A Diagnostic Tool for Identification of Etiologies of Fever of Unknown Origin in Adult Patients

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Summary: The diagnosis and treatment of fever of unknown origin (FUO) are huge challenges to clinicians. Separating the etiologies of FUO into infectious and non-infectious disease is conducive to clinical physicians not only on making decisions rapidly concerning the prescription of suitable antibiotics but also on further analysis of the final diagnosis. In order to develop and validate a diagnostic tool to efficiently distinguish the etiologies of adult FUO patients as infectious or non-infectious disease, FUO patients from the departments of infectious disease and internal medicine in three Chinese tertiary hospitals were enrolled retrospectively and prospectively. By using polynomial logistic regression analysis, the diagnostic formula and the associated scoring system were developed. The variables included in this diagnostic formula were from clinical evaluations and common laboratory examinations. The proposed tool could discriminate infectious and non-infectious causes of FUO with an area under receiver operating characteristic curve (AUC) of 0.83, sensitivity of 0.80 and specificity of 0.75. This diagnosis tool could predict the infectious and non-infectious causes of FUO in the validation cohort with an AUC of 0.79, sensitivity of 0.79 and specificity of 0.70. The results suggested that this diagnostic tool could be a reliable tool to discriminate between infectious and non-infectious causes of FUO.

Key words: fever of unknown origin; prediction model; diagnostic tool; etiology; empiric therapy

Fever of unknown origin (FUO) is defined as a temperature rising above 38.3°C on several occasions over a period of more than 3 weeks. Although the laboratory tests and diagnostic imaging techniques have been greatly improved[1], the diagnosis and treatment of FUO remain a major challenge to clinicians. The etiologies of FUO[2–4] are numerous and complex, and among the various etiologies, infectious diseases are still the major cause of FUO[5], especially, in developing countries[2, 6–8]. In order to distinguish the infectious disease rapidly and efficiently, we developed and validated a diagnostic tool by using various predicting factors, which can largely facilitate the clinicians to analyse the final diagnosis of FUO.

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1 PATIENTS AND METHODS

1.1 Patients

The retrospective cohort was enrolled from Tongji Hospital and Union Hospital (Wuhan, China) between January 2012 and June 2014 to develop the diagnostic tool. Besides these two hospitals, the patients from the First Affiliated Hospital of Medical College of Zhengzhou University were included in the prospective study from July 2014 to September 2015. The data from this cohort were used to validate the diagnostic tool.

The inclusion criteria were a syndrome of fever lasting for more than 3 weeks with a temperature higher than 38.3°C on several occasions with the causes that remained uncertain after 3 outpatient visits or 3 days of in-hospital evaluation. All the FUO cases were

reviewed by a final diagnostic committee composed by three specialist physicians (with experience in infectious disease, malignancies and autoimmune diseases) and a radiologist and laboratory specialist if necessary.

The diagnostic workup for the patients who met the criteria was recorded by using a structured data collecting form. The symptoms collected from the medical history were independently recorded by two physicians (Zhao MZ and Wu ZH), including chills accompanied by fever, muscle pain and weight loss during the course of the disease. Clinical signs found during the physical examination, such as enlargement of the lymph nodes, hepatomegaly and/or splenomegaly and multi-cavity effusion, were confirmed by two physicians independently. The nonspecific laboratory examinations included complete blood count, C reactive protein (CRP), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), serum ferritin (SF). Additionally, advanced or specific diagnostic evaluations were listed as follows: procalcitonin (PCT), interferon-gamma release, T cell-SPOT.Tuberculosis (T-SPOT.TB), anti-neutrophil cytoplasmatic antibodies (ANCA), antinuclear antibodies (ANA) and rheumatoid factor (RF). For the validation cohort, all data were independently prospectively collected by three physicians (Xing MY, Xu D and Zhu JL).

The outcome was the definitive diagnosis of infectious or non-infectious disease. There were a variety of infectious diseases included in the definite diagnosis of infection (i.e., bacterial, viral, and parasitic infections). The diagnosis was decided according to any of the following results plus imaging changes of the body parts related to the symptoms if necessary: a positive body fluid culture, a positive serology result, and a positive polymerase chain reaction and immune assay for a pathogenic organism[9]. The diagnosis of non-infection included 3 categories of diseases[10]: (1) malignancies, (2) autoimmune diseases and (3) miscellaneous causes. We followed up the patients for a maximum of 6 months to confirm the final diagnosis. Overall, 243 and 219 patients were diagnosed during hospitalization and 32 and 21 patients were diagnosed during the follow-up period in the retrospective and validation cohorts, respectively.

1.2 Statistical Analysis

The normality of the data distribution was assessed by using the Shapiro-Wilk and Kolmogorov-Smirnov tests. In the retrospective cohort, the Chi-square test or Fischer's exact test was used for categorical variables, and the unpaired Student's *t* test was used for continuous variables. In each group, the odds ratios (OR) and 95% confidence interval (CI) of each predicting variable were used to estimate the association between them and the risk of infectious disease as a cause of FUO. The univariate logistic regression model was established to evaluate the risk. The polynomial predicted model was constructed in the retrospective population using a logistic regression model including all predicting variables. Akaike's information criterion (AIC) was used to judge the fitness of the models. The difference in AIC between models was evaluated by the likelihood ratio test (LRT)[11]. The final predicted model was identified as having the significantly lowest AIC value. In order to make it easier for clinical application, we rounded the coefficient of each variable in the model to calculate the score and predict the risk of an infectious cause of FUO. The area under the receiver operating characteristic (ROC) curve was used to evaluate the performance of the prediction model and scoring system.

All statistical testing was performed using 2-tailed tests; $P<0.05$ was considered statistically significant. All analyses were performed using the SPSS statistical software, version 18.0 (SPSS, USA) and Empower Stats (http://www.empowerstats.com).

2 RESULTS

2.1 Distribution of Etiologies and Characteristics of Patients

According to the definition of FUOs, a total of 565 patients with fever as the diagnosis at admission [254 (45%) and 311 (55%) from Union Hospital and Tongji Hospital, respectively] were initially enrolled in the study. Of them, 290 were excluded due to certain reasons (fig. 1). The remaining 275 cases that met the criteria were subjected to the final analysis.

Not surprisingly, infectious diseases were the most common potential diagnosis during hospitalization. A variety of antibiotics were administered before the infection was confirmed in most of the patients (89.5%). The distributions of diagnoses during the follow-up were similar between the retrospective and validation cohorts (table 1). The most prevalent FUO causes in order of frequency were tuberculosis, malignant lymphoma, adult-onset Still's disease, sepsis, pulmonary fungal infection and systemic lupus. Diagnostic methods consisted of cultures (22.2%), history and evaluation (17.0%), biopsy (14.1%), and serologic assays (9.9%). The patients' demographic characteristics, the common presenting symptoms and signs, the results of laboratory examinations in the retrospective and validation cohorts are presented in table 2.

2.2 Development and Performance of Diagnostic Tool

A total of 18 variables, including demographic factors, clinical symptoms and signs and laboratory test results, were taken into account as the potential predicting variables for the development of the diagnostic tool. Among them, male gender and chills

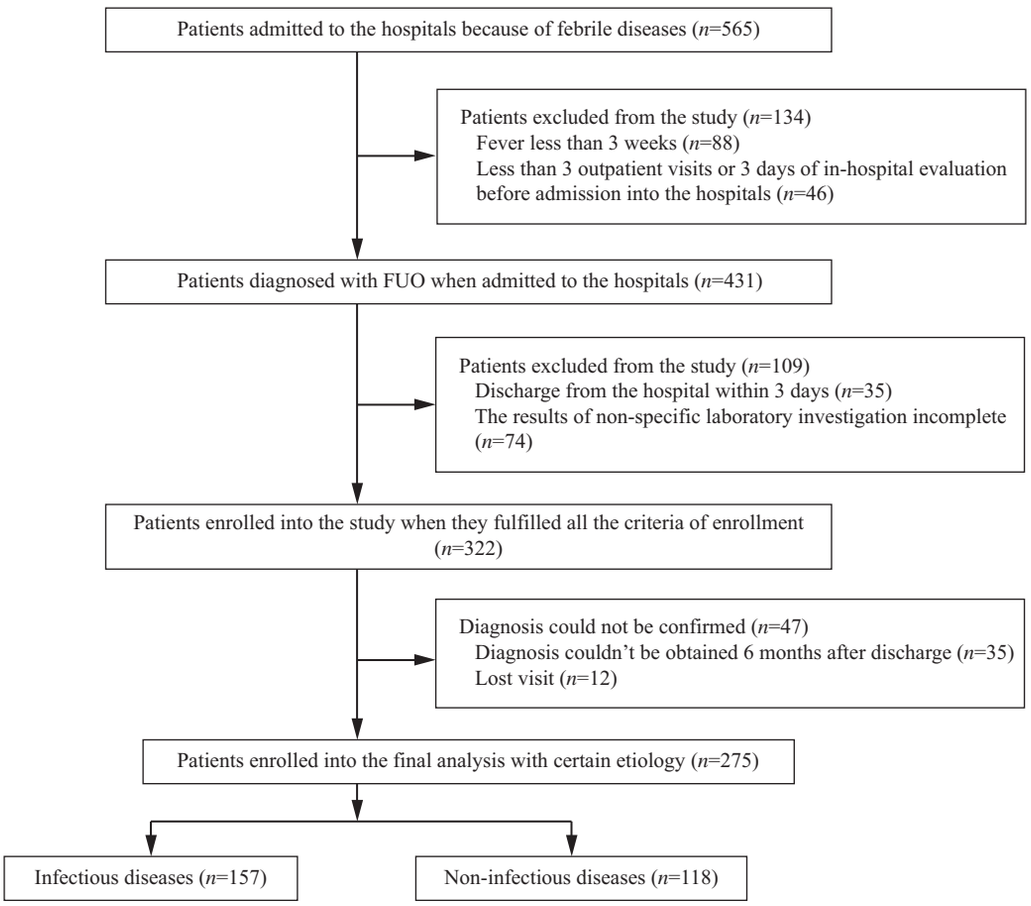

Fig. 1 Flow diagram of participants of the retrospective cohort for diagnostic model derivation

Table 1 The distributions of the etiologies in the retrospective cohort and prospective cohort

	Retrospective population			Prospective population			
	Tongji hospital (*n*)	Union hospital (*n*)	Proportion (%)	Tongji hospital (*n*)	Union hospital (*n*)	The first hospital (*n*)	Proportion (%)
Infectious causes	94	63		92	29	19	
Bacterial	54	39	59.2	55	18	13	61.4
Tuberculosis	15	11	16.6	15	4	4	16.4
Sepsis	8	6	8.9	7	3	2	8.6
Pulmonary infection	5	4	5.7	6	3	2	7.9
Brucellosis	5	4	5.7	6	2	1	6.4
Endocarditis	4	4	5.1	4	1	1	4.3
Pyogenic meningitis	3	2	3.2	7	1	0	5.7
Intra-abdominal Abscess	3	1	2.5	2	0	0	1.4
Typhoid fever	2	1	1.9	2	0	0	1.4
Others	9	6	9.5	6	4	3	9.3
Viral	20	12	20.4	17	6	3	18.5
Epstein-Barr virus	7	3	6.4	8	5	1	10
Cytomegalovirus	5	3	5.1	4	0	1	3.5
Virus meningitis	3	2	3.2	3	0	0	2.2
Others	5	4	5.7	2	1	1	2.8
Fungal	16	10	16.6	17	5	3	17.9
Pulmonary fungal infection	8	4	7.6	8	3	2	9.3
Intestinal fungus infection	4	1	3.2	3	1	0	2.9
Fungal meningitis	2	2	2.6	2	0	0	1.4
Others	2	3	3.2	4	1	1	4.3
Malaria	4	2	3.8	3	0	0	2.2

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	Retrospective population			Prospective population			
	Tongji hospital (*n*)	Union hospital (*n*)	Proportion (%)	Tongji hospital (*n*)	Union hospital (*n*)	The first hospital (*n*)	Proportion (%)
Non-infectious causes	68	50		61	23	16	
Autoimmune diseases	32	18	42.4	27	10	8	45
Adult-onset Still disease	9	5	11.9	9	2	3	14
UCTD	4	2	5.1	4	2	2	8
SLE	3	3	5.1	5	1	1	7
Rheumatoid arthritis	2	2	3.4	2	1	0	3
IBS	1	2	2.5	1	1	0	2
Sjogren's syndrome	3	0	2.5	2	1	0	3
ANCA associated vasculitis	4	2	5.1	2	1	1	4
Others	6	2	6.8	2	1	1	4
Neoplasms	30	24	45.8	27	10	6	43
Malignant lymphoma	14	13	22.9	18	8	4	30
Leukemia	4	2	5.1	3	1	0	4
Multiple myeloma	2	1	2.5	2	0	0	2
Solid tumor	5	5	8.5	3	1	1	5
Others	5	3	6.8	1	0	1	2
Miscellaneous	6	8	11.9	7	3	2	12
Subacute thyroiditis	3	2	4.2	3	1	1	5
Lymphadenitis	1	4	4.2	2	1	1	4
Others	2	2	3.4	2	1	0	3

UCTD: undifferentiated connective tissue diseases; The first hospital: The First Affiliated Hospital of Medical College of Zhengzhou University; SLE: systemic lupus erythematosus; IBS: inflammatory bowel disease

Table 2 General characteristics of the included population

Patients' characteristics	Retrospective population (*n*=275)	Prospective population (*n*=240)
Age (years), median (interquartile range)	47 (30, 59)	47 (34, 60)
Males, *n* (%)	137 (49.8)	137 (57.1)
Duration of fever before admission (days), median (interquartile range)	28 (25, 56)	30 (25, 60)
Duration of hospitalization (days), median (interquartile range)	21 (15, 35)	19 (15, 37)
Highest temperature before admission (°C)	39.4 (38.7, 39.7)	39.5 (38.7, 39.6)
Symptoms and signs		
Chills	101(36.7)	84 (35.0)
Muscle pain	86 (31.3)	61 (25.4)
Lymph node enlargement	68 (24.7)	56 (23.34)
Hepatomegaly and/or splenomegaly	85 (30.9)	53 (22.1)
Multi-cavity effusion	70 (25.5)	28 (11.7)
Diagnosis distribution		
Infectious diseases	157 (57.1)	140 (58.3)
Autoimmune diseases	50 (18.2)	33 (13.8)
Neoplasms	54 (19.6)	50 (20.8)
Miscellaneous diseases	14(5.1)	17 (7.1)
T-SPOT.TB positivity, *n* (%)	51 (18.5)	73 (30.4)
Antinuclear antibodies positivity, *n* (%)	31 (11.3)	20 (8.3)
Anti-neutrophil cytoplasm antibody positivity, *n* (%)	4 (1.5)	3 (1.3)
Rheumatoid factor positivity, *n* (%)	10 (3.6)	22 (9.2)
White blood cell count (×1000/mm^3)	6.37 (4.40, 10.21)	6.83 (471, 10.24)
Percentage of neutrophil (%)	72.8 (61.7, 84.5)	73.6 (64.15, 81.80)
Erythrocyte sedimentation rate (mm/h)	40 (14, 74)	50 (20, 85)
C-reactive protein (mg/L)	57.6 (22.3, 110.1)	52.9 (20.1, 105.6)
Serum ferritin (μg/L)	660.9 (341.3, 1950.9)	542.9 (284.5, 1144.1)
Lactate dehydrogenase (U/L)	243 (172, 446)	215 (166, 362)
Procalcitonin (ng/mL)	0.23 (0.11, 0.55)	0.15 (0.06, 0.37)

Values are presented as number [percentages] unless stated otherwise.

tended to be more common among the infectious patients (table 3), whereas hepatomegaly and/or splenomegaly, lymph node enlargement and multi-cavity effusion were more frequently observed in the patients with non-infectious diseases (table 3). There were no significant differences in age and the frequency of muscle pain during pyrexia between infectious and non-infectious groups.

With regard to the laboratory profile, patients with infections did not have higher white blood cell (WBC) counts, a greater proportion of neutrophils, or higher average CRP and ESR values than those with non-infectious conditions (table 3). In contrast, the SF and LDH levels were significantly lower in infectious group than those in the non-infectious group. The PCT level was higher in infectious group than in non-infectious group. Additionally, the positive rate of T-SOPT.TB was higher in the infectious patients. On the contrary, higher positive rate of ANCA, RF and ANA was detected in the non-infectious conditions. Notably, the whole positive rates of these serum antibodies tests were relatively lower in both groups.

Based on the results from the univariate logistic regression model, multinomial logistic regression analysis was used to develop a diagnostic prediction tool comprised of 10 variables, including gender, chills, multi-cavity effusion, hepatomegaly and/or splenomegaly, lymph node enlargement, and laboratory examination parameters (ANA, T-SPOT.TB, SF, LDH, and PCT) (table 4). Among them, the predicting variables, male gender, chills, T-SPOT.TB and PCT were positive indicators of infectious causes with an OR value greater than 1, while the other 6 variables had an OR value less than 1.

After rounding the coefficients of each variable in the tool, a scoring system was developed as follows: SCORE=63+6×(Gender=1)+18×(T-SPOT.TB=1)–6×(Multi-cavity effusion=1)–11×(Lymph node enlargement =1)–7×(Hepatomegaly and/or Splenomegaly=1)+7×(Chills=1)–21×(ANA=1)–5×ln(LDH)–4×ln(SF)+4×ln(PCT). The best cut-off point was 3.

The AUC of the ROC curve was 0.83 (95% CI, 0.78 to 0.88) (fig. 2). The risk cut-off value was 2.96, the sensitivity was 0.80 (95% CI, 0.72 to 0.85),

Table 3 General characteristics of infectious and non-infectious diseases in retrospective population

Variables	ID (*n*=157)	NID (*n*=118)	*P* value
Age (years), median (interquartile range)	48 (34, 58)	43 (26, 59)	0.107
Male, *n* (%)	88 (56.1%)	49 (41.5%)	0.017
White blood cell count (×1000/mm^3)	6.37 (4.56, 10.82)	6.36 (3.72, 10.06)	0.298
Percentage of neutrophil (%)	73.60 (64.20, 84.80)	72.45 (60.05, 83.60)	0.497
Erythrocyte sedimentation rate (mm/h)	38.0 (14.0, 74.0)	43.5 (14.3, 74.0)	0.639
C-reactive protein (mg/L)	58.8 (25.0, 109.0)	53.8 (18.0, 110.9)	0.629
Procalcitonin (ng/ml)	0.25 (0.10, 0.60)	0.22 (0.12, 0.47)	0.627
Ferritin (μg/L)	474.0 (250.5, 1240.0)	1114.2 (463.5, 5655.8)	<0.001
Lactate dehydrogenase (U/L)	211.0 (164.0–331.0)	373.5 (197.3, 608.5)	<0.001
T-SPOT.TB positivity, *n* (%)	43 (27.4%)	8 (6.8%)	<0.001
Antinuclear antibodies positivity, *n* (%)	4 (2.5%)	27 (22.9%)	<0.001
Anti-neutrophilcytoplasm antibodies positivity, *n* (%)	1 (0.6%)	3 (2.5%)	0.317
Rheumatoid factor positivity, *n* (%)	5 (3.2%)	5 (4.2%)	0.749
Chills, *n* (%)	64 (40.8%)	37 (31.4%)	0.109
Muscle pain, *n* (%)	43 (27.4%)	43 (36.4%)	0.109
Lymph node enlargement, *n* (%)	25 (15.9%)	43 (36.4%)	<0.001
Hepatomegaly and/or splenomegaly, *n* (%)	37 (23.6%)	48 (40.7%)	0.002
Multi-cavity effusion, *n* (%)	33 (21.0%)	37 (31.4%)	0.051

ID: infectious diseases; NID: non-infectious diseases

Table 4 The details of the prediction model in the retrospective cohort

Variables	Parameter estimate	Standard error	*P* value	OR	95% CI
T-SPOT positivity	1.81	1.48	0.000	6.09	2.37–15.65
Multi-cavity effusion	–0.57	0.38	0.131	0.57	0.27–1.18
Lymph node enlargement	–1.13	0.37	0.000	0.32	0.16–0.67
Hepatomegaly and/or splenomegaly	–0.65	0.33	0.048	0.52	0.27–0.99
Chills	0.66	0.33	0.047	1.94	1.01–3.72
ANA positivity	–2.12	0.64	0.001	0.12	0.03–0.42
Male	0.61	0.31	0.052	1.83	0.99–3.83
lnLDH (lnU/L)	–0.54	0.29	0.060	0.58	0.33–1.03
lnSF (lnμg/L)	–0.36	0.14	0.008	0.70	0.53–0.91
lnPCT (lnng/mL)	0.38	0.13	0.003	1.47	1.13–1.89

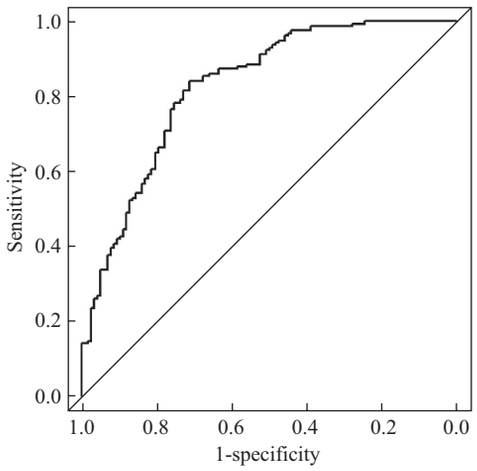

Fig. 2 The area under receiver operating characteristic curve of the diagnostic tool in the retrospective population

the specificity was 0.75 (95% CI, 0.66 to 0.83), the negative likelihood ratio was 0.27 (95% CI, 0.20 to 0.37), and the positive likelihood ratio was 3.24 (95% CI, 2.34 to 4.49). The positive and negative predicted values were 0.81 (95% CI, 0.74 to 0.87) and 0.74 (95% CI, 0.65 to 0.81), respectively.

2.3 Validation of Diagnostic Tool

In the prospective cohort, 140 (58.3%) infectious cases and 100 (41.7%) non-infectious cases were recruited from three different hospitals (tables 1 and 2).

The performance of the scoring system in the validation population was also assessed by ROC curve (fig. 3). The AUC was 0.79 (95% CI, 0.73 to 0.85) and the sensitivity and specificity were 0.79 (95% CI, 0.72 to 0.86) and 0.70 (95% CI, 0.60 to 0.78), respectively. The negative likelihood ratio was 0.30 (95% CI, 0.21 to 0.41) and the positive likelihood ratio was 2.62 (95% CI, 1.92 to 3.58). The positive and negative predicted values were 0.78 (95% CI, 0.71 to 0.85) and 0.70 (95% CI, 0.60 to 0.79), separately.

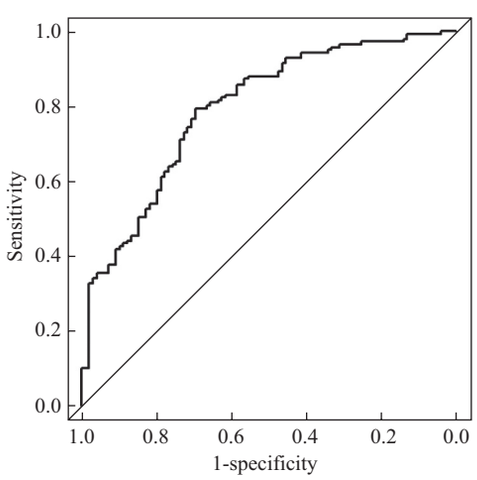

Fig. 3 The area under receiver operating characteristic curve of the diagnostic tool in validation population

3 DISCUSSION

The etiologies of FUO are numerous and diverse, and the small sample sizes of FUO in one hospital are usually not sufficient enough to undergo a statistical analysis and draw a powerful conclusion[2, 12, 13]. Different diagnostic methods were proposed for identification of etiologies of FUO, depending on the different situations of the FUO patients[14]. Single indicators, such as CRP, SF and eosinophil counts, were less effective for the determination of etiologies of FUO. Some studies examined the causes of FUO by using PET/CT[15]. Admittedly, PET/CT is useful to localize infection or malignancy[16, 17], but the false-positive possibility[18, 19] and the high cost make it less attractive as a diagnostic option. Therefore, single biomarkers or one diagnose technique was insufficient to discriminate the etiologies of FUO[20–22] due to the complexity of FUO.

Several studies on the establishment of clinical prediction models suggested that the diagnostic method should be systematic and efficient. Wang *et al* developed a computerized diagnostic model by using a multinomial logistic regression method[14]. Nijman *et al* included 40 clinical features into a diagnostic system, which was proved to be useful in helping paediatric physicians in the emergency department to detect serious bacterial infections, thereby improving early treatment[23]. These diagnose models are able to not only discriminate some serious infectious diseases in febrile children but also evaluate the clinical symptoms and signs to rule out other causes[24]. In our study, we collected the patients' fundamental information, clinical symptoms and signs and laboratory markers to develop a diagnostic tool to identify infectious causes in adult FUO patients. It was demonstrated that this tool could help the clinicians to distinguish the etiologies of FUO as infectious or non-infectious rapidly and accurately in more than 500 adult patients.

The main strength of this study is that we validated this diagnostic tool by using a separate prospective cohort from three large teaching hospitals in two different Chinese provinces. This study is by far the largest clinical study designed to establish a diagnostic strategy for FUO patients in developing countries. All variables included in this diagnostic tool were derived from medical history and physical examinations as well as first-line blood examinations without extra expenses required, which made the diagnostic tool much more feasible to apply in clinical practice. This tool also introduced the latest laboratory testing indicators (i.e., PCT, SF, and T-SPOT.TB) to increase our knowledge of the FUO diagnosis[25, 26]. Last but not least, this diagnostic tool we developed could reduce the inappropriate administration of empirical broad-spectrum antibiotics to FUO patients.

The infectious and non-infectious diseases differ from each other in terms of the onset and progressive nature and the triggered immune responses and so on[27, 28]. For infectious diseases, pathogens invade the body prior to the emergence of clinical symptoms and signs. Therefore, we proposed a new strategy called the "two step" diagnostic algorithm to quickly distinguish the etiologies of FUO as infectious or non-infectious. The related clinical study has been registered on the website http://www.clinical trials.gov since 2013 under the registration number NCT02035670. The first step was to look for and analyse the possibility and route of pathogen invasion into the body at the onset of the disease. The related data have been published[29]. The second step (i.e., this study) is to focus on the development of the disease and the obvious symptoms. Future research regarding the "two step" diagnostic algorithm aims to enable physicians to accurately decide whether empirical antibiotic therapy is necessary and which types of antibiotics should be selected[30, 31].

In the future, new laboratory indicators with potential value can be continuously introduced into the tool, which will improve its accuracy[32, 33]. We currently evaluate whether the sensitivity and specificity of this diagnostic tool will be improved by the introduction of the time of fever alleviation by the administration of glucocorticoids as an indicator.

In conclusion, this diagnostic tool consisted of gender, clinical symptoms and signs and laboratory examination results, and it was helpful to identify the cause of infection in adult FUO patients rapidly and accurately. This tool may well guild physicians in their diagnostic work-ups and decision-making processes to administer antibiotic therapy and re-establish the FUO diagnostic strategy.

Conflict of Interest Statement

None of the other authors have any conflicts of interest to declare.

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