Original Article

A Clinical Analysis of 293 FUO Patients, A Diagnostic Model Discriminating infectious Diseases from Non-infectious Diseases

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Objective A diagnostic model was established to discriminate infectious diseases from non-infectious diseases.

Methods The clinical data of patients with fever of unknown origin (FUO) hospitalized in Xiangya Hospital Central South University, from January, 2006 to April, 2011 were retrospectively analyzed. Patients enrolled were divided into two groups. The first group was used to develop a diagnostic model: independent variables were recorded and considered in a logistic regression analysis to identify infectious and non-infectious diseases ($\alpha_{in} = 0.05$, $\alpha_{out} = 0.10$). The second group was used to evaluate the diagnostic model and make ROC analysis.

Results The diagnostic rate of 143 patients in the first group was 87.4%, the diagnosis included infectious disease (52.4%), connective tissue diseases (16.8%), neoplastic disease (16.1%) and miscellaneous (2.1%). The diagnostic rate of 168 patients in the second group was 88.4%, and the diagnosis was similar to the first group. Logistic regression analysis showed that decreased white blood cell count ($WBC < 4.0 \times 10^9/L$), higher lactate dehydrogenase level ($LDH > 320 U/L$) and lymphadenectasis were independent risk factors associated with non-infectious diseases. The odds ratios were 14.74, 5.84 and 5.11 ($P \leq 0.01$), respectively. In ROC analysis, the sensitivity and specificity of the positive predictive values was 62.1% and 89.1%, respectively, while that of negative predicting values were 75% and 81.7%, respectively ($AUC = 0.76$, $P = 0.00$).

Conclusions The combination of $WBC < 4.0 \times 10^9/L$, $LDH > 320 U/L$ and lymphadenectasis may be useful in discriminating infectious diseases from non-infectious diseases in patients hospitalized as FUO.

Key words: Fever of unknown origin; Diagnostic model; White blood cell; Lactate dehydrogenase; Lymphadenectasis

Fever of unknown origin (FUO) remains a great clinical challenge despite the advanced clinical knowledge and effective diagnostic instruments, the proportion of undiagnosed cases is about 10%-50% and the portion is soaring by time.¹⁻¹⁰ The diagnosis of FUO has always been a knotty problem for physicians due to its complex pathogenic and specific detection means. The aim of the study was to develop a simple and reliable diagnostic model. An clinical analysis of 293 FUO patients (from January, 2006 to April, 2011) in infectious diseases department with diagnostic criteria was carried out in order to aid physicians to

discriminate infectious diseases from non-infectious diseases.

PATIENTS AND METHODS

Patients and diagnostic criteria

From January, 2006 to April, 2011, data of 293 inpatients admitted as FUO in Infectious Diseases Department from Xiangya Hospital, Central South University were collected. There were 171 males and 122 females in a ratio of 1.40 : 1 with an age range of 12-79 years (average age as 40.9 ± 16.9 years). The diagnostic criteria for FUO were: body temperature $> 38.3^\circ C$, the period fo fever since onset > 3 weeks, and the etiology was unclear after one week's hospitalization.¹¹

Case data processing

All cases were devided into 2 groups: the established

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diagnostic model group of 125 cases and the assessed diagnostic model group of 168 members.

Established diagnostic model group

From January, 2006 to December, 2008, 125 out of 143 patients admitted as FUO confirmed a final diagnosis, with the diagnostic rate as 87.4%. Methods used for diagnosis were presented as follows: (1) clinical history and treatment, therapeutic response and follow-up study (37 cases, 29.6%); (2) humoral and serum laboratory etiological detection (49 cases, 39.2%); (3) imaging studies (18 cases, 14.4%); (4) pathological examination including tissue biopsy and bone marrow cytological examination (21 cases, 16.8%). These 125 cases were divided into two groups, the infectious diseases group included patients with bacterial, ricketts, mycobacterial, viral, fungal, parasitic and protozoon infections; the non-infectious group included patients with connective tissue disease, neoplastic disease, drug fever and other diseases. A thorough record of age, sex, prognosis, fever persisted time before admission, time of diagnosis, symptoms and signs of patients and results of routine laboratory tests after admission within 24 hours was made. This complex examination included white blood cell (WBC), polymorphonuclear neutrophil (PMN) counts, percentage of neutrophils (N), lymphocyte (LYM) counts, percentage of lymphocytes (L), eosinophil (EOS) counts, percentage of eosinophils (E), hemoglobin (Hb), platelet (PLT) counts, serum C-reactive protein (CRP), ESR, hepatic and renal function, myocardial enzyme, the liver-enzyme, antinuclear antibody, rheumatoid factor, X-ray in the chest, abdominal ultrasound B (hepatobiliary pancreatic), computed tomography (CT), heart color Doppler, vascular ultrasound, cytological examination of bone marrow, etiological examination and histopathological examination. Then suitable statistical methods were used to analyze data from both groups and find meaningful elements that could discriminate infectious diseases from non-infectious diseases. Logistic stepwise regression was used to select risk factors. All cases were strictly complied with criteria.

Diagnostic model assessment group

The results of 168 cases (from January, 2009 to April, 2011) post-discharge and follow-up was used as a golden criterion for evaluating diagnostic tests. The established diagnostic model was assessed and an

ROC analysis was carried out.

Statistical analysis

Statistical analysis was performed by SPSS 17.0. Normal distribution were presented as mean $\pm$ standard deviation and the comparison between the two groups was assessed by non-paired t test. The abnormal distribution measurement were presented by median, and quartile range and the comparison between the two groups was assessed by Mann-Whitney U test. Enumeration data was assessed by χ^2 test. Two-category logistic regression principle was used to filter out risk factors ($\alpha_{in}=0.05$, $\alpha_{out}=0.10$) for discrimination of infectious diseases and non-infectious diseases. Cases with more than two risk factors were set as diagnostic model and ROC analysis was made. The area under ROC curve (AUC), sensitivity, specificity, positive and negative predictive values and the consistency of diagnosis model were analyzed, $P < 0.05$ was considered statistically significant.

RESULTS

The etiologies for two groups

In the first group, 125 out of 143 cases were diagnosed, with the diagnostic rate of 87.4%. Infectious diseases included bacterial infections, *Mycobacterium tuberculosis* infection, connective tissue diseases, adult-onset Still diseases (AOSD), neoplastic diseases, non-Hodgkin's lymphoma (NHL) and 3 other diseases such as drug fever, pyoderma gangrenosum and necrotizing lymphadenitis (Table 1). In the second group, 168 out of 190 cases were diagnosed, with a diagnostic rate of 88.4%. Infectious disease included bacterial infections, *Mycobacterium tuberculosis* infection, connective tissue disease, adult-onset Still disease, neoplastic disease, non-Hodgkin lymphoma and other diseases (Table 2). The distribution of etiology for these two groups had no significant differences.

Analysis of case data (group 1)

Patients in group one were divided into infectious group (75 patients) and non-infectious group (50 patients) according to diagnostic model. Comparison was made on general data and symptoms between the two groups and analyzed through non-paired t -test (Table 3). And data were assessed by χ^2 test. The results showed that there existed significant

Table 1. Causes of fever in the first group (from 2006 to 2009, n = 143)

Causes of fever	n (%)	Causes of fever	n (%)
Infectious diseases	75 (52.4)	Connective tissue diseases	24 (16.8)
Septicemia	19 (13.3)	Adult-onset Still disease	14 (9.8)
Infective endocarditis	8 (5.6)	Systemic lupus erythematosus	3 (2.1)
Pulmonary infection	4 (2.8)	ANCA correlation vasculitis	1 (0.7)
Urinary tract infection	3 (2.1)	Polyarteritis nodosa	1 (0.7)
Cholelithiasis and infection	3 (2.1)	Dermatomyositis	1 (0.7)
Hepatic abscess	2 (1.4)	Polymyalgia rheumatica	1 (0.7)
Pelvic mass and infection	1 (0.7)	Unclassified connective tissue diseases	3 (2.1)
Brain abscess	1 (0.7)	Neoplasms	23 (16.1)
Tuberculous meningitis	5 (3.5)	Non-Hodgkin lymphoma	12 (8.4)
Pulmonary tuberculosis	3 (2.1)	Hodgkin lymphoma	2 (1.4)
Tuberculous pleurisy	1 (0.7)	Acute lymphoblastic leukemia	4 (2.8)
Tuberculous peritonitis	1 (0.7)	Mixed phenotype acute leukemia	1 (0.7)
Lymphoid tuberculosis	1 (0.7)	Malignant histiocytosis	2 (1.4)
Tuberculosis of intestine	1 (0.7)	Myelodysplastic syndrome	1 (0.7)
Other parts of tuberculosis infection	2 (1.4)	Cervical carcinoma	1 (0.7)
Typhoid/Paratyphoid fever	8 (5.6)	Miscellaneous	3 (2.1)
Infectious mononucleosis	5 (3.5)	Drug fever	1 (0.7)
Viral encephalitis	1 (0.7)	Pyoderma gangrenosum	1 (0.7)
Histoplasmosis	4 (2.8)	Necrotic lymphadenitis	1 (0.7)
Paragonimiasis	1 (0.7)	Fever of unknown origin	18 (12.6)
Lyme disease	1 (0.7)		

Table 2. Causes of fever in the second group (From 2009 to 2011, n = 190)

Causes of fever	n (%)	Causes of fever	n (%)
Infectious diseases	110 (57.9)	Connective tissue diseases	31 (16.3)
Septicemia	26 (13.7)	Adult-onset Still disease	19 (10.0)
Infective endocarditis	12 (6.3)	Systemic lupus erythematosus	4 (2.1)
Pulmonary infection	11 (5.8)	Dermatomyositis	3 (1.6)
Urinary tract infection	6 (3.2)	Rheumatoid arthritis	1 (0.5)
Cholelithiasis and infection	1 (0.5)	Polymyalgia rheumatica	1 (0.5)
Pylephlebitis	2 (1.1)	Behcet's disease	1 (0.5)
Hepatic abscess	3 (1.6)	ANCA correlation vasculitis	1 (0.5)
Brain abscess	1 (0.5)	Unclassified connective tissue diseases	1 (0.5)
Pyogenic osteoarthritis	1 (0.5)	Neoplasms	22 (11.6)
Purulent meningitis	3 (1.6)	Non-Hodgkin lymphoma	12 (6.3)
Nephropostasis and septic shock	1 (0.5)	Hodgkin lymphoma	1 (0.5)
Multiple cellulitis	1 (0.5)	Acute lymphoblastic leukemia	2 (1.1)
Tuberculous meningitis	8 (4.2)	Malignant histiocytosis	2 (1.1)
Pulmonary tuberculosis	5 (2.6)	Eosinophilia	1 (0.5)
Tuberculous peritonitis	1 (0.5)	Multiple myeloma	1 (0.5)
Tuberculous pleurisy	1 (0.5)	Mediastinal tumor	1 (0.5)
Lymphoid tuberculosis	1 (0.5)	Hepatoma	2 (1.1)
Other parts of tuberculosis infection	8 (4.2)	Miscellaneous	5 (2.6)
Typhoid/Paratyphoid fever	6 (3.2)	Autoimmune hemolytic anemia	1 (0.5)
Virus infection	2 (1.1)	Drug fever	3 (1.6)
Infectious mononucleosis	3 (1.6)	Necrotic lymphadenitis	1 (0.5)
Cryptococcal meningitis	1 (0.5)	Fever of unknown origin	22 (11.6)
Histoplasmosis	1 (0.5)		
Rickettsiosis	1 (0.5)		
Paragonimiasis	3 (1.6)		
Malaria	1 (0.5)		

Table 3. Comparison of general information and symptoms

Patients characteristics	Overall (n = 125)	Infectious diseases group (n = 75)	Non-infectious diseases group (n = 50)	<i>t</i>	χ^2	<i>P</i>
Age (years)	39.54 ± 17.19	42.47±17.74	35.14±15.48	2.38		0.02*
Male sex (%)	74 (59.2)	46 (61.3)	28 (56.0)		0.35	0.55
Prognosis	15 (12.0)	2 (2.7)	13 (26.0)		15.47	0.00*
Symptoms and signs						
Rash	34 (27.2)	19 (25.3)	15 (30.0)		0.33	0.57
Arthritis	29 (23.2)	14 (18.7)	15 (30.0)		2.16	0.14
Lymph node enlargement	44 (35.2)	16 (21.3)	28 (56.0)		15.81	0.00*
Hepatomegaly	27 (21.6)	14 (18.7)	13 (26.0)		0.95	0.33
Splenomegaly	52 (41.6)	24 (32.0)	28 (56.0)		7.11	0.01*
Cough	24 (19.2)	15 (20.0)	9 (18.0)		0.08	0.78
Headache	26 (20.8)	18 (24.0)	8 (16.0)		1.17	0.28
Muscle pain	33 (26.4)	16 (21.3)	17 (34.0)		2.48	0.12
Abdominal pain and diarrhea	20 (16.0)	15 (20.0)	5 (10.0)		2.23	0.14
Weight loss > 5 kg	28 (22.4)	15 (20.0)	13 (26.0)		0.62	0.43

Notes: * stands for $P < 0.05$.**Table 4. Comparison of laboratory findings**

Results of laboratory tests	Overall (n = 125)	Infectious diseases group (n = 75)	Non-infectious diseases group (n = 50)	<i>t</i>	χ^2	<i>P</i>
White cell count ($\times 10^9/L$)	11.54 ± 8.80	10.99 ± 7.03	12.38 ± 10.97	0.79		0.430
Granulocytosis (neutrophil percent > 75%)	65 (52.0)	44 (58.7)	21 (42.0)		3.34	0.070
Lymphocytosis (lymphocyte percent > 40%)	6 (4.8)	4 (5.3)	2 (4.0)		0.00	1.000
Eosinophilia (eosinophil percent > 5%)	8 (6.4)	5 (6.7)	3 (6.0)		0.00	1.000
Leukopenia (leukocyte < $4.0 \times 10^9/L$)	24 (19.2)	5 (6.7)	19 (38.0)		18.99	0.000
Lymphopenia (lymphocyte percent < 20%)	83 (66.4)	56 (74.7)	27 (54.0)		5.74	0.020
Eosinopenia (eosinophil percent < 0.5%)	66 (52.8)	38 (50.7)	28 (56.0)		0.34	0.560
Platelet count ($\times 10^9/L$)	244.52 ± 137.37	244.60 ± 104.47	244.4 ± 176.83	0.01		0.990
Thrombocytosis ($> 400 \times 10^9/L$)	16 (12.8)	6 (8.0)	10 (20.0)		3.87	0.049
Thrombopenia ($< 150 \times 10^9/L$)	30 (24.0)	13 (17.3)	17 (34.0)		4.57	0.030
Anemia (M < 120 g/L, F < 110 g/L)	94 (75.2)	54 (72.0)	40 (80.0)		1.03	0.310
Hemoglobin (g/L)	100.16 ± 22.44	104.21 ± 20.25	94.08 ± 24.33	2.53		0.010
Erythrocyte sedimentation rate (mm/h)	58.00 ± 30.08	56.77 ± 29.82	59.84 ± 30.68	-0.56		0.580
Antinuclear antibodies titer ($> 1 : 160$)	4 (3.2)	1 (1.3)	3 (6.0)		0.87	0.350
Rheumatoid factor (> 20 U)	14 (11.2)	9 (12.0)	5 (10.0)		0.12	0.730
Lactic dehydrogenase (> 245 U/L)	76 (60.8)	35 (46.7)	41 (82.0)		15.72	0.000
Creatine kinase (> 190 U/L)	6 (4.8)	5 (6.7)	1 (2.0)		0.59	0.440
CK-Mb (> 24 U/L)	17 (13.6)	10 (13.3)	7 (14.0)		0.01	0.920
Abnormal liver functional test						
Total protein (g/L)	62.17 ± 8.75	63.75 ± 8.10	59.79 ± 9.22	2.54		0.010
Albumin (g/L)	29.94 ± 6.32	30.85 ± 6.75	28.57 ± 5.39	2.00		0.048
Globulin (g/L)	32.23 ± 6.93	32.91 ± 6.67	31.22 ± 7.27	1.34		0.180
Glutamic-pyruvic transaminase (≥ 40 U/L)	58 (46.4)	33 (44.0)	25 (50.0)		0.43	0.510
Glutamic-oxalacetic transaminase (≥ 40 U/L)	55 (44.0)	30 (40.0)	25 (50.0)		1.22	0.270
Abnormal renal function test						
Blood urea nitrogen (≥ 7.14 mmol/L)	9 (7.2)	7 (9.3)	2 (4.0)		0.60	0.44
Creatinine (≥ 132.6 μ mol/L)	6 (4.8)	5 (6.7)	1 (2.0)		0.59	0.44
Abnormal chest radiography	57 (45.6)	37 (49.3)	20 (40.0)		1.05	0.31

differences on age, prognosis, lymphadenectasis and splenomegaly between the two groups ($P < 0.05$). Compared with the infectious group, patients in non-infectious group were with younger age (35.14 ± 15.48), poorer prognosis, more lymphadenectasis and splenomegaly.

Comparison of laboratory results on patients from both groups (non-paired t test) was shown in Table 4. It is obvious that there were significant statistical differences between the two groups in Hb, TP and ALB ($P < 0.05$). In non-infectious group, the reduction in Hb, TP, ALB was more obvious. Other indexes took normal value as boundary, the percentage of increase/decrease was analyzed by χ^2 test. The decrease of WBC, abnormal PLT and increase of LDH is more obvious ($P < 0.05$) in non-infectious group than that in infectious group. The reduction of LYM was more obvious in infectious group ($P < 0.05$).

Data of abnormal distribution included fever time before admission, diagnostic time, PMN count, LYM count, EOS count, CRP, ALT/GPT, AST/GOT, BUN, Cr, LDH, CK and CK-Mb. Mann-Whitney U test was applied and the results showed significant statistical differences ($P < 0.05$) on fever time before admission, diagnostic time and LDH. For non-infectious group, fever time before admission and diagnostic time were longer than that of infectious group, and LDH was higher (Table 5). Median and Quartile range were

used for presenting discrepancy in index records by Mann-Whitney U test (Table 6).

As shown in Table 7, discrepancy indexes in group 3, 4 and 5 were regarded as meaningful elements (X1-X14) for discriminating infectious and non-infectious diseases before reassignment. According to the previous results, the normal distributed data such as age, Hb, TP and ALB took average number as assignment boundary. While the abnormal distributed data median is the assignment boundary such as fever time before admission, diagnostic time and LDH. Other index records took normal value as assignment boundary such as WBC, lymphocytes percentage and PLT count. Two-category variable such as poor prognosis, lymphadenectasis, splenomegaly were assigned by 0 or 1. During the research, 0 stood for non-infectious disease and 1 stood for infectious disease. Logistic regressive model was used to filter out risk factors for discriminating infectious diseases and non-infectious diseases ($\alpha_{in}=0.05$, $\alpha_{out}=0.10$), results were shown in Table 8.

The risk factors for discriminating infectious and non-infectious diseases were obtained by logistic regression analysis, including decreased WBC ($WBC < 4.0 \times 10^9/L$), increased PLT ($PLT > 400 \times 10^9/L$), decreased TP ($TP < 60 \text{ g/L}$), increased LDH ($LDH \geq 320 \text{ U/L}$) and lymphadenectasis, with OR values of 14.74, 15.00, 4.41, 5.84 and 5.11, respectively ($P < 0.05$) (Table 9).

Table 5. Rank sum test in the first group

Patients' characteristics and laboratory findings	Infectious diseases group (n = 75)		Non-infectious diseases group (n = 50)		Z	P
	Mean rank	Sum of ranks	Mean rank	Sum of ranks		
Duration of fever before admission	57.15	4286.0	71.78	3589.0	-2.226	0.03
Diagnosis time	51.81	3886.0	79.78	3989.0	-4.231	0.00
Neutrophil count	64.53	4840.0	60.70	3035.0	-0.580	0.56
Lymphocyte count	66.25	4969.0	58.12	2906.0	-1.232	0.22
Eosinophil count	65.03	4877.5	59.95	2997.5	-0.843	0.40
C-reactive protein	62.04	4653.0	64.44	3222.0	-0.363	0.72
Glutamic-pyruvic transaminase	61.41	4605.5	65.39	3269.5	-0.602	0.55
Glutamic-oxalacetic transaminase	58.87	4415.0	69.20	3460.0	-1.562	0.12
Blood urea nitrogen	60.31	4523.5	67.03	3351.5	-1.015	0.31
Creatinine	65.69	4927.0	58.96	2948.0	-1.018	0.31
Lactic dehydrogenase	50.68	3801.0	81.48	4074.0	-4.657	0.00
Creatine kinase	65.19	4889.5	59.71	2985.5	-0.829	0.41
CK-Mb	63.43	4757.0	62.36	3118.0	-0.161	0.87

Notes: The normality of data distribution was assessed by Kolmogorov-Smirnov tests. In the first group, inter-group comparisons were made by Mann-Whitney U test, as appropriate for abnormal distribution data. * $P < 0.05$.

Table 6. Descriptive statistics: the abnormal distribution data

Patients' characteristics and laboratory findings	Overall (n = 125)		Infectious diseases group (n = 75)		Non-infectious diseases group (n = 50)	
	Median	QR	Median	QR	Median	QR
Duration of fever before admission (days)	27	30.5	24.0	17	33.0	50.5
Diagnosis time (days)	42	38.0	35.0	18	56.0	58.5
Lactic dehydrogenase (U/L)	311	301.5	239.5	170	460.5	552.8

Notes: Median = P50, QR: quartile range = P75-P25.

Table 7. A reassignment method for discrepancy indexes

Variables	Variable name	Assignment
Age (years)	X ₁	≥40 = 1, < 40 = 0
Duration of fever before admission (days)	X ₂	< 30 = 1, ≥ 30 = 0
Diagnosis time (days)	X ₃	< 45 = 1, ≥ 45 = 0
Prognosis	X ₄	Prognosisbona = 1, Prognosismala = 0
Leukocyte (×10 ⁹ /L)	X ₅	≥ 4.0 = 1, < 4.0 = 0
Lymphocyte percent	X ₆	< 20% = 1, ≥ 20% = 0
Hemoglobin (g/L)	X ₇	≥ 100 = 1, < 100 = 0
Thrombocytosis (×10 ⁹ /L)	X ₈	≤ 400 = 1, > 400 = 0
Thrombopenia (×10 ⁹ /L)	X ₉	≥ 150 = 1, < 150 = 0
Total protein (g/L)	X ₁₀	≥ 60 = 1, < 60 = 0
Albumin (g/L)	X ₁₁	≥ 30 = 1, < 30 = 0
Lactic dehydrogenase (U/L)	X ₁₂	< 320 = 1, ≥ 320 = 0
Splenomegaly	X ₁₃	No = 1, yes = 0
Lymph node enlargement	X ₁₄	No = 1, yes = 0

Notes: 0 stands for non-infectious diseases, 1 stands for infectious diseases.

Table 8. Logistic regression analysis for diagnosis of non-infection in the first group

Variables	B	S.E.	Wald	P	OR	95% CI
X ₁	0.84	0.59	2.05	0.15	2.31	[0.73, 7.31]
X ₂	-0.23	0.86	0.07	0.79	0.80	[0.15, 4.31]
X ₃	1.24	0.86	2.10	0.15	3.47	[0.65, 18.66]
X ₄	1.44	1.02	2.00	0.16	4.22	[0.57, 31.15]
X ₅	2.69	1.07	6.36	0.01*	14.74	[1.82, 119.31]
X ₆	0.25	0.70	0.13	0.72	1.28	[0.32, 5.08]
X ₇	0.03	0.63	0.00	0.96	1.03	[0.30, 3.55]
X ₈	2.71	0.87	9.79	0.00*	15.00	[2.75, 81.78]
X ₉	-1.72	1.04	2.76	0.10	0.18	[0.02, 1.36]
X ₁₀	1.49	0.67	4.88	0.03*	4.41	[1.18, 16.47]
X ₁₁	-0.91	0.69	1.73	0.19	0.40	[0.11, 1.56]
X ₁₂	1.77	0.60	8.59	0.00*	5.84	[1.79, 19.01]
X ₁₃	0.62	0.68	0.84	0.36	1.86	[0.49, 7.01]
X ₁₄	1.63	0.60	7.41	0.01*	5.11	[1.58, 16.53]

Notes: B stands for regression coefficient; S.E. stands for standard error; OR stands for odds ratio; 95%CI stands for 95% confidence intervals; * $P < 0.05$.

Table 9. The AUC of 5 risk factors

Variables	Area	S.E.	P	95% CI
Leukopenia (leukocyte < 4.0×10 ⁹ /L)*	0.60	0.05	0.03	[0.51, 0.70]
Thrombocytosis (> 400×10 ⁹ /L)	0.50	0.05	0.68	[0.39, 0.57]
Total protein (< 60 g/L)	0.50	0.05	0.66	[0.39, 0.57]
Lactic dehydrogenase (> 320 U/L)*	0.65	0.05	0.00	[0.56, 0.74]
Lymph node enlargement*	0.71	0.04	0.00	[0.62, 0.79]

Notes: * The risk factors: area under curve (AUC) > 0.5, $P < 0.05$.

Table 10. Evaluation of the first group and second group cases by the three risk factors

Number of risk factors	Number of patients	Infectious diseases group	Non-infectious diseases group	Proportion of patients with non-infectious among patients with the respective factors
The first group (n = 125)				
No factors	43	35	8	18.6%
One factor	49	36	13	26.5%
Two factors	22	4	18	81.8%
Three factors	11	0	11	100.0%
The second group (n = 168)				
No factors	55	48	7	12.7%
One factor	65	50	15	23.1%
Two factors	41	11	30	73.2%
Three factors	7	1	6	85.7%

Table 11. Comparative the AUC with three risk factors analyzed independently and combined factors

Variables	Area	S.E.	P	95% CI
Leukopenia (leukocyte $< 4.0 \times 10^9/L$)	0.60	0.05	0.03	[0.51, 0.70]
Lactic dehydrogenase (> 320 U/L)	0.65	0.05	0.00	[0.56, 0.74]
Lymph node enlargement	0.71	0.04	0.00	[0.62, 0.79]
Coexistence of 2 or 3 risk factors	0.76	0.04	0.00	[0.67, 0.84]

Table 12. Fourfold table was made to evaluate the diagnostic model

The diagnostic model	The 168 patients of the second group		Total
	Non-infectious diseases group	Infectious diseases group	
Non-infectious diseases	36	12	48
Infectious diseases	22	98	120
Total	58	110	168

Notes: Se (sensitivity) = 62.1%; Sp (specificity) = 89.1%; π (total consistent rate) = 79.8%; PV+ (positive predictive value) = 75%; PV-(negative predictive value) = 81.7%; Kappa value = 0.53, $P < 0.001$.

Figure 1. Discriminatory capacity of the model and its components in the second group (5 factors).

Notes: The results of the 168 cases (from January, 2009 to April, 2011) post-discharge and follow-up was a golden criterion for evaluating diagnostic tests. Filtered out by logistic regressive analysis, 5 risk factors were made as an index for future evaluation. Using the ROC curve, the area under ROC curve (AUC) was calculated and compared (Figure 1, Table 9). Results: WBC $< 4.0 \times 10^9/L$, LDH > 320 U/L, lymphadenectasis, AUC of these 3 risk factors are 0.60, 0.65 and 0.71, which has low diagnostic value ($P < 0.05$). AUC of PLT $> 400 \times 10^9/L$, TP < 60 g/L shared the same number of 0.50 with no diagnostic value ($P > 0.05$).

Figure 2. Discriminatory capacity of the risk factors and its components in the second group.

Notes: The coexistence of risk factors (≥ 2) were used as prediction indexes, ROC curve was used for AUC calculation and then compared with AUC of the three risk factors existed independently.

Analysis of case data (group 2): assessment of diagnostic model

Three risk factors for discriminating non-infectious disease ($\text{WBC} < 4.0 \times 10^9/\text{L}$, $\text{LDH} > 320 \text{ U/L}$ and lymphadenectasis) were analyzed in both groups (Table 10). Cases in the second group showed 55 cases with no risk factors, 7 with non-infectious disease, 65 with one risk factor, 15 with potential infectious disease (23.1%); 48 cases with two or three risk factors showed a high differential rate, among which 36 with non-potential infectious disease (75%).

As shown in Table 11, AUC (risk factors ≥ 2) was 0.76, 95% confidence intervals was [0.67, 0.84], $P = 0.00$, which was larger than AUC with three risk factors analyzed independently.

Among the 168 patients in the second group, the presence of more than two risk factors predicted non-infectious disease. The sensitivity was 62.1%; specificity was 89.1%; total consistent rate was 79.8%; positive predictive value was 75%; negative predictive value was 81.7%; Kappa value was 0.53, $P < 0.001$ (Table 12).

DISCUSSION

FUO, as a complicated matter in internal clinic for its complex etiology, the proportion of undiagnosed cases is about 10%-50% and the portion is soaring by time.¹⁻¹⁰ It can be divided into the following four kinds: infectious disease, connective tissue disease, neoplastic disease and other diseases. The research

divided the enrolled hospitalized patients into two groups and the diagnosis included infectious disease (52.4%, 57.9%), connective tissue disease (16.8%, 16.3%), neoplastic disease (16.1%, 11.6%), other diseases (2.1%, 2.6%) and undiagnosed diseases (12.6%, 11.6%). The most common diseases were bacterial infections, AOSD, NHL. There were no differences in the spectrums between two disease groups, which was coincident with reports from Peking Union Medical College Hospital and other hospitals.^{3,4,6,10} Disease spectrum of FUO in China was different from that in Europe and America.^{1,2,7-9} In Greece, Stamatis etc, reported that non-infectious inflammatory disease (NIID) (33%) was the most common disease for FUO patients, systemic lupus erythematosus (SLE) and vasculitis were the mostly common diseases in NIID.⁷ Considering that different disease spectrum leads to different diagnostic model, we propose a suitable model based on FUO patients in China to guide practical diagnosis.

Due to lack of efficient diagnostic system, FUO has been regarded as a difficult problem in clinical diagnosis. It can be divided into infectious group and non-infectious group according to disease classification. Infectious diseases include bacterial, fungi, virus, tuberculosis, parasite, rickettsia, protozoa infection. Non-infectious diseases include AOSD, SLE, vasculitis, connective tissue disease, lymphoma, solid tumor, neoplastic disease, drug fever and other diseases. Whether a union of several indexes was essential to guide clinical discrimination and

diagnosis instead of an independent index for early stage diagnosis and interference was the objective of our study. The results showed that the coexistence of two or three clinical indexes such as $WBC < 4.0 \times 10^9/L$, $LDH > 320 U/L$ and lymphadenectasis were important for discriminating infectious diseases. In clinics, reduction in WBC showed no specificity because it can be found in gram negative bacillus infection, virus infection, some serious infectious and non-infectious diseases such as lymphoma. For FUO patients in China, bacterial and *Mycobacterium tuberculosis* infections were most common, usually with mild increased LDH and no superficial or deep lymphadenectasis. Significantly elevated LDH often appeared in non-infectious diseases such as tumor, because increased LDH reflected metastasis and highly degree of malignant tumor.¹² Blood etc. which were related with tumor tissue contained increased LDH.¹³ So it is meaningful to take the three indexes into account in distinguishing infectious disease. The diagnostic model of coexisting indexes ($X \geq 2$) had a consistency of 89.1% in specificity. These three indexes can be obtained within 24 hours for early discrimination, diagnosis, therapy and can avoid abuse of antibiotics. These three indexes were available in domestic hospitals and convenient on procedures.

Some shortages still existed in this study: low efficiency in sensitivity, positive predictive value and negative predictive value. The etiology of FUO is so complicated that it's difficult to establish an ideal model that can completely discriminate infectious and non-infectious diseases. Completely correct classification of disease is difficult. For example, a patient with normal temperature and recovered from diagnostic antituberculous therapy, was diagnosed as *Mycobacterium tuberculosis* infection, but in fact, it may be tumor disease rather than tuberculosis while fever is self-limited remission. The specificity of traditional inflammatory indexes are low. In China, bacterial infections with increased WBC/PMN count, CRP and ESR are the most common infectious diseases; while in non-infectious diseases, AOSD with the same symptoms was the most common. All cases in this research were collected from 2006 to 2011 and some reference indexes value (serum ferritin and calcitonin zymogen) can't be analysed because methods were inconsistent, while these indexes were very important factors for discriminating infectious diseases from non-infectious diseases.¹⁴⁻¹⁷ The sensitivity was low due to lack of indexes with high

sensitivity and specificity. The disease spectrum of FUO in China is different from Europe and America. 18F-FDG PET/CT, a new way for tumor detection and displaying infection and inflammatory lesions has high sensitivity and specificity and is important for the diagnosis of FUO.^{18,19} But this equipment is expensive, not available for small medical institution, which limited its popularization and thus is only used as a second-line examination item.

In a word, FUO is a difficult problem for clinical diagnosis and our research can only be a reference for diagnosis because of its lack in sample size and the deficiency of the model. In clinics, factors such as history, physical examination and symptoms are important; golden criteria such as pathogenic examination, bone marrow cytology examination and pathology examination can't be replaced by diagnostic models. As for establishment of sensitive diagnostic model, large size samples, more representative case data and more new meaningful indexes for discrimination and diagnosis are furtherly needed.

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