antineutrophil cytoplasmic antibodies (ANCA), immunoglobulin levels, and soluble CD25 were requested in some cases. Echocardiography, as well as ultrasonographic examination of the abdomen, pelvis, and lymph node, were also requested.
3. The third-stage investigations as needed based on clinical presentation and the first and second-stage investigations; computed tomography (CT), magnetic resonance angiography (MRI), and nuclear medicine (Gallium and bone scans). Additionally, a bone marrow aspirate or tissue biopsy was performed, along with a bone marrow biopsy. Furthermore, molecular diagnosis for virology and molecular DNA analysis were requested in selected patients.

Based on the final diagnosis, the studied cases were classified into four categories: infectious, collagenic, malignancy, and miscellaneous.

Statistical analysis

Statistical analysis was conducted using the IBM SPSS Statistics program, Version 28. Quantitative data were summarized by mean, standard deviation, median, and Interquartile range; While categorical variables were summarized using frequency, percent, and bar chart as appropriate. Bivariate analysis was conducted using Kruskal-Walli's test based on the distribution of quantitative variables after testing for normality. Additionally, Pearson's Chi-square test was used to compare different demographic and clinical parameters between categories of infection, malignancy, and collagen vascular conditions. Fisher exact (FEp) and Montecarlo significance (MCp) were performed if more than 20% of total expected cell counts < 5. All statistical tests were two-sided and judged at a 0.05 significance level.

Results

From January 2020 to December 2021, one hundred ten (110) children fulfilled the case definition of FUO, 50.9% ($n=56$) were males and 49.1% ($n=54$) were females. Ages ranged from 6 months to 15 years, with an average age of 81.65 ± 46.14 months. Children in the age group 5 to 12 years were the most common (52.7%) followed by the age group one to five years (30.0%). The average duration of the fever before admission was 36 days, with a range of 2–180 days. Most of the patients, 56.4%, were from urban areas, and 85.5% of patients had received antibiotics before being referred for treatment (Table 1). Regarding the clinical characteristics of the studied cases, lymphadenopathy [61.8% ($n=68$)],

Table 1 The demographic characteristics of studied children ($n=110$)

	Frequency	%
Age		
Mean ± SD	81.65 ± 46.14	
Median (IQR)	84(40.50–120)	
Min–Max	(6–180) months	
≤ 1 year	8	7.3%
1–5 years	33	30.0%
5–12 years	58	52.7%
> 12 years	11	10.0%
Sex		
Male	56	50.9%
Female	54	49.1%
Residence		
Urban	62	56.4%
Rural	48	43.6%
Relevant family history	9	8.2%
Contact with animal	19	17.3%
Received antibiotics before admission	94	85.5%
Received steroids before admission	19	17.3%
Duration of fever before admission (days)		
Mean ± SD	36.76 ± 31.73	
Min–Max	2–180	
Lag to reach diagnosis (days)		
Mean ± SD	10.75 ± 12.37	
Min–Max	1–90	
Duration of admission (days)		
Mean ± SD	18.75 ± 17.04	
Min–Max	0–120	
Degree of fever on initial examination (Celsius)		
Mean ± SD	39.17 ± 0.68	
Min–Max	38–40	

hepatomegaly [36.4% ($n=40$)], skin rash [24.5% ($n=27$)], and arthritis [21.8% ($n=24$)] were the most common clinical signs (Fig. 1).

The final diagnosis was established in 105 (95.5%) cases, including cases with collagen vascular diseases (31.8%), infectious (28.2%), miscellaneous (18.2%), and malignancy categories (17.3%). Five cases (4.5%) remained undiagnosed (Table 2). Systemic lupus erythematosus (SLE) [45.7% ($n = 16$)] and systemic onset juvenile idiopathic arthritis (JIA) [37.1% ($n = 13$)] were the most common collagen vascular diseases. In the infectious category, Katayama fever was the most common established diagnosis in 16.1% ($n = 5$), followed by brucellosis and urinary tract infection (UTI), which were equally distributed [12.9% ($n = 4$) each].

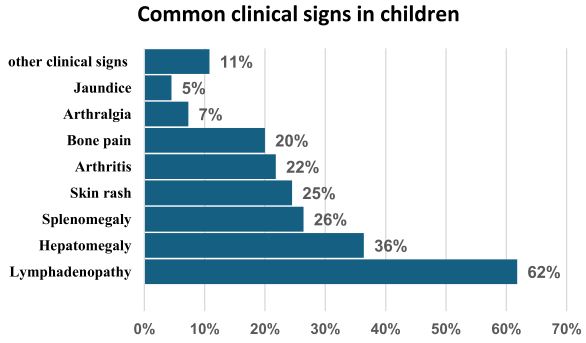

Fig. 1 Common clinical signs in children with FUO

In the malignant category, acute lymphoblastic leukaemia (ALL) was the most common, accounting for 68.4% ($n=13$) of cases. Finally, post-Covid MIS-C was the most common diagnosis in the miscellaneous category accounting for 52.4% ($n=11$), followed by hemophagocytic lymphohistiocytosis (HLH) in 23.8% ($n=5$) of cases (Table 2).

A comparison between collagen vascular, infectious, and malignancy categories regarding clinical and demographic categories is presented in Table 3. Among the infectious category, preschool children (1–5 years) were the most common (38.7%), while school-age children were the most common age group in the collagen and malignancy categories [19 (55.9%) and 10 (52.6%) respectively]. However, this difference was found to be statistically insignificant (P-value 0.575). There is a statistically significant difference ($P=0.007$) regarding sex where females (64.7%) were more common in the collagen vascular group, while males were more common in the infectious (61.3%), and malignancy (78.9%) categories.

In the clinical presentations, children with malignancy had a significant ($P=0.010$) delay in diagnosis [8.00 (5.75–17.00) days] with a longer duration of hospital admission [19.00 (11.75–30.50) days]. Moreover, lymphadenopathy and bone pain were significantly higher among children with malignancy [$n=15$ (78.9%)] and [$n=13$ (68.4%) respectively] ($P=0.002$ and 0.001). On the other hand, lymphadenopathy and arthritis were significantly higher among children in the collagen category [$n=21$ (63.6%)] and [$n=13$ (38.2%)], respectively.

Moreover, comparing the laboratory investigations (Table 4) children in the infectious category significantly had higher median neutrophil count [5.76 (2.28–7.92) × 10^3/µl] and median lymphocytic count [4.2 (2.04–5.91) × 10^3/µl]; ($P<0.001$ and <0.010 respectively). In the collagen category the median lymphocytic count was lower [1.95 (1.47–2.73) × 10^3/µl] with significant ($P<0.010$) higher neutrophil/ lymphocyte ratio [2.30

Table 2 Common causes of fever of unknown origin among studied children

	Frequency	Percent
Collagen vascular diseases	**35**	**31.8%**
Systemic Lupus Erythematosus (SLE)	16	45.7%
Systemic Onset JIA	13	37.1%
Familial Mediterranean fever (FMF)	3	8.6%
DADA2 vasculitis	1	2.8%
Spondyloenchondro-dysplasia with immune dysregulation	1	2.8%
Cryopyrin-associated periodic syndromes (CAPS)	1	2.8%
Infectious diseases	**31**	**28.2%**
Katayama fever (Acute schistosomiasis)	5	16.1%
Brucellosis	4	12.9%
Urinary Tract Infection (UTI)	4	12.9%
Epstein-Barr Virus (EBV) Infection	2	6.5%
Pneumonia	2	6.5%
Sepsis	2	6.5%
Lung abscess	2	6.5%
Acute COVID-19 infection	1	3.2%
Splenic abscesses	1	3.2%
Fascioliasis	1	3.2%
Human Immunodeficiency Virus (HIV)	1	3.2%
Infective endocarditis	1	3.2%
Meningitis	1	3.2%
Parotid abscesses	1	3.2%
Rat-bite fever	1	3.2%
Rectal abscess	1	3.2%
Typhoid Fever	1	3.2%
Malignancy ($n=19$)	**19**	**17.3%**
Acute lymphoblastic leukemia (ALL)	13	68.4%
Lymphoma	5	26.3%
Neuroblastoma	1	5.3%
Miscellaneous ($n=20$)	20	18.2%
Post covid MIS-C	11	55.0%
Hemophagocytic lymphohistiocytosis (HLH)	5	25.0%
Factitious fever	2	10.0%
Diabetes Insipidus	1	5.0%
Drug fever	1	5.0%
Undiagnosed	5	4.5%

(1.53–3.91)]. Other laboratory markers showed no significant difference between the three groups.

Discussion

Fever of unknown origin is still considered one of the most difficult clinical scenarios in children. The current study included 110 children with FUO, the most common diagnostic categories were collagen vascular diseases (30.9%; $n=34$), infectious (28.2%; $n=31$), miscellaneous (19.1%; $n=21$), and malignancy (17.3%; $n=19$). In 4.5% of cases (5 cases), the diagnosis was not reached. These findings are contrary to the results of other published studies, which found infectious causes to be the most common [8–13]. A previous study conducted at the Infectious Disease Unit at Mansoura University Children's Hospital, from 2006 to 2011, found that the infectious category was the most common (36.22%) [14]. Matched results detected by Kasai et al. in Japan as collagen vascular diseases were detected in 58% followed by infectious diseases (23%) [15].

Several factors contribute to the diversity in the causes of FUO. Several factors contribute to the diversity in the

Table 3 Comparison between different categories regarding clinical and demographic characteristics

	Infections ($n=31$)	Collagen vascular ($n=34$)	Malignancy ($n=19$)	Sig
Age Median (IQR)	**72.0[a] (36.90–96.0)**	**103.50[b] (57.00–132.00)**	**65.0[a b] (39.0–108.0)**	**0.058**
Age category				
< 1 year	3(9.7%)	2(5.9%)	1(5.3%)	**[MC]p0.575**
1–5 years	12(38.7%)	7(20.6%)	7(36.8%)	
5–12 years	13(41.9%)	19(55.9%)	10(52.6%)	
12 years	3(9.7%)	6(17.6%)	1(5.3%)	
Sex				**[MC]p0.007***
Male	19(61.3%)[ab]	12(35.3%)[b]	15(78.9%)[a]	
Female	12(38.7%)[ab]	22(64.7%)[b]	4 (21.1%)[a]	
Clinical characteristics				
Duration of fever (days)	30.0 (21.0–45.0)	30.0 (14.00–60.00)	45.0 (21.0–68.0)	**0.390**
Days lag in diagnosis	4.0[a] (2.0–10.0)	8.00 [b] (5.75–17.00)	6.0[ab] (1.0–8.0)	**0.010***
Days of admission	14.0(5.0–25.0)[a]	19.00(11.75–30.50)[ab]	5(3.0–8.0)[c]	**< 0.001***
Degree of fever	39 (38.50–39.75)	39 (39–40.00)	39 (38.5–39.50)	**0.368**
Hepatomegaly	13(41.9%)	9 (26.5%)	9 (47.4%)	**[MC]p0.244**
Splenomegaly	11(35.5%)	5 (14.7%)	8 (42.1%)	**[MC]p0.060**
Lymphadenopathy	10(32.3%)[a]	21 (63.6%)[b]	15 (78.9%)[b]	**[MC]p0.002***
Arthritis	0 (0.0%)[a]	13 (38.2%)[b]	4 (21.1)[b]	**[MC]p0.035***
Bone pain	2 (6.5%)[a]	5 (14.7%)[a]	13(68.4%)[b]	**[MC]$p < 0.001$***
Jaundice	1 (3.2%)	0 (0.0%)	1 (5.3%)	**[MC]p0.520**
Conclusive test				
Imaging	8 (25.8%)[a]	0 (0%)[b]	4 (21.1%)[a]	**[MC]$p < 0.001$***
Laboratory investigations	21 (67.7%)[a]	19 (55.9%)[a]	0 (0%)[b]	
Bone marrow aspirate or biopsy	0 (0%)[a]	0 (0%)[a]	14 (73.7%)[b]	
Lymph node biopsy	0 (0%)[a]	0 (0%)[a]	1 (5.3%)[a]	
Combined	2 (6.5%)[a]	15(44.1%)[b]	0 (0%)[a]	

Different letter superscript per column denotes significant pairwise comparison

Undiagnosed and miscellaneous categories were removed from the bivariate analysis

IQR Interquartile range

* Results ≤ .05 are statistically significant

MC p, Monte-Carlo Significance

causes of FUO. Firstly, infants less than one year old, who are more susceptible to infections, account for only a small percentage (7.3%) of studied cases Secondly, most cases of FUO are referred to specialized fever hospitals. Thirdly, 85.5% of cases had received antibiotics before being hospitalized, which might interfere with the growth of microorganisms in cultures. Finally, the impact of the COVID-19 pandemic could be a cause of increased other categories as a cause of fever of unknown origin [16].

In the infectious category, Acute schistosomiasis (Katayama fever) was the most common cause (16.1%; $n=5$), followed by urinary tract infection (UTI) and brucellosis which were equally represented, (12.9%; $n=4$) each. The five cases of acute schistosomiasis were diagnosed based on history, clinical presentation (cercarial dermatitis, acute enterocolitis, fever, malaise, hepatomegaly, and splenomegaly), laboratory assays (eosinophilia, schistosome serology, and or presence of eggs in stool). In one case colonoscopy and biopsy were performed due to suspicion of inflammatory bowel disease, revealing Schistosoma colitis.

Different findings were detected by Chien Yl et al. in Tawain [10], Sumathi Sri R et al. in India [13], and Atia et al. in Egypt [14]. The former two studies found that respiratory infections were the most common, while the latter one reported that enteric fever was the most common. In the current study, UTI and brucellosis were the second most common causes (12.9% ($n=4$) each) consistent findings were detected by Reddy PA et al. [11] and Attia et al. [14]. On the contrary, tuberculosis and enteric fever were the leading causes in other studies [12, 13, 17, 18].

Table 4 Comparison between different categories of FUO regarding the laboratory characteristics

Median (IQR)	Category of final diagnosis			
	Infections ($n=31$)	Collagen vascular ($n=34$)	Malignancy ($n=19$)	Sig
WBC (10^3/μl)	12.0[a] (7.1–15.3)	7.86[ab] (4.93–16.04)	7.6[b] (4.9–11.4)	0.121
Neutrophils (10^3/μl)	5.76[ac] (2.28–7.92)	5.227[b] (4.16–5.83)	2.356[c] (0.684–3.138)	< .001*
Lymphocytes (10^3/μl)	4.2[ab] (2.04–5.91)	1.95[b] (1.47–2.73)	4.18[c] (2.5–5.77)	0.001*
Neutrophil/Lymphocyte ratio	1.3[a] (0.5–4.2)	2.30[ab] (1.53–3.91)	0.6[b] (0.1–1.0)	< 0.010*
Platelets (10^3/μl)	329 (241.0–384.0)	338 (186.50–509.00)	192 (50.0–425.0)	0.838
HGB (g/dl)	10.6 (7.8–11.3)	8.65 (7.90–9.70)	8.8 (6.8–9.7)	0.251
Ferritin ($n=78$)	429 (114–10000)	502 (13–27000)	499 (262–5567)	0.669
CRP (mg/dl)	28.8 (12.5–123.3)	32 (3.68–147.75)	23.3 (11.6–139.1)	0.746
ESR (mm/hr)	71 (48.3–120.0)	87.5 (55.00–130.00)	110 (55.0–140.0)	0.073
Procalcitonin ng/ml ($n=53$)	0.54 (0.20–0.70)	0.44 (0.22–0.61)	0.21 (.03-.47)	0.354

Different letter superscript per column denotes significant pairwise comparison

Undiagnosed and miscellaneous categories were removed from the bivariate analysis. HGB (hemoglobin level), WBC (white blood cell count), CRP (C- reactive protein), ESR (erythrocyte sedimentation rate)

IQR Interquartile range

* Results ≤ .05 are statistically significant

Two cases of Epstein-Barr virus (EBV) were identified, making it the most common viral pathogen [6.5% ($n=2$)]. The diagnosis of these cases was based on the classical presentation of mononucleosis-like illness, accompanied by positive serology of EBV VCA IgM or rising titer of IgG. In addition, HIV and COVID-19 infections were each detected in 3.2% of infectious cases. Matched results were also detected [12, 17]. Geographical considerations, referral patterns, time of the study, and patient age may all contribute to the differences in the infectious category's aetiologies. In the current study, connective tissue diseases accounted for 30.9% of cases. Systemic lupus erythematosus (SLE) (47.1%) and systemic-onset juvenile idiopathic arthritis (38.2%) were the most common causes. This was like studies carried out by Chien et al. [10] and Lodhi et al. [18]. Meanwhile, juvenile idiopathic arthritis was the most common in other studies [9, 12, 14].

In the miscellaneous group, post-COVID-19 Multisystem inflammatory syndrome in children (MIS-C) was the most common cause accounting for 52.4% ($n=11$) of cases, this was not reported in previous studies as the current study was conducted following the COVID-19 pandemic in 2019. The diagnosis of MIS-C was based on the World Health Organization (WHO) case definition [19]. The second most common diagnosis in this category was hemophagocytic lymphohistiocytosis (HLH) which accounted for 23.8% of cases (5 cases).

The possibility of HLH should be kept in mind in all febrile patients with organomegaly and cytopenia involving one or more cell lines. Similar findings were observed in other studies [6, 12]. Acute lymphoblastic leukemia [68.4%($n=13$)] and lymphoma [26.3% ($n=5$)] were the most common in the malignant category. Additionally, there was only one case of neuroblastoma detected with positive flow cytometric immunophenotyping from a bone marrow aspirate. Similar findings were matched with other studies [10, 14, 20].

Though, a comparison between collagen vascular, infectious, and malignancy categories regarding demographic categories found a difference in the distribution of age this was found to be statistically insignificant ($P=0.575$). In the infectious category, preschool children (1–5 years) were the most common (38.7%), while school-age children were the most common age group in the collagen and malignancy categories [(55.9%) and (52.6%) respectively]. Additionally, adolescent children were mainly presented in the collagen category (17.6%).

In contrast to age, sex was significantly different ($P=0.007$); females (64.7%) were common in the collagen vascular category, while males were more common in the infectious (61.3%), and malignancy (78.9%) categories. Comparable findings were also detected in studies done in Taiwan and Korea [9, 20].

Comparing the duration of fever; though the median duration of fever before admission [45.0 (21.0–68.0) days] was longer in the malignant category this difference was not statistically significant ($P=0.390$) similar findings were detected by Reddy et al. and Joshi et al.; who also detected longest duration of fever in malignancy too [11, 21].

Regarding the clinical presentations, children in the infectious category showed higher rates of hepatomegaly (41.9%) and splenomegaly (35.5%), but these differences were not statistically significant (p-values of 0.24 and 0.06, respectively). On the other hand, lymphadenopathy was significantly more prevalent in the collagen (63.6%) and malignant (78.9%) categories. Additionally, arthritis (38.2%) and bone pain (68.4%) were significantly more common in the collagenic and malignant categories, respectively.

In addition to clinical presentation, laboratory data can offer important clues for making a differential diagnosis. Children in the infectious category significantly had higher neutrophil count [5.76 (2.28–7.92)×10^3/µl] and lymphocytic count [4.2 (2.04–5.91)×10^3/µl]; ($P<0.001$ and <0.010 respectively). In the collagen category the median lymphocytic count was lower [1.95 (1.47–2.73)×10^3/µl] with significant ($P<0.010$) higher neutrophil/ lymphocyte ratio [2.30 (1.53–3.91)]. Other laboratory markers showed no significant difference between the three groups. Therefore, a higher neutrophil and lymphocytic count can predict infectious causes in children with FUO while a low lymphocytic count could predict collagen diseases. Similar results were documented by Ching-Yi Cho in Tawain [20].

Though inflammatory markers, including C-reactive protein (CRP), and ferritin, were higher in the collagen category, and erythrocyte sedimentation rate (ESR) was the highest in the malignant categories; these differences were statistically insignificant. Different results were detected by Bing et al. in China where WBC, CPR, ESR, and PCT in the inflammatory group were significantly higher than those in other groups ($p<0.05$) [12]. Moreover Ching-Yi Cho in Tawain [20] found a significant elevation of CRP levels in the infectious group ($p<0.01$) and hemoglobin level was significantly lower (12 g/dL) in autoimmune and malignancy ($p<0.01$).

Limitation

First, it is one tertiary-centre study that receives more complicated cases that may not fully explain the pattern of FUO in children. Multicentre studies are needed in the future to validate these results.

Second, given the limited number in each category, though there were significant differences in some clinical presentations and laboratory parameters the current data can't be used statistically to identify predictors for the diagnosis of FUO.

Conclusions

In the current study, the emergency of COVID-19 could have an impact on the change of the etiology of FUO as collagen vascular diseases increase as the most common cause of FUO in children. In the infectious category, acute schistosomiasis (Katayama fever) and urinary tract infections (UTI) are the most common causes. Emergency of post-COVID-19 Multisystem inflammatory syndrome (MIS-C) as a cause of FUO in the miscellaneous category. Children in the infectious category tend to have high neutrophil and lymphocytic counts versus low lymphocytic counts in collagen diseases.

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Authors' contributions
WS revised and analyzed the data, regarding collagenic and autoinflammatory diseases, and contributed in the writing of the manuscript. AG revised the results and edited the final manuscript. AM collected the data following the parent's consent and shared it in statistical processing with an interpretation of the data. EH revised and analyzed data regarding the diagnosis of the infectious category and was a major contributor in the writing and finalization of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The data used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted following the Declaration of Helsinki and approved by the ethical committee of the Faculty of Medicine, Alexandria University. Informed written consent was obtained from all parents or caregivers of children before enrolment with ascertainment of the confidentiality of personal data.

Consent for publication
Not applicable.

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

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