Clinical Features and Long-term Outcomes of Lymphoma Patients Initially Presenting as Fever With Unknown Origin

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Research Article

Keywords: fever of unknown origin, lymphoma, clinical features, outcomes

Posted Date: September 24th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-847421/v1>

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Abstract

Background

Lymphoma is found to be the main source of non-infectious fever of unknown origin (FUO). However, there is a lack of clinical features and outcomes in lymphoma patients initially presenting as FUO.

Methods

From January 1, 2013 to December 31, 2019, our center enrolled 185 patients who initially presented as FUO then confirmed to be lymphoma in Huadong Hospital of Fudan University. During the same study period, 332 lymphoma patients without FUO received treatment in our center. After the exclusion, 509 patients were included in the retrospectively study. The differences in clinical manifestations, laboratory examinations, overall response rates and survival rates between the FUO and non-FUO groups were analyzed. The clinical endpoints were overall survival (OS) and progress-free survival (PFS).

Results

In the non-FUO group (329 in total), Hodgkin's lymphoma (HL) was 17 (5.2%), B cell non-Hodgkin's lymphoma (B-NHL) was 276 (83.9%), T cell non-Hodgkin's lymphoma (T-NHL) was 32 (9.7%) and NK/T cell lymphoma (NK/T-CL) was 4 (1.2%). In the FUO group (180 in total), B-NHL was 88 (48.9%), T-NHL was 60 (33.3%), NK/T-CL was 24 (13.3%) and HL was 8 (4.4%). During the hospitalization, the maximum body temperature of the FUO group diagnosed with B-NHL, T-NHL and NK/T-CL was statistically higher than that of the non-FUO group (all $P < 0.05$). Concerning the overall response rates, there was no difference between the FUO and non-FUO groups, whatever the pathological subtype was. The differences in OS between the FUO and non-FUO groups were significant for HL ($P = 0.006$), B-NHL ($P = 0.007$) and T-NHL ($P = 0.013$). No difference in overall survival was observed in the two groups for the subtype of NK/T-CL ($P = 0.141$). In terms of PFS, there was no significant difference between FUO and non-FUO groups for any subtype (all $P > 0.05$).

Conclusion

We found that the major subtypes of lymphoma initially presenting as FUO were B-NHL and T-NHL. The main diagnostic biopsy sites were subcutaneous lymphnodes, bone marrow and spleen for lymphoma patients with FUO. Patients with FUO suffered from a higher risk of all-cause death in the long term.

Introduction

Clinically, classic fever of unknown origin (FUO) is defined as body temperature $\geq 38.3^{\circ}\text{C}$, fever lasting for > 3 weeks, and uncertain diagnosis after one week's examination.¹ In 1991, the definition of FUO was re-discussed and the observation period was abridged to 3 days instead of 1 week.² Given the numerous diseases associated with FUO, accurate diagnosis requires comprehensive information gathered from medical history, physical examination, laboratory and imaging studies.³ Among those with FUO, lymphoma is the leading cause of neoplastic diseases and accounts for 8.7%-31%.⁴ However, there is a lack of data demonstrating the differences in clinical characteristics and outcomes of lymphoma patients initially presenting as FUO.

This study aimed to indicate clinical features and outcomes of lymphoma patients with FUO.

Methods

Study design

From January 1, 2013 to December 31, 2019, our center enrolled 185 patients who initially presented as FUO then confirmed to be lymphoma in Huadong Hospital of Fudan University. During the same study period, 332 lymphoma patients without FUO received treatment in our center.

FUO was defined as $\geq 38.3^{\circ}\text{C}$, lasting > 3 weeks, and uncertain diagnosis after three outpatient visits or three days of in-hospital investigation.^{1,2} Ann Arbor classification system was utilized to identify the stage of lymphoma.⁵ Pathology was classified according to the World Health Organization (WHO) classification of hematopoietic and lymphoid tissue tumors in 2018.⁶

Exclusion criteria were as follows: clinical or instrumental evidence of infection; immunodeficiency disorders; incomplete data. Among 517 patients, 4 were excluded due to HIV infection, 2 were due to the diagnosis of immunodeficiency disorders and 2 due to incomplete data. The remaining 509 patients were included in the study population.

Patients were divided into the FUO and non-FUO groups, based on whether the initial symptom of lymphoma was FUO. The clinical manifestations, diagnostic biopsy locations, pathological results, laboratory examinations, outcomes of the FUO and non-FUO groups were reviewed and analyzed. This study was approved by the ethics committee of Huadong Hospital (2021K052, May, 2021). Consent of patients was waived because of the retrospective study.

Chemotherapy

Patients in the two groups were given cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or CHOP-like chemotherapy as the first line.^{7–9} Patients with relapse and refractory were given iceifosfamide, carboplatin, etoposide (ICE), gemcitabine, dexamethasone, cisplatin (GDP) and other second-line regimens as the guideline recommended and some high-risk patients were given autologous hematopoietic stem cell transplantation or maintenance treatment with lenalidomide or chidamide.¹⁰

Clinical endpoints

Overall response rate (ORR) included complete remission (CR), partial remission (PR) and stable disease (SD). The primary outcomes were overall survival (OS). The second outcomes were progress-free survival (PFS). The patients were followed up on June 1, 2020.

Statistical analysis

SPSS 19.0 software was utilized to compare the count data of the two groups. Graphs were drawn by Prism Version 8.0.1 (San Diego, CA, USA). Categorical variables were presented as n (%) and continuous variables were as mean ± standard deviations or median (interquartile range, IQR). The comparison of the two groups' variables was utilizing the Chi-square test, Fisher exact test or student t test as appropriate. Kaplan Meier survival analysis was used to evaluate the OS and PFS. Log-rank test was used to compare the survival rates between the two groups. The value of $P < 0.05$ was considered statistically significant.

Results

Pathological subtypes of lymphoma

In this retrospective study, there were 509 lymphoma patients included. Figure 1A showed that, in the non-FUO group (329 cases in total), occupying ratios of Hodgkin's lymphoma (HL, 17 cases) was 5.2%, B cell non-Hodgkin's lymphoma (B-NHL, 276 cases) was 83.9%, T cell non-Hodgkin's lymphoma (T-NHL, 32 cases) was 9.7% and NK/T cell lymphoma (NK/T-CL, 4 cases) was 1.2%. In the FUO group (180 cases in total), the proportion of B-NHL (88 cases) reduced to 48.9%, followed by T-NHL (60 cases, 33.3%), NK/T-CL (24 cases, 13.3%) and HL (8 cases, 4.4%) (Fig. 1C).

As Fig. 1B demonstrated, in patients without FUO, the most common sites of the diagnostic biopsy were subcutaneous lymphnodes for HL (82.4%), B-NHL (35.1%) and T-NHL (78.1%), while the nasal lesions for NK/T-CL (75%). When in the FUO group, the most common diagnostic biopsy locations were subcutaneous lymphnodes for B-NHL (27.3%), T-NHL (36.7%) and NK/T-CL (41.7%), while the bone marrow for HL (50.0%) (Fig. 1D).

Clinical characteristics

Table 1 showed the clinical characteristics of lymphoma patients initially presenting as FUO or not stratified with four pathological subtypes. In the subgroup of HL, patients with FUO were significantly older than those without FUO (median age, 61.5 vs. 34.0, $P = 0.047$). No difference in age was observed in other subpopulations. There was no difference in male prevalence between the two groups in any subpopulation (all $P > 0.05$). In terms of comorbidities, the prevalence of diabetes mellitus (DM) was significantly higher in the FUO group diagnosed with B-NHL than that without FUO (12.5% vs. 3.6%, $P = 0.002$).

Table 1
Baseline characteristics of lymphoma patients initially presenting as FUO or not stratified with four pathological subtypes

	Hodgkin's lymphoma			B cell non-Hodgkin's lymphoma			T cell non-Hodgkin's lymphoma			NK/T cell lymphoma		
Variables	non-FUO	FUO	P value	non-FUO	FUO	P value	non-FUO	FUO	P value	non-FUO	FUO	P value
	N = 17	N = 8		N = 276	N = 88		N = 32	N = 60		N = 4	N = 24	
Age, years	34.0 (28.0–52.0)	61.5 (47.8–69.0)	0.047	61.0 (51.0–69.0)	60.0 (51.0–66.2)	0.435	52.5 (35.2–62.2)	47.5 (29.5–62.0)	0.634	47.0 (40.5–50.5)	42.0 (31.5–51.8)	0.718
Male, n (%)	6 (35.3%)	4 (50.0%)	0.667	158 (57.2%)	50 (56.8%)	0.944	24 (75.0%)	38 (63.3%)	0.256	4 (100.0%)	18 (75.0%)	0.549
Comorbidities, n (%)												
DM	1 (5.9%)	0 (0.0%)	1	10 (3.6%)	11 (12.5%)	0.002	3 (9.4%)	3 (5.0%)	0.416	0 (0.0%)	0 (0.0%)	1
Hypertension	0 (0.0%)	0 (0.0%)	1	18 (6.5%)	5 (5.7%)	0.778	4 (12.5%)	3 (5.0%)	0.232	0 (0.0%)	0 (0.0%)	1
CAD	0 (0.0%)	0 (0.0%)	1	1 (0.4%)	2 (2.3%)	0.146	0 (0.0%)	0 (0.0%)	1	0 (0.0%)	0 (0.0%)	1
CKD	0 (0.0%)	0 (0.0%)	1	1 (0.4%)	0 (0.0%)	1	0 (0.0%)	0 (0.0%)	1	0 (0.0%)	0 (0.0%)	1
COPD	0 (0.0%)	0 (0.0%)	1	1 (0.4%)	0 (0.0%)	1	1 (3.1%)	0 (0.0%)	0.348	0 (0.0%)	0 (0.0%)	1
Previous stroke	0 (0.0%)	0 (0.0%)	1	2 (0.7%)	0 (0.0%)	1	0 (0.0%)	0 (0.0%)	1	0 (0.0%)	0 (0.0%)	1
Cirrhosis	0 (0.0%)	0 (0.0%)	1	1 (0.4%)	2 (2.3%)	0.146	0 (0.0%)	0 (0.0%)	1	0 (0.0%)	0 (0.0%)	1
Solid tumor	0 (0.0%)	1 (12.5%)	0.32	3 (1.1%)	3 (3.4%)	0.155	0 (0.0%)	0 (0.0%)	1	0 (0.0%)	0 (0.0%)	1
Other initial symptoms, n (%)												
Night sweat	1 (5.9%)	2 (25.0%)	0.231	22 (8.0%)	18 (20.5%)	0.001	4 (12.5%)	14 (23.3%)	0.212	0 (0.0%)	5 (20.8%)	1
Weight loss	2 (11.8%)	1 (12.5%)	1	33 (12.0%)	15 (17.0%)	0.219	2 (6.2%)	11 (18.3%)	0.113	0 (0.0%)	4 (16.7%)	1
The highest temperature during hospitalization, °C	37.2 ± 0.7	37.6 ± 0.8	0.179	38.4 ± 0.7	39.3 ± 0.7	< 0.001	37.0 ± 0.8	39.2 ± 0.8	< 0.001	37.6 ± 0.7	40.3 ± 0.7	0.003
Initial symptom to diagnosis, months	3.0 (2.0–5.0)	2.0 (1.8–3.5)	0.23	2.0 (1.0–4.0)	2.0 (1.4–5.0)	0.561	2.0 (1.0–3.5)	3.0 (2.0–5.0)	0.079	2.0 (1.5–2.0)	3.0 (2.0–4.0)	0.192
ECOG score, n (%)	0.02			< 0.001			0.009			0.013		
0	8 (47.1%)	0 (0.0%)		35 (12.7%)	2 (2.3%)		5 (15.6%)	6 (10.0%)		2 (50.0%)	0 (0.0%)	
1	7 (41.2%)	3 (37.5%)		138 (50.0%)	34 (38.6%)		18 (56.2%)	14 (23.3%)		1 (25.0%)	10 (41.7%)	
2	1 (5.9%)	0 (0.0%)		53 (19.2%)	20 (22.7%)		5 (15.6%)	13 (21.7%)		0 (0.0%)	5 (20.8%)	

Categorical variables are reported as frequency and percentage; continuous variables are reported as median (interquartile range) or mean ± standard deviation as appropriate.

FUO = fever of unknown origin; DM = diabetes mellitus; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; ECOG score = Eastern Cooperative Oncology Group score; ORR = overall response rate.

	Hodgkin's lymphoma			B cell non-Hodgkin's lymphoma		T cell non-Hodgkin's lymphoma		NK/T cell lymphoma				
3	1 (5.9%)	4 (50.0%)		29 (10.5%)	20 (22.7%)	3 (9.4%)	16 (26.7%)	0 (0.0%)	4 (16.7%)			
4	0 (0.0%)	1 (12.5%)		13 (4.7%)	10 (11.4%)	0 (0.0%)	9 (15.0%)	1 (25.0%)	3 (12.5%)			
5	0 (0.0%)	0 (0.0%)		8 (2.9%)	2 (2.3%)	1 (3.1%)	2 (3.3%)	0 (0.0%)	2 (8.3%)			
Ann Arbor Stage, n (%)	0.073			< 0.001		0.003		0.304				
I/II	6 (35.3%)	0 (0.0%)		74 (26.8%)	4 (4.5%)	10 (31.2%)	3 (5.0%)	1 (25.0%)	6 (25.0%)			
III	6 (35.3%)	2 (25.0%)		57 (20.7%)	13 (14.8%)	7 (21.9%)	16 (26.7%)	1 (25.0%)	1 (4.2%)			
IV	5 (29.4%)	6 (75.0%)		145 (52.5%)	71 (80.7%)	15 (46.9%)	41 (68.3%)	2 (50.0%)	17 (70.8%)			
Extranodal involvement, n (%)												
Bone involvement	1 (5.9%)	0 (0.0%)	1	31 (11.2%)	34 (38.6%)	< 0.001	5 (15.6%)	19 (31.7%)	0.095	1 (25.0%)	6 (25.0%)	1
Spleen involvement	3 (17.6%)	3 (37.5%)	0.344	48 (17.4%)	54 (61.4%)	< 0.001	10 (31.2%)	39 (65.0%)	0.002	2 (50.0%)	17 (70.8%)	0.574
Liver involvement	0 (0.0%)	1 (12.5%)	0.32	15 (5.4%)	16 (18.2%)	< 0.001	2 (6.2%)	14 (23.3%)	0.039	0 (0.0%)	5 (20.8%)	1
Other involvement	0 (0.0%)	0 (0.0%)	1	0 (0.0%)	21 (23.9%)	< 0.001	0 (0.0%)	12 (20.0%)	0.007	0 (0.0%)	2 (8.3%)	1
ORR, n (%)	17 (100.0%)	8 (100.0%)	1	258 (93.5%)	84 (95.5%)	0.498	30 (93.8%)	51 (85.0%)	0.218	4 (100.0%)	21 (87.5%)	1
Categorical variables are reported as frequency and percentage; continuous variables are reported as median (interquartile range) or mean ± standard deviation as appropriate.												
FUO = fever of unknown origin; DM = diabetes mellitus; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; ECOG score = Eastern Cooperative Oncology Group score; ORR = overall response rate.												

In the subpopulation of B-NHL, there was a significant difference in the prevalence of night sweat between the FUO and non-FUO groups (20.5% vs. 8.0%, $P = 0.001$). During the hospitalization, the maximum body temperature of the FUO group diagnosed with B-NHL, T-NHL and NK/T-CL were $39.3 \pm 0.7^\circ\text{C}$, $39.2 \pm 0.8^\circ\text{C}$ and $40.3 \pm 0.7^\circ\text{C}$ respectively, which were statistically higher than that of the non-FUO group (vs. $38.4 \pm 0.7^\circ\text{C}$, $P < 0.001$; vs. $37.0 \pm 0.8^\circ\text{C}$, $P < 0.001$; vs. $37.6 \pm 0.7^\circ\text{C}$, $P = 0.003$). No difference was found in the duration from initial symptom to diagnosis between the FUO and non-FUO groups in any pathological subtypes (all $P > 0.05$).

The FUO group presented higher Eastern Cooperative Oncology Group (ECOG) scores than that of the non-FUO group regardless of which pathological subtypes (all $P < 0.05$). Regarding Ann Arbor Classification, the higher prevalences of the FUO group were only observed in the subtypes of B-NHL and T-NHL ($P < 0.001$ and $= 0.003$, respectively). For extranodal involvement, in the subtypes of B-NHL and T-NHL, the FUO groups showed higher prevalences than that of the non-FUO groups.

Concerning the ORR, there was no difference between the FUO and non-FUO groups, whatever the pathological subtype was.

Laboratory examination

Table 2 presented the laboratory examinations of lymphoma patients initially presenting as FUO or not stratified with four pathological subtypes.

Table 2
Laboratory examinations of lymphoma patients initially presenting as FUO or not stratified with four pathological subtypes

Variables	Hodgkin's lymphoma			B cell lymphoma			T cell lymphoma			NK/T cell lymphoma		
	non-FUO	FUO	P value	non-FUO	FUO	P value	non-FUO	FUO	P value	non-FUO	FUO	P value
	N = 17	N = 8		N = 276	N = 88		N = 32	N = 60		N = 4	N = 24	
EBV positive, n (%)	2 (11.8%)	1 (12.5%)	1	37 (13.4%)	21 (23.9%)	0.02	10 (31.2%)	36 (60.0%)	0.009	2 (50.0%)	19 (79.2%)	0.253
HBV positive, n (%)	2 (11.8%)	2 (25.0%)	0.57	43 (15.6%)	22 (25.0%)	0.045	1 (3.1%)	5 (8.3%)	0.661	0 (0.0%)	0 (0.0%)	1
Hematologic abnormality, n (%)												
Anemia	8 (47.1%)	8 (100.0%)	0.022	98 (35.5%)	74 (84.1%)	< 0.001	12 (37.5%)	48 (80.0%)	< 0.001	1 (25.0%)	17 (70.8%)	0.116
Leukopenia	4 (23.5%)	6 (75.0%)	0.028	40 (14.5%)	34 (38.6%)	< 0.001	3 (9.4%)	26 (43.3%)	< 0.001	2 (50.0%)	9 (37.5%)	1
Neutropenia	0 (0.0%)	2 (25.0%)	0.093	8 (2.9%)	10 (11.4%)	0.001	0 (0.0%)	13 (21.7%)	0.004	1 (25.0%)	5 (20.8%)	1
Thrombocytopenia	0 (0.0%)	0 (0.0%)	1	8 (2.9%)	30 (34.1%)	< 0.001	1 (3.1%)	18 (30.0%)	0.002	0 (0.0%)	9 (37.5%)	0.273
Biochemical abnormality, n (%)												
Elevated total bilirubin	0 (0.0%)	0 (0.0%)	1	10 (3.6%)	15 (17.0%)	< 0.001	1 (3.1%)	9 (15.0%)	0.081	0 (0.0%)	4 (16.7%)	1
Elevated direct bilirubin	0 (0.0%)	0 (0.0%)	1	16 (5.8%)	23 (26.1%)	< 0.001	4 (12.5%)	9 (15.0%)	0.743	0 (0.0%)	4 (16.7%)	1
Elevated alanine transaminase	2 (11.8%)	7 (87.5%)	< 0.001	11 (4.0%)	20 (22.7%)	< 0.001	1 (3.1%)	24 (40.0%)	< 0.001	0 (0.0%)	11 (45.8%)	0.132
Elevated aspartate transaminase	1 (5.9%)	7 (87.5%)	< 0.001	18 (6.5%)	30 (34.1%)	< 0.001	1 (3.1%)	28 (46.7%)	< 0.001	1 (25.0%)	9 (37.5%)	1
Elevated lactate dehydrogenase	6 (35.3%)	7 (87.5%)	0.03	108 (39.1%)	71 (80.7%)	< 0.001	13 (40.6%)	43 (71.7%)	0.004	2 (50.0%)	17 (70.8%)	0.574
Elevated alkaline phosphatase	4 (23.5%)	4 (50.0%)	0.359	11 (4.0%)	26 (29.5%)	< 0.001	1 (3.1%)	14 (23.3%)	0.012	0 (0.0%)	5 (20.8%)	1
Elevated β 2-microglobulin	2 (11.8%)	5 (62.5%)	0.017	65 (23.6%)	55 (62.5%)	< 0.001	9 (28.1%)	35 (58.3%)	0.006	1 (25.0%)	13 (54.2%)	0.596
Hypoalbuminemia	1 (5.9%)	6 (75.0%)	0.001	48 (17.4%)	58 (65.9%)	< 0.001	4 (12.5%)	36 (60.0%)	< 0.001	1 (25.0%)	11 (45.8%)	0.613
Elevated serum ferritin	0 (0.0%)	0 (0.0%)	1	11 (4.0%)	38 (43.2%)	< 0.001	1 (3.1%)	22 (36.7%)	< 0.001	1 (25.0%)	11 (45.8%)	0.613
Hypertriglyceridemia	2 (11.8%)	0 (0.0%)	1	17 (6.2%)	38 (43.2%)	< 0.001	4 (12.5%)	21 (35.0%)	0.021	0 (0.0%)	10 (41.7%)	0.265
Inflammatory status, n (%)												
CRP $\geq$ 10mg/L	5 (29.4%)	4 (50.0%)	0.394	66 (23.9%)	55 (62.5%)	< 0.001	8 (25.0%)	33 (55.0%)	0.006	0 (0.0%)	9 (37.5%)	0.273
ESR > 15mm/h	5 (29.4%)	0 (0.0%)	0.14	79 (28.6%)	23 (26.1%)	0.651	5 (15.6%)	8 (13.3%)	0.764	1 (25.0%)	3 (12.5%)	0.481
Categorical variables are reported as frequency and percentage.												
FUO = fever of unknown origin; EBV = Epstein-Barr virus; HBV = hepatitis B virus; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.												

In the subtype of HL, compared with that of the non-FUO group, the FUO group showed the higher prevalences of anemia (100.0% vs. 47.1%, $P = 0.022$), leukopenia (75.0% vs. 23.5%, $P = 0.028$), elevated alanine transaminase (87.5% vs. 11.8%, $P < 0.001$), elevated aspartate transaminase (87.5% vs. 5.9%, $P < 0.001$), elevated aspartate transaminase (87.5% vs. 35.3%, $P = 0.03$), elevated β 2-microglobulin (62.5% vs. 11.8%, $P = 0.017$) and hypoalbuminemia (75.0% vs. 5.9%, $P = 0.001$).

In comparison with the non-FUO group diagnosed as B-NHL, higher incidences of EBV positive, HBV positive, hematologic abnormality, biochemical abnormality and elevated CRP concentration were observed in patients with FUO (all $P < 0.05$).

Except for total and direct bilirubin, the FUO group with T-NHL presented higher prevalences of EBV positive hematologic abnormality, biochemical abnormality and elevated CRP concentration than that of the patients without FUO (all $P < 0.05$).

In terms of the subtype of NK/T-CL, there was no difference in laboratory examinations between the FUO and non-FUO groups (all $P > 0.05$). Notably, the rates of EBV positive in both FUO and non-FUO groups for NK/T-CL were $\geq 50\%$.

Outcomes

As shown in Fig. 2A, C and E, the differences in overall survival between the FUO and non-FUO groups were significant for HL ($P = 0.006$), B-NHL ($P = 0.007$) and T-NHL ($P = 0.013$). No difference was observed in the two groups for the subtype of NK/T-CL ($P = 0.141$) (Fig. 2G).

In terms of PFS, there was no significant difference between FUO and non-FUO groups for any subtype (all $P > 0.05$) (Fig. 2B, D, F, H).

Discussion

Although lymphoma is one of the major causes of FUO, it is always a very difficult condition to diagnose a patient who initially presents as FUO with lymphoma. In this context, there is a need to investigate the clinical characteristics and outcomes in this special population. To our best knowledge, this is the largest sample size focusing on the clinical features and long-term outcomes of lymphoma patients with FUO.

In our study, the prevalences of T-NHL and NK/T-CL in the FUO group were considerably higher than that of the non-FUO group. 83.9% of the patients in the non-FUO group were B-NHL, which was similar to Zhang et al.'s study.¹¹ In the case reports, most of the lymphoma with FUO is various T-NHL, while some rare types of B-NHL could be found, such as intravascular diffuse large B-cell lymphoma.^{12–14} In our study, the major proportion of lymphoma with the FUO was also B-NHL (48.9%).

Previous studies merely focused on the total population of lymphoma patients with FUO.^{3,15,16} In Zhou et al.'s study,¹⁵ the median age of lymphoma patients with FUO was 42 years old and the prevalence of male was 48.3%. In our study, the median age of the FUO group in NK/T-CL was 42.0 years old, which was consistent with Zhou's study. In the meanwhile, the median ages of the FUO group were older in the subtype of HL (61.5 years old), B-NHL (60.0 years old) and T-NHL (47.5 years old).

It was believed that FUO may delay the diagnosis of disease, which finally induces poorer outcomes.¹⁷ In our study, however, no difference was observed between the FUO and non-FUO groups in the duration of initial symptom to diagnosis. The explanation for the phenomenon may be that before presenting as FUO, lymphoma has developed for a long time. The theoretical basis supporting this conjecture in this study was that patients with FUO usually presented with higher ECOG score, Ann Arbor Stage and survived from more organ damages.

The laboratory examinations of lymphoma patients with FUO were usually abnormal according to previous studies.^{15,16} In our study, further subgroup analyses were performed to compare the differences in laboratory index between the FUO and non-FUO groups stratified with four pathological subtypes. Our study found that, for patients with B-NHL or T-NHL, there was a higher incidence of EBV positive in the FUO group. In the meanwhile, the prevalence of EBV positive in patients with NK/T-CL was higher than other pathological subtypes. In our study, the results of laboratory examination suggested that patients in the FUO group were more likely to have a decrease in hemogram, and the three lines could be significantly decreased. In addition, liver function damage is more likely to occur in the FUO group than in the non-FUO group. In addition to the similar increase of liver enzymes in the previous studies, the total bilirubin and direct bilirubin of our patients also increased significantly.¹⁸ Inflammation-related indicators like CRP were also significantly increased. In addition, patients in the FUO group are more likely to suffer from hypoalbuminemia, which may be related to long-term fever, physical consumption and liver function damage.

After chemical therapy, the ORR in the FUO group and the non-FUO group was similar. The outcome analyses showed that patients with FUO suffered from a higher risk of all-cause death in the long term, which was similar to that reported in the literature.¹⁹ However, the differences in disease progress survival were not observed in any subgroup. Zhang et al.¹⁹ found that age, splenomegaly and abdominal lymph node enlargement were the factors influencing the survival of lymphoma patients in the FUO Group. A further multi-center cohort study is needed to conduct the subgroup analyses for each pathological subtype of lymphoma.

Conclusions

We found that the majority of lymphoma initially presenting as FUO were B-NHL and T-NHL. The main diagnostic biopsy sites were subcutaneous lymphnodes, bone marrow and spleen for lymphoma patients with FUO. Patients with FUO suffered from a higher risk of all-cause death in the long term. In the future, more advanced examinations such as second-generation sequencing or the establishment of a better evaluation system may help clinicians to formulate better diagnoses and treatment plans, and new treatments for these patients need to be further explored.

Abbreviations

FUO
fever of unknown origin
ECOG score
Eastern Cooperative Oncology Group score
ORR
overall response rate
PFS
progress-free survival
OS
overall survival
WHO
World Health Organization
CHOP
cyclophosphamide, doxorubicin, vincristine and prednisone
ICE
ifosfamide, carboplatin, etoposide
GDP
gemcitabine, dexamethasone, cisplatin
CR
complete remission
PR
partial remission
SD
stable disease
HL
Hodgkin's lymphoma
NHL
non-Hodgkin's lymphoma
NK/T-CL
NK/T cell lymphoma
IQR
interquartile range
DM
diabetes mellitus
CAD
coronary artery disease
CKD
chronic kidney disease
COPD
chronic obstructive pulmonary disease

Declarations

Ethics approval and consent to participate

This retrospective study was in accordance with the guideline of Declaration of Helsinki and approved by the Institutional Review Board of Huadong Hospital, Fudan University (2021K052, May, 2021). Retrospective design waived individual informed consent.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated during the current study are not publicly available since they will contain patient data. An anonymized form of the data could be made available from the corresponding author upon reasonable request.

Competing interests:

The authors have no potential conflicts of interest relevant to this study.

Funding

The study, and collection, analysis, interpretation of data, and preparation of the manuscript were supported by the source of funding as follows: Shanghai Science and Technology Project (19DZ1910301) and Fund for Fostering Talents in Basic Science of Shanghai Huadong Hospital (20191c014).

Authors' Contributions

MW and FW: Investigation and Writing. JM, WQ and SS: Providing data. PC and YX: Editing. LS and YX: Conceptualization, Project administration. All authors read and approve the final version of the manuscript, and ensure it is the case.

Acknowledgements

None.

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Figures

Figure 1

A. The pie chart illustrated the percentages of HL, B-NHL, T-NHL and NK/T-CL in patients without FUO. B. The bar chart gave the number of diagnostic biopsy locations stratified with the HL, B-NHL, T-NHL and NK/T-CL in the non-FUO group. C. The pie chart illustrated the percentages of HL, B-NHL, T-NHL and NK/T-CL in patients initially presenting as FUO. D. The bar chart gave the number of diagnostic biopsy locations stratified with the HL, B-NHL, T-NHL and NK/T-CL in the FUO group. HL=Hodgkin's lymphoma; NHL=non-Hodgkin's lymphoma; FUO=fever of unknown origin.

Figure 2

Kaplan-Meier survival analysis of overall survival (OS) and progress-free survival (PFS) between FUO group and non-FUO group. The differences between the FUO and non-FUO groups were assessed with log-rank test. A-B. In the subpopulation of HL, difference in OS between the FUO and non-FUO groups was significant ($P=0.006$), while the difference in PFS was not significant ($P=0.895$). C-D. In the subpopulation of B-NHL, difference in OS between the FUO and non-FUO groups was significant ($P=0.007$), while the difference in PFS was not significant ($P=0.265$). E-F. In the subpopulation of T-NHL, difference in OS between the FUO and non-FUO groups was significant ($P=0.013$), while the difference in PFS was not significant ($P=0.126$). G-H. In the subpopulation of NK/T-CL, differences in OS and PFS between the FUO and non-FUO groups were not significant ($P=0.141$ and 0.126 respectively). HL=Hodgkin's Lymphoma; NHL=non-Hodgkin's lymphoma; FUO=fever of unknown origin.