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Clinical Features of Spontaneous Remission in the Classic Fever of Unknown Origin: A Retrospective Study

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ABSTRACT

Objective To summarize the clinical features of spontaneous remission in classic fever of unknown origin (FUO).

Methods Medical records of 121 patients diagnosed with FUO at admission in Peking Union Medical College Hospital between January 2018 and June 2018 were reviewed retrospectively. Patients who were discharged without etiological diagnoses were followed for 2 years. The clinical features and outcomes of these patients were summarized. Multivariate *logistic* regression was used to analyze related factors of spontaneous remission of FUO.

Results After excluding 2 patients who lost to follow-up, the etiology of 119 FUO patients were as follows: infectious diseases in 30 (25.2%) cases, connective tissue diseases in 28 (23.5%) cases, tumor diseases in 8 (6.7%) cases, other diseases in 6 (5.0%) cases, and unknown diagnoses in 47 (39.5%) cases. Totally, 41 patients experienced spontaneous remission of fever (the median time from onset to remission was 9 weeks, ranging from 4 to 39 weeks). In patients with spontaneous remission in FUO, lymphadenopathy was less common clinical manifestation, the levels of inflammatory markers including leukocyte count, neutrophil count, neutrophil ratio, C-reactive protein, and ferritin were lower, and the proportion of CD8 positive T lymphocytes expressing CD38 was lower. Multivariate *logistic* regression analysis of factors with a P-value < 0.05 in univariate analysis shown that white blood cell count (OR: 0.545, 95%CI: 0.306-0.971, $P = 0.039$), neutrophil count (OR: 2.074, 95%CI: 1.004-4.284, $P = 0.049$), and proportion of neutrophils (OR: 0.928, 95%CI: 0.871-0.990, $P = 0.022$) were independent significant factors associated with spontaneous remission in FUO.

Conclusions This study suggested that most patients discharged with undiagnosed classic FUO would remit spontaneously. Thus, for patients with stable clinical conditions, follow-up and observation could be the best choice. Patients with lower level of some inflammatory factors may have a high likelihood of spontaneous remission in classic FUO.

Key words: fever of unknown origin; follow-up; spontaneous remission; diagnosis

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INTRODUCTION

Classic fever of unknown origin (FUO) is one common and refractory disease. FUO is defined as 1) a community-acquired fever lasting over 3 weeks, 2) with a temperature rising above 38.3 ℃ on several occasions, 3) for which no diagnosis has been reached despite 3 outpatient visits or 1 week of inpatient investigation with complete medical history inquiry, physical examination, and routine laboratory test[1]. FUOs were caused by infections, malignancy, connective tissue diseases, and miscellaneous other causes. No cause was determined in some patients with FUOs after systematic investigations. Despite the improvement of diagnostic technology, including advanced serological, imaging, culturing, and molecular diagnostic techniques, more FUO cases remain undiagnosed after extensive diagnostic workup. Due to the development of medical science, variations in the definitions of FUOs, and geographical differences, the etiologies of FUOs in different times and locations were not consistent. 20%-50% of FUOs have eluded diagnosis according to literature[2,3]. But most of the undiagnosed FUO patients remitted spontaneously during clinical follow-ups, as many studies have shown[4-9]. However, how to identify patients with a higher possibility to remit spontaneously and manage such patients remains challenging for physicians. We retrospectively reviewed 121 patients diagnosed with FUO in the Department of Infectious Disease at Peking Union Medical College Hospital and the patients who were discharged with undiagnosed FUOs were followed. The clinical characteristics of patients with spontaneous remission of FUO were summarized, and the related factors of spontaneous remission of FUO were explored.

PATIENTS AND METHODS

Study population

Study participants were 121 patients with fever as the main clinical manifestation, who were admitted in the Department of Infectious Disease at Peking Union Medical College Hospital from January 2018 through June 2018. All 121 patients met Petersdorf and Beeson's diagnostic criteria for FUO[1] at admission. This study was approved by the Ethics Committee of Peking Union Medical College Hospital (No. S-K1428). The data are anonymous, and the informed consent was waived.

We performed a retrospective analysis on clinical data of 121 inpatients with FUOs. We summarized the etiological diagnoses at the time of discharge. For those who were discharged without clear etiological diagnoses, we carried out a 2-year follow-up to clarify the diagnosis, treatment process, and outcomes after discharge. The clinical characteristics of patients with spontaneously remitted FUOs were analyzed, and the related factors of spontaneous remission in FUOs were explored.

Diagnosis and treatment process of FUOs

Initially, manipulation of the thermometer needs to be excluded. Then we searched potential diagnostic clues (PDCs) based on detailed medical history collection, physical examination, and fundamental laboratory examinations. All non-essential medications were discontinued to exclude drug-induced fever. For patients with PDCs, further investigation was performed accordingly; for patients without PDCs or etiological diagnoses, PET-CT was considered for further clues. If the etiological diagnosis was not reached, we took follow-up observation, diagnostic anti-tuberculosis treatment, or further investigations based on their general conditions. The specific diagnosis and treatment process are shown in **Fig. 1**.

Statistical analysis

Multivariate *logistic* regression was used to evaluate potential predictive factors, and variables that showed a significant association in the univariate analysis were entered into the multivariable *logistic* regressions model (Backward Logistic Regression, entry 0.05, removal 0.10). P-value < 0.05 was considered significant.

RESULTS

Etiological diagnosis

From January 2018 through June 2018 a total of 121 patients diagnosed with FUO were admitted to the Department of Infectious Disease in Peking Union Medical College Hospital. 70 (57.9%) of 121 patients had etiological diagnoses by the time of discharge. Their FUOs were caused by infectious diseases (30, 24.8%), connective tissue diseases (28, 23.1%), malignancy (8, 6.6%), and miscellaneous other diseases (5, 4.1%). 51 (42.1%) patients remained undiagnosed when discharged, with follow-up data available for 49 cases. No

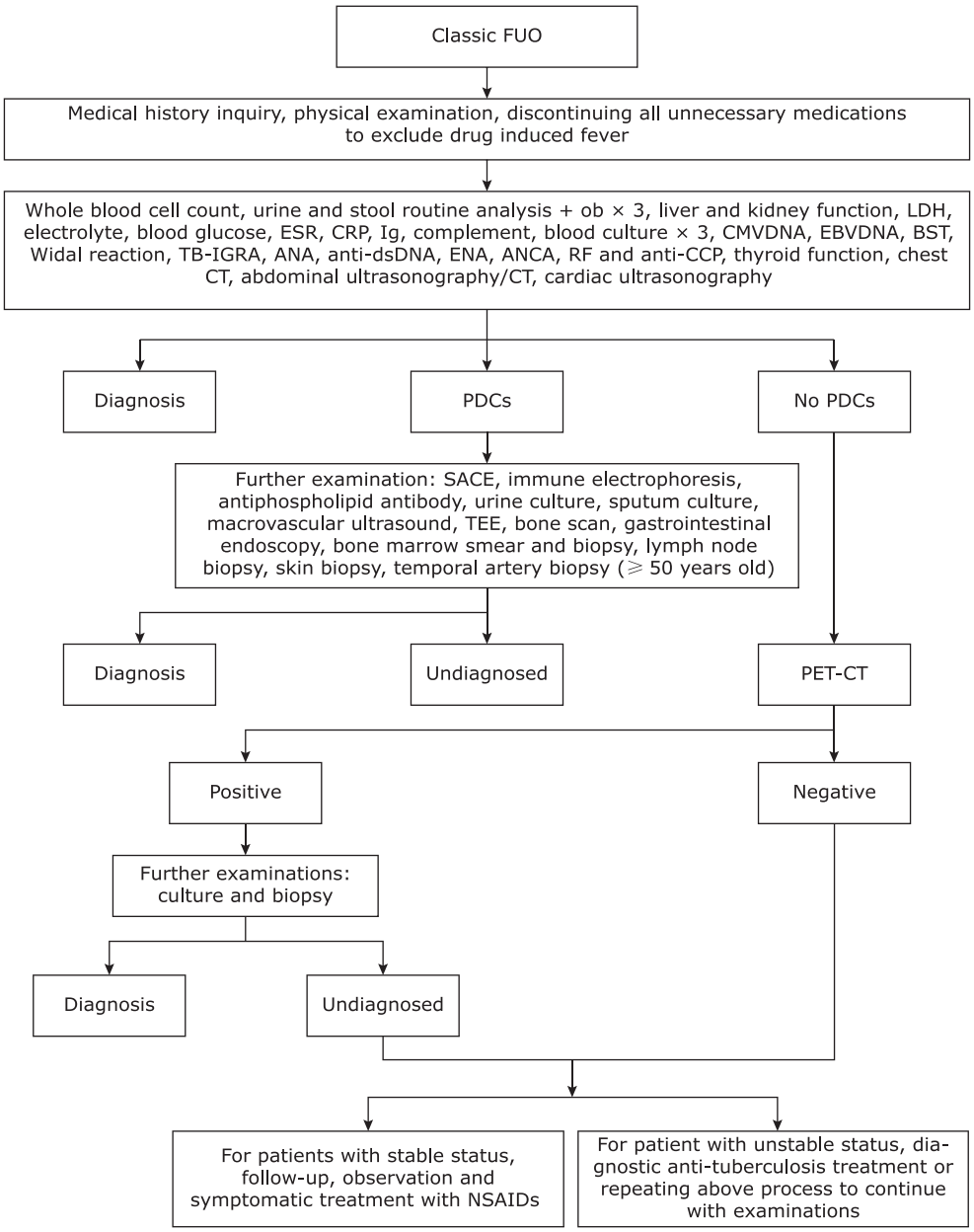

Figure 1. Diagnosis and treatment process of classic FUO.

FUO: fever of unknown origin; LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Ig: immunoglobulin; CMVDNA: cytomegalovirus DNA; EBVDNA: Epstein-Barr virus; BST: blood serologic test; TB-IGRA: interferon-gamma release assay for Mycobacterium tuberculosis; ANA: antinuclear antibody; ENA: extractable nuclear antigen; ANCA: antineutrophil cytoplasmic antibody; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide; CT: computed tomography; PDCs: potential diagnostic clues; SACE: serum angiotensin converting enzyme; TEE: trans esophageal echocardiography; PET/CT: positron emission tomography/computed tomography; NSAIDs: nonsteroidal antiinflammatory drugs.

patients died during hospitalization.

The 2-year follow-up of undiagnosed FUO patients shown that diagnoses were established in 2 cases after discharge, which was adult-onset Still's disease and hemophagocytic syndrome, respectively; 47 cases remain undiagnosed, of which 41 cases experienced spontaneous remission of fever (the median time from onset to remission was 9 weeks, ranging from 4 to 39 weeks), and 6 patients still had recurrent fevers. Only 1 patient died during the fol-

low-up period, who is the patient diagnosed with hemophagocytic syndrome.

Overall, after excluding 2 patients who lost follow-up, the etiology of 119 FUO patients were as follows: infectious diseases in 30 (25.2%) cases, connective tissue diseases in 28 (23.5%) cases, tumor diseases in 8 (6.7%) cases, other diseases in 6 (5.0%) cases, and unknown diagnoses in 47 (39.5%) cases (see **Table 1** for details). The median time from onset to diagnosis was 14.5 weeks, ranging from 4 to 299 weeks.

Clinical features

The median age of 119 patients was 43±17 years. 66 (55.5%) patients were male, and 53 (44.5%) were female. Hyperpyrexia was the most common clinical manifestation. A maximum body temperature between 39℃ and 41°C was observed in 77 (64.7%) patients. Other common clinical manifestations were anemia (60.9%), hypoproteinemia (54.6%), splenomegaly/hepatosplenomegaly (42.9%), lymphadenopathy (37.8%), rash (33.6%), liver damage (19.3%), and arthritis (18.5%). Inflammatory markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and ferritin were elevated in different levels. In treatment, almost all patients received empirical antibiotic therapy, 38.7% of patients received glucocorticoid treatment before diagnosed, and 11.8% of patients received diagnostic anti-tuberculosis treatment (**Table 2**).

Factors associated with spontaneous remission in FUO

Univariate analysis showed that in patients with spontaneous remission in FUO lymphadenopathy was less common clinical manifestation [*OR*: 0.396, 95%*CI*: 0.171-0.919, *P* = 0.031), the levels of inflammatory markers including leukocyte count (*OR*: 0.892, 95%*CI*: 0.811-0.981, *P* = 0.019), neutrophil count (*OR*: 0.884, 95%*CI*: 0.794-0.994, *P* = 0.024), neutrophil ratio (*OR*: 0.967, 95%*CI*: 0.941-0.995, *P* = 0.018), CRP (*OR*: 0.993, 95%*CI*: 0.986-1.000, *P* = 0.049), and ferritin (*OR*: 1.000, 95%*CI*: 0.999-1.000, *P* = 0.063) were lower, and the proportion of CD8 positive T lymphocytes expressing CD38 was lower (*OR*: 0.977, 95%*CI*: 0.956-0.997, *P* = 0.028, **Table 3**). Multivariate *logistic* regression analysis of factors with a *P*-value < 0.05 in univariate analysis showed that white blood cell count (*OR*: 0.545, 95%*CI*: 0.306-0.971, *P* = 0.039), neutrophil count (*OR*: 2.074, 95%*CI*: 1.004-4.284, *P* = 0.049), and proportion of neutrophils (*OR*: 0.928, 95%*CI*: 0.871-0.990, *P* = 0.022) were independent significant related to spontaneous remission in FUO.

Table 1. Etiological diagnosis of 119 classic FUO cases

Items	Case number (%)
Infectious diseases	30 (25.2)
Bacterial infections	21 (17.6)
Tuberculosis	8 (6.7)
Infective endocarditis	5 (4.2)
Osteomyelitis	5 (4.2)
Disseminated nontuberculous mycobacteria infection	3 (2.5)
Viral infections	9 (7.6)
Epstein-Barr virus infection	7 (5.9)
Cytomegalovirus infection	2 (1.7)
Connective tissue diseases	28 (23.5)
Adult-onset Still's disease	16 (13.4)
Polymyalgia rheumatica	3 (2.5)
Rheumatoid arthritis	2 (1.7)
Systemic vasculitis	2 (1.7)
Takayasu arteritis	1 (0.8)
Nodular feverish non-suppurative panniculitis	1 (0.8)
Systemic lupus erythematosus	1 (0.8)
Undifferentiated connective tissue diseases	2 (1.7)
Malignant tumors	8 (6.7)
Castleman's disease	2 (1.7)
Colonic sarcoma	1 (0.8)
Prostate cancer	1 (0.8)
Renal carcinoma	1 (0.8)
Gastric carcinoma	1 (0.8)
Undifferentiated carcinoma	2 (1.7)
Miscellaneous other diseases	6 (5.0)
Hemophagocytic syndrome	3 (2.5)
Necrotizing lymphadenitis	2 (1.7)
Drug induced fever	1 (0.8)
Undiagnosed: follow up results	47 (39.5)
Spontaneous remission	41 (34.5)
Recurrent fever	6 (5.0)

Table 2. Clinical characteristics of classic FUOs with different causes

Items	Classic FUO	Spontaneous remission	Infections	Autoimmune diseases	Malignancies	Others	Recurrent FUO
n	119	41	30	28	8	6	6
Age (yrs, mean±SD)	43±17	43±17	43±19	42±17	48±13	37±16	45±13
Gender [*n* (%)]							
Male	66 (55.5)	22 (53.7)	19 (63.3)	11 (39.3)	6 (75.0)	3 (50.0)	5 (83.3)
Female	53 (44.5)	19 (46.3)	11 (36.7)	17 (60.7)	2 (25.0)	3 (50.0)	1 (16.7)
T_{max} [*n* (%)]							
⩽ 39℃	41 (34.5)	15 (36.6)	12 (40.0)	7 (25.0)	4 (50.0)	2 (33.3)	1 (16.7)
39°C-41°C	77 (64.7)	26 (63.4)	18 (60.0)	20 (71.4)	4 (50.0)	4 (66.7)	5 (83.3)
> 41℃	1 (0.8)	0	0	1 (3.6)	0	0	0
Rash [*n* (%)]	40 (33.6)	8 (19.5)	7 (23.3)	19 (67.9)	1 (12.5)	5 (83.3)	0
Arthritis [*n* (%)]	22 (18.5)	5 (12.2)	2 (6.7%)	12 (42.9)	0	1 (16.7)	2 (33.3)
Lymphadenopathy [*n* (%)]	45 (37.8)	10 (24.4)	10 (33.3)	17 (60.7)	2 (25.0)	4 (66.7)	2 (33.3)
Spleno/hepatosplenomegaly [*n* (%)]	51 (42.9)	12 (29.3)	15 (50.0)	13 (46.4)	2 (25.0)	4 (66.7)	3 (50.0)
Digestive system involvement [*n* (%)]	5 (4.2)	0	1 (3.3)	0	3 (37.5)	1 (16.7)	0
Renal involvement [*n* (%)]	8 (6.7)	2 (4.9)	1 (3.3)	2 (7.1)	3 (37.5)	0	0
Respiratory system involvement [*n* (%)]	7 (5.9)	1 (2.4)	1 (3.3)	3 (10.7)	1 (12.5)	0	1 (16.7)
Neural system involvement [*n* (%)]	5 (4.2)	1 (2.4)	3 (10.0)	1 (3.6)	0	0	0
Cardiovascular involvement [*n* (%)]	4 (3.4)	0	3 (10.0)	1 (3.6)	0	0	0
WBC ($\times 10^9$/L, mean±SD)	8.45±4.90	6.94±3.84	8.26±5.20	10.8±5.61	10.07±4.28	6.60±3.98	8.28±4.67
NEUT [$\times 10^9$/L, median (IQR)]	5.29 (2.96, 7.94)	3.82 (2.49, 6.28)	5.26 (2.48, 7.95)	6.48 (4.69, 12.4)	6.46 (5.29, 7.84)	3.86 (2.45, 5.49)	5.77 (3.23, 10.44)
NEUT% (mean±SD)	69.4±15.3	63.8±15.9	69.9±17.0	75.0±12.4	72.9±9.1	63.8±15.0	80.1±8.1
HB (g/L, mean±SD)[a]	108±20	112±15	110±23	103±21	92±18	110±21	112±19
PLT ($\times 10^9$/L, mean±SD)[b]	293±132	309±116	244±150	332±114	304±145	251±70	267±198
Anemia [*n* (%)][a]	70 (60.9)	19 (51.4)	18 (60.0)	19 (67.9)	7 (87.5)	4 (66.7)	3 (50.0)
Liver damage [*n* (%)]	23 (19.3)	9 (22.0)	8 (26.7)	3 (10.7)	1 (12.5)	2 (33.3)	0
Hypoproteinemia [*n* (%)]	65 (54.6)	20 (48.8)	18 (60.0)	15 (53.6)	7 (87.5)	3 (50.0)	2 (33.3)
ALB (g/L, mean±SD)	34±6	35±6	34±5	33±5	29±5	34±3	35±4
ESR (mm/h, mean±SD)	73±38	69±37	58±39	90±32	106±27	51±36	62±33
CRP [mg/L, median (IQR)]	56.69 (23.66, 115.55)	32.40 (17.1, 108.2)	37.85 (21.64, 97.77)	91.96 (57.40, 136.55)	133.56 (73.85, 236.32)	50.59 (27.63, 83.02)	46.10 (24.27, 97.98)
Ferritin [ng/ml, median (IQR)][c]	551 (253, 1,570)	380 (103, 601)	576 (253, 1,675)	2501 (581, 7,459)	382 (255, 1,534)	1126 (567, 3,674)	272 (101, 445)
PET/CT positive [ratio (%)][d]	42/51 (82.4)	8/12 (66.7)	9/10 (90.0)	13/16 (81.3)	5/5 (100)	4/4 (100)	3/4 (75.0)
Antibiotic treatment [*n* (%)]	116 (97.5)	40 (97.6)	30 (100)	28 (100)	8 (100)	5 (83.3)	5 (83.3)
Antivirus treatment [*n* (%)]	12 (10.1)	4 (9.8)	4 (13.3)	3 (10.7)	0	0	1 (16.7)
Diagnostic anti-tuberculosis treatment [*n* (%)]	14 (11.8)	2 (4.9)	7 (23.3)	3 (10.7)	0	0	2 (33.3)
Glucocorticoid treatment [*n* (%)]	46 (38.7)	10 (24.4)	8 (26.7)	20 (71.4)	1 (12.5)	4 (66.7)	3 (50.0)

WBC: white blood cell; NEUT: neutrophil; HB: hemoglobin; PLT: platelet; ALB: albumin.

a. 4 patients with iron deficiency anemia were excluded. b. 1 patient with idiopathic thrombocytopenia was excluded. c. 17 patients did not check ferritin, 4 patients with iron deficiency anemia were excluded. d. PET/CT positive criteria: any focal or diffuse FDG uptake: 1) intensity higher than that of surrounding tissues, 2) localized to an area that did not correspond to the physiologic distribution in correlation with the corresponding CT slices.

Table 3. Univariate analysis of related factors of spontaneous remission in FUO patients

Items	Spontaneous remissions in FUO (*n*=41)	Non-spontaneous remission in FUO (*n*=78)	*OR* (95%*CI*)	*P*-value
Age (yrs, mean±SD)	43±17	43±17	1.002 (0.980-1.025)	0.876
Gender [*n* (%)]			0.895 (0.419-1.913)	0.774
Male	22 (53.7)	44 (56.4)		
Female	19 (46.3)	34 (43.6)		
Rash [*n* (%)]	8 (19.5)	31 (39.7)	0.426 (0.179-1.015)	0.054
Arthritis [*n* (%)]	5 (12.2)	17 (21.8)	0.498 (0.169-1.466)	0.206
Lymphadenopathy [*n* (%)]	10 (24.4)	35 (44.9)	0.396 (0.171-0.919)	0.031
Splenomegaly/hepatosplenomegaly [*n* (%)]	12 (29.3)	37 (47.4)	0.459 (0.205-1.027)	0.058
Liver damage [*n* (%)]	9 (22.0)	14 (17.9)	1.286 (0.503-3.287)	0.600
WBC ($\times10^9$/L, mean±SD)	6.94±3.84	9.24±5.22	0.892 (0.811-0.981)	0.019
NEUT [$\times10^9$/L, median (IQR)]	3.82 (2.49, 6.28)	5.93 (3.74, 8.62)	0.884 (0.794-0.994)	0.024
NEUT% (mean±SD)	63.8±15.9	72.3±14.3	0.967 (0.941-0.995)	0.018
HB (g/L, mean±SD)[a]	112±15	106±21	1.016 (0.995-1.037)	0.136
PLT ($\times10^9$/L, mean±SD)[b]	309±116	285±139	1.001 (0.999-1.004)	0.331
ALB (g/L, mean±SD)	35±6	33±5	1.058 (0.989-1.133)	0.101
ESR (mm/h, mean±SD)	69±37	74±39	0.997 (0.987-1.007)	0.551
CRP [mg/L, median (IQR)]	32.40 (17.1, 108.2)	72.2 (32.2, 117.2)	0.993 (0.986-1.000)	0.049
Ferritin [(ng/ml, median (IQR)][c]	380 (103, 601)	760 (331, 3476)	1.000 (0.999-1.000)	0.063
IL-6 [pg/ml, median (IQR)][d]	10.1 (2.0, 21.5)	21.0 (6.3, 45.2)	0.980 (0.947-1.014)	0.244
IL-8 [pg/ml, median (IQR)][d]	58 (42, 120)	108 (57, 372)	0.996 (0.990-1.001)	0.151
IL-10 [pg/ml, median (IQR)][d]	5.0 (5.0, 5.0)	5.0 (5.0, 10.5)	0.826 (0.552-1.235)	0.351
TNF-α[pg/ml, median (IQR)][d]	24.4 (9.2, 39.9)	25.1 (18.1, 44.2)	0.979 (0.938-1.023)	0.343
Lymphocyte [$\times10^9$/L, median (IQR)][e]	1266 (873, 1629)	1189 (874, 1720)	1.000 (0.999-1.000)	0.482
Lymphocyte percentage [median (IQR)]	21.2 (15.9, 31.1)	16.6 (11.5, 23.7)	1.034 (0.999-1.070)	0.058
B lymphocyte [$\times10^6$/L, median (IQR)]	76 (40, 132)	65 (42, 105)	1.002 (0.996-1.007)	0.508
B lymphocyte percentage [median (IQR)]	6.9 (3.5, 9.8)	5.2 (2.8, 8.1)	1.037 (0.940-1.144)	0.472
NK cell [$\times10^6$/L, median (IQR)]	142 (62, 196)	116 (61, 194)	1.001 (0.998-1.005)	0.407
NK cell percentage [median (IQR)]	10.7 (6.2, 14.5)	9.0 (6.4, 13.9)	1.023 (0.966-1.085)	0.434
T lymphocyte [$\times10^6$/L, median (IQR)]	1042 (712, 1278)	976 (683, 1329)	1.000 (0.999-1.000)	0.338
T lymphocyte percentage [median (IQR)]	81.6 (77.4, 84.7)	82.8 (76.2, 88.5)	0.981 (0.936-1.029)	0.433
CD4+ T lymphocyte [$\times10^6$/L, median (IQR)]	552 (374, 725)	480 (328, 689)	1.000 (0.999-1.001)	0.698
CD4+ T lymphocyte percentage [median (IQR)]	44.6 (33.8, 50.8)	43.7 (33.8, 47.9)	1.017 (0.979-1.057)	0.383
CD8+ T lymphocyte [$\times10^6$/L, median (IQR)]	382 (228, 473)	356 (238, 647)	0.999 (0.998-1.000)	0.189
CD8+ T lymphocyte percentage [median (IQR)]	29.9 (21.8, 38.9)	30.7 (24.9, 38.5)	0.983 (0.948-1.019)	0.344
CD8+HLA-DR+/CD8+ percentage [median (IQR)]	45.0 (26.9, 57.6)	53.8 (32.0, 73.8)	0.983 (0.965-1.002)	0.076
CD8+CD38+/CD8+ percentage [median (IQR)]	67.0 (43.5, 78.8)	73.1 (55.4, 87.0)	0.977 (0.956-0.997)	0.028
PET-CT positive [*n* (%)][f]	8 (66.7)	34 (87.2)	0.294 (0.064-1.350)	0.115

IL: interleukin; TNF-α: tumor necrosis factor α; NK: nature killer cell.

a. 4 patients with iron deficiency anemia were excluded. b. 1 patient with idiopathic thrombocytopenia was excluded. c. 30 patients in the spontaneous remissions group and 68 patients in the non-spontaneous group were included in the analysis of ferritin. d. 10 patients in the spontaneous remissions group and 29 patients in the non-spontaneous group were included in the analysis of IL-6 and IL-10; 10 patients in the spontaneous remissions group and 27 patients in the non-spontaneous group were included in the analysis of IL-8; 10 patients in the spontaneous remissions group and 23 patients in the non-spontaneous group were included in the analysis of TNF-α. e. 30 patients in the spontaneous remissions group and 68 patients in the non-spontaneous group were included in the analysis of lymphocyte. f. PET/CT positive criteria: any focal or diffuse FDG uptake: 1) intensity higher than that of surrounding tissues, 2) localized to an area that did not correspond to the physiologic distribution in correlation with the corresponding CT slices.

DISCUSSION

Classic FUO is caused by over 200 various clinical entities and remains a diagnostic challenge for practitioners[10]. Some retrospective studies tracked the changing cause of these fevers, and only a few studies had reported outcomes of patients discharged with undiagnosed FUO. Although these patients underwent systematic investigations and remained undiagnosed, their prognosis is relatively good. Previous studies showed that after follow-ups of 1-10 years, the mortality rate was 2.7%-15.5%, and the spontaneous remission rate was 44.8%-78.4% (**Table 4**)[4-9]. In our study, in 51 patients who were discharged with undiagnosed FUO, only 1 mortality was observed during a 2-year follow-up. Therefore, for patients with relatively stable clinical manifestations and unclear etiological diagnoses, prolonged observation and follow-up can be adopted as a treatment strategy.

Identifying predictors of spontaneous remission may optimize management strategies, by reducing unnecessary invasive examinations such as biopsy, and empiric use of steroids or antibiotics. However, the study about identifying patients with a higher likelihood to remit spontaneously is limited. A meta-analysis showed that negative PET/CT results indicate a higher possibility of spontaneous remission in undiagnosed classic FUO patients (r*RR*=1.2 per 1 year, 95%*CI*: 1.0-1.3, $P=0.13$)[11]. Nevertheless, in some serious or fatal diseases such as adult-onset Still's disease, tuberculosis, and some hematological malignancies, PET/CT usually shows no located lesions. Therefore, PET/CT results as a predictor of spontaneous remission in FUO still need further study to validate, and other predictors should be evaluated to establish a reliable predicting system. In this study, limited data suggested that there was no significant difference in PET/CT positive rate between the spontaneous remission group and the non-spontaneous remission group.

In this study, follow-up data revealed that undiagnosed FUO patients with lower levels of inflammatory factors including white blood cell count, neutrophil count, neutrophil ratio, CRP, and ferritin had a high likelihood of spontaneous remission during 2-year follow-up. Thus, inflammation-related factors may be predictors of spontaneous remission in FUO. FUO is a systemic response to inflammation. In acute or chronic inflammation, the concentration of some serum protein such as CRP and ferritin will increase, which is called acute phase reactant (APR), which is observed in a variety of diseases, including infection, trauma, infarction, systemic autoimmune and inflammatory diseases, as well as malignancies. ESR is an indirect APR, which is a clue for plasma viscosity, acute-phase protein (especially fibrinogen), and miscellaneous other factors. The changes in APR levels were mainly caused by cytokines, especially interleukin 6 (IL-6), IL-8, IL-1β, tumor necrosis factor-α, and interferon γ. Among the numerous cytokines that can alleviate inflammation, IL-10 and transforming growth factor-β are the most important anti-inflammatory cytokines[12]. For cases of undiagnosed FUO without spontaneous remission, the essential mechanism of prolonged inflammation is the persistent existence of inflammatory stimuli. In undiagnosed FUO cases with spontaneous remission, no definite sign of infection, malignancy, or autoimmune diseases was observed. It is possible that after the removal of triggers like virus infection and allergens, inflammation lasted for some time before remission. Therefore, patients with spontaneously remitted undiagnosed FUO have relatively mild inflammatory responses, compared with those who have prolonged

Table 4. Outcomes of FUO patients undiagnosed at discharge in literatures

Study	Number of FUO[a]	Follow-up time	Patients with spontaneous remission [*n* (%)]	Deaths [*n* (%)]
Knockaert *et al*.[4]	61	5 years	41 (67.2)	6/2[b] (3.2)
Vanderschueren *et al*.[5]	95	574 (125-2052) days	63 (66.3)	3 (3.2)
Zenone[8]	37	/	29 (78.4)	1 (2.7)
Bleeker-Rovers *et al*.[6]	37	12 (6-23) months	21 (56.8)	1 (2.7)
Mansueto *et al*.[7]	29	2 years	13 (44.8)	4 (13.8)
Tan *et al*.[9]	58	518 (0.4-830) weeks	35 (60.3)	10/9[c] (15.5)

a. Total number of patients discharged with undiagnosed FUO. b. Six patients died, although the cause of death was considered to be related to the disease that caused FUO in only two cases. c. Ten patients died, although the cause of death was considered to be related to the disease that caused FUO in nine cases.

undiagnosed FUO.

The limitation of this study is that this study is a retrospective study with a small sample size in a single center. Further prospective studies are needed to validate the potential predictors of spontaneous remission in FUO.

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Conflict of interest

The authors declare that they have no competing interests.

Author contribution

Shi XC and Liu CY wrote the manuscript. Shi XC analyzed the data. Liu XQ revised the manuscript. All have reviewed and approved the final version of this paper.

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