의학 석사 학위논문

Risk factors of delayed diagnosis in extrapulmonary tuberculosis

폐외결핵 진단 지연의 위험인자에 대한 연구

2021 년 2월

서울대학교 대학원

의학과 내과학 전공

이 민 경

A thesis of the Degree of Master of Science

폐외결핵 진단 지연의 위험인자에 대한 연구

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February 2021

The Department of Internal Medicine

Seoul National University College of Medicine

Min Kyeong Lee

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지도교수 박 상 원

이 논문을 의학 석사 학위논문으로 제출함

2020 년 10월

서울대학교 대학원

의학과 내과학 전공

이 민 경

이민경의 석사 학위논문을 인준함

2021 년 1월

위 원 장 박서원 (인)

부 위 원 장 박상원 (인)

위 원 오윤규 (인)

Abstract

Risk factors of delayed diagnosis in extrapulmonary tuberculosis

Min Kyeong Lee

Department of Internal Medicine

The Graduate School

Seoul National University

Background:

The proportion of extrapulmonary tuberculosis (EPTB) of overall tuberculosis (TB) cases is increasing. EPTB significantly contributes to increase of TB-related mortality, complications, sequelae, and disabilities. EPTB is more difficult to diagnose than pulmonary TB. The delayed diagnosis and treatment of EPTB can cause complications, lifelong sequelae, and increase in socioeconomic burden. This study aimed to understand the detailed epidemiologic data on EPTB in South Korea and identify risk factors associated with its delayed diagnosis and treatment.

Methods:

Patients newly diagnosed with EPTB were retrospectively enrolled from eleven general hospitals nationwide in South Korea from January 2017 to December 2018. Recent epidemiologic status and basic characteristics of patients with EPTB were described. The subjects were subdivided into early versus delayed diagnosis groups, depending on the duration from the first visit to TB medication: ≤7 or >7 days, respectively. Univariable and multivariable analysis of the early and delayed groups were performed to identify risk factors for delayed diagnosis and treatment in EPTB.

Results:

Final 594 patients were enrolled. Lymph node TB (28.3%) was predominant form followed by abdominal (18.4%) and disseminated TB (14.5%). Concurrent lung involvement was 17.8%. The rate of treatment success and failure were 86.2% and 0.5%, respectively. The all-cause mortality rate was 2.2%. The duration from the onset of illness to first visit, from the first visit to diagnostic testing and TB medication were median 22, 9 and 19 days, respectively. Diagnostic tests showed no significant difference in positivity between groups. Acute nature of clinical manifestation in immunosuppression (odd ratio [OR] 0.269, 95% confidence interval [95%CI] 0.077–0.943), disseminated TB (OR 0.306, 95%CI 0.131-0.714), pericardial TB (OR 0.135, 95%CI 0.042–0.438) and meningeal TB (OR 0.066, 95%CI 0.020–0.224) was associated with early diagnosis. Delayed diagnosis was associated with outpatient-clinic visits (OR 2.323, 95%CI 1.320–4.087), delayed sample acquisition, diagnostic departments other than infection or pulmonology (OR 3.360, 95%CI 1.070–10.553 for

gastroenterology, OR 3.113, 95%CI 1.385–6.997 for surgical departments).

Conclusion:

The delay in diagnosis and treatment of EPTB was related not to differences in microbiologic characteristics of EPTB itself but to the acuteness of clinical manifestation, promptness of sample acquisition, route of patient visits and expertise in TB. Therefore, it is necessary to establish a clinical system that promptly acquires diagnostic samples, and reinforcing consultation and collaboration with TB specialists for earlier diagnosis of EPTB to reduction of complications and socioeconomic burden.

Keywords : extrapulmonary tuberculosis, delayed diagnosis, risk factor, clinical characteristics

Student number : 2019-20529

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Introduction

Tuberculosis (TB), caused by Mycobacterium tuberculosis (MTB), predominantly affects the lungs; however, it can also affects any organs throughout the body. TB was among the top 10 causes of death worldwide, with 10 million incident cases in 2018.[1] The most common location of extrapulmonary TB (EPTB) were known as lymph node (LN) or pleura, and it could affects gastrointestinal tract, genitourinary system, cardiovascular system, central nervous system, etc.[2, 3] EPTB could also affects multiple organs simultaneously with hematogenous dissemination of MTB.[4]

South Korea, an intermediate-burden country with a TB incidence of 59 cases per 100,000 in 2019, experienced a 25.9% incidence reduction between 2015 and 2019.[5] However, from 2016, the proportion of new-case EPTB steadily increased to 21.2% in 2019.[5] Globally, EPTB accounted for 15% of all TB cases and 17% in the World Health Organization (WHO) South-East Asia region in 2018.[1] Studies conducted in the WHO European region (TB incidence of 28 cases per 100,000) and the United States (3 cases per 100,000), known as low-burden countries, reported an increase in the proportion of EPTB of overall TB cases as South Korea.[2, 3] However, recent study conducted in China, intermediate-burden country, with TB incidence of 61 cases per 100,000, reported a decrease in the proportion of EPTB between 2012 and 2017.[6]

EPTB is harder to diagnose than pulmonary TB (PTB), and the timing of diagnosis tends to be delayed due to several factors.[4, 7, 8] Nonspecific and sometimes asymptomatic clinical

manifestations make suspicion difficult. Even when EPTB is clinically suspected, extrapulmonary specimens in EPTB are usually more difficult to obtain than respiratory specimens in PTB. The extrapulmonary specimens frequently fail to reveal the causative pathogen due to the paucibacillary nature, and nucleic acid amplification (NAA) tests, such as Xpert® MTB/RIF Assay (Cepheid, Sunnyvale, CA, USA), are performed less than for respiratory specimens. Additionally, it takes quite a long time to obtain histopathologic results, important for the diagnosis of EPTB. EPTB influences the spread of TB less; however, its treatment period is longer, admission rate higher, and cost of hospitalization greater than that of PTB alone.[9, 10] Delayed diagnosis can lead to have sequelae, accompany complications, and increase disease cost and social burden.[10, 11] Some EPTB cases, including meningeal or peritoneal TB, are associated with higher mortality compared to PTB.[12]

The proportion of EPTB out of total TB is increasing, so it is important to manage EPTB in controlling TB infection.[2, 3] EPTB contributes significantly to increase of TB-related disease cost and social burden, associated with mortality, complications and lifelong sequelae.[9-11] Despite clinical significance of EPTB, its epidemiologic data are more limited than those of PTB. South Korea's annual TB report classifies EPTB concurrent with PTB as PTB and doesn't provide sufficient detailed clinical data to guide the integrated clinical approach. In addition, there is no large multicenter study that can reflect the domestic epidemiology of EPTB. Although data on individual, organ-specific EPTB have been published, comprehensive data on the entire scope of EPTB are still insufficient.

Unlike previous studies on organ-specific EPTB, this study on the entire EPTB tried to obtain data that might be contribute to the establishment of a policy to manage EPTB.

In this study, the process leading to diagnosis and treatment of EPTB was reviewed retrospectively at eleven general hospitals in South Korea, from January 2017 to December 2018. Data on performed degree of various diagnostic tests in extrapulmonary specimens and factors affecting the timing of diagnosis in EPTB were investigated. I aimed to understand the recent epidemiologic status of EPTB in South Korea and identify factors associated with its delayed diagnosis and treatment.

METHOD

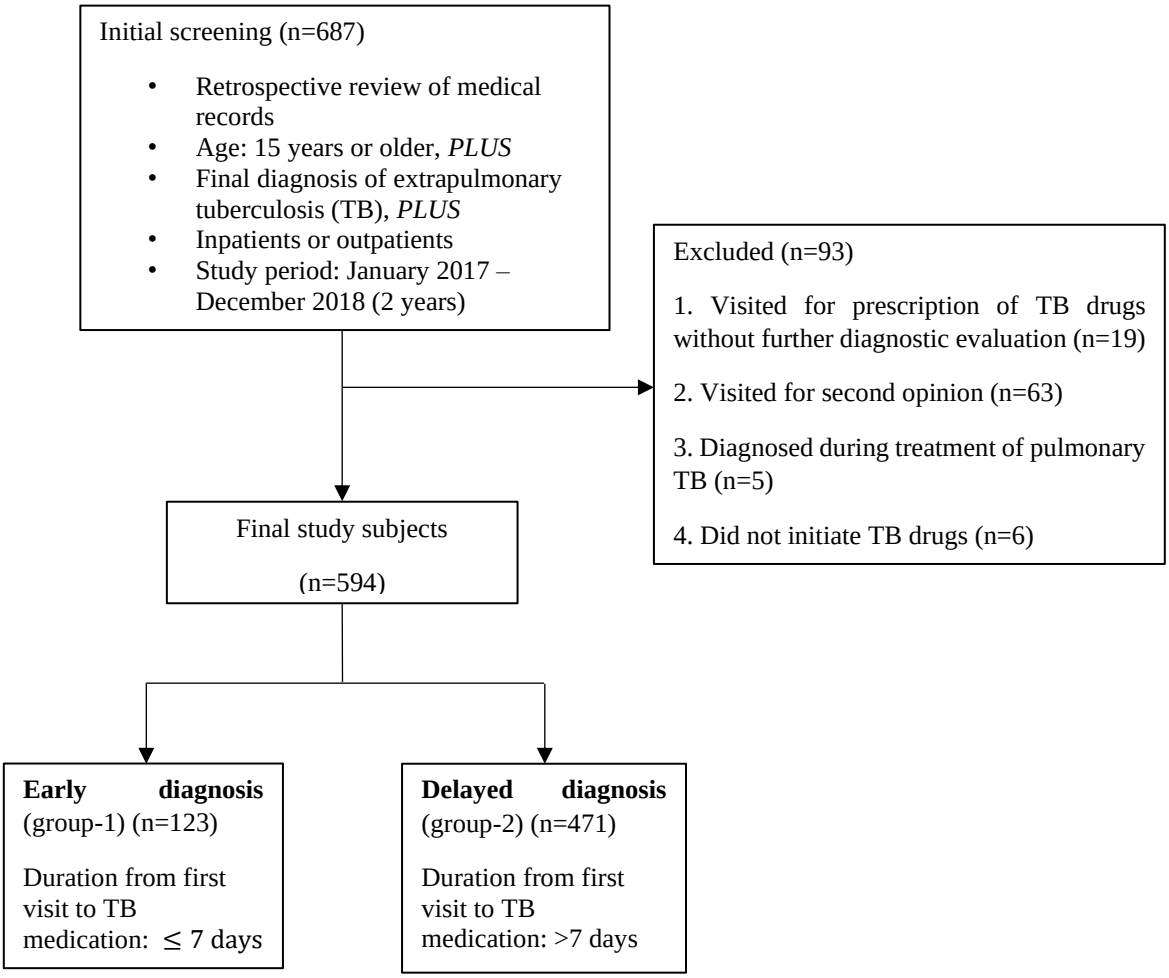
Subjects and study design

This retrospective case-series analysis was conducted at eleven general hospitals nationwide in South Korea, Boramae Medical Center, Hallym University Pyeongchon Sacred Heart Hospital, Inje University Busan Paik Hospital, Inje University Ilsan Paik Hospital, Inje University Sanggye Paik Hospital, National Cancer Center, Seoul National University Hospital, Seoul National University Bundang Hospital, SoonChunHyang University Seoul Hospital, Veterans Health Service Medical Center and Wonkwang University Hospital, from January 2017 to December 2018. All patients aged ≥15 years and newly diagnosed with EPTB were screened (Figure 1). Both inpatient and outpatient visits were included. Patients who were transferred for a second opinion or visited for medication only were excluded. EPTB cases diagnosed later during TB medication for PTB or those not eventually initiating TB medication were excluded. When patients experienced >1 EPTB diagnosis episode during the study, only the first episode was included. Subjects were subdivided into early-diagnosis (group-1) and delayed-diagnosis (group-2) groups, depending on the duration from the first visit to TB medication: ≤7 or >7 days, respectively. I analyzed the overall features of EPTB and performed multivariable analysis of the early-/delayed-diagnosis groups to identify risk factors of delayed diagnosis and treatment.

Boramae Medical Center (No. 30-2019-60) and other participating hospitals' Institutional Review Boards approved the study, and they waived informed consent because of the

study's retrospective nature. Personal identifiers were anonymized for confidentiality before data processing, and the study complied with the Declaration of Helsinki.

Figure 1. Study design.



TB = tuberculosis

Data collection

Patient lists were extracted from electronic medical records using 99 disease codes from the Korean Standard Classification of Diseases, or TB-patient lists were extracted and then screened according to stipulated criteria.[13] I collected demographic variables, TB-treatment history, and comorbidities, such as diabetes mellitus, hypertension, chronic kidney disease, chronic viral hepatitis or liver cirrhosis, cerebrovascular accident, human immunodeficiency virus (HIV) infection, possible chemotherapy for solid or hematologic malignancy, other immunosuppressive therapy for autoimmune disease or organ transplantation. The collected data included route of first visit, presence of localized or systemic symptoms, location of EPTB, expertise of department in charge, treatment outcome, and dates of variables. The diagnostic performance of microbiological, histopathological, radiological, biochemical, NAA, and drug-susceptibility tests was assessed. I only included diagnostic tests related to the first episode, which were performed within 7 days after the date of diagnosis.

Definition of terms

Involvement of any extrapulmonary site except pleura was classified as EPTB, regardless of pulmonary involvement. I classified the location of EPTB into LN TB, abdominal TB, disseminated TB, musculo-skeletal TB, lung miliary TB, pericardial TB, genitourinary TB, meningeal TB and others. Most pleural-TB cases were accompanied by PTB or resulted

in hypersensitivity reactions by MTB rather than bloodstream dissemination; therefore, isolated pleural TB was excluded.[14, 15] Lung miliary TB were enrolled because it was resulted from massive lympho-hematogenous dissemination of MTB.[16] Disseminated TB was defined as TB involving >1 noncontiguous anatomical site. Lung miliary TB was defined as TB with hematogenous spread patterns that characteristically consist of innumerable 1 to 3-mm diameter nodules randomly distributed throughout both lungs.[17]

TB diagnosis was categorized as definite, probable, or possible.[18, 19] Definite TB was defined as being culture-positive for MTB, positive for both MTB-polymerase chain reaction (PCR) and acid-fast bacilli (AFB) smear, or both MTB-PCR and typical histopathological tests. Probable TB was defined as not being definite TB yet being positive for ≥1 of the following: AFB smear, biochemical, NAA, and histopathological tests. Possible TB was defined as not being definite nor probable TB yet having clinical symptoms or radiological/endoscopic findings suggesting TB improved by empirical TB medication. Positive results for both AFB smear and histopathological tests were classified as probable TB due to the possibility of nontuberculous mycobacteria. I did not include interferon-gamma release assay (IGRA) in the evidence of probable TB. Because IGRA did not distinguish active TB from latent TB and the data on applying IGRA in extrapulmonary specimens were insufficient.[20, 21]

The drug susceptibility test was classified as 3 groups: mono-resistant, polyresistant, multi-drug resistant TB (MDR TB). Polyresistant TB refers to TB resistant to more than single anti-TB agent but not both of isoniazid and rifampicin. MDR TB refers to TB

resistant to both isoniazid and rifampicin and possibly additional agents. Treatment outcomes were categorized as success, failure, death, default, and transferred.[22] Diagnosis date was defined as the date of acquisition of the specimen leading to the final diagnosis, or date of TB medication initiation in case of possible TB. Localized symptoms were manifestations related to the location of EPTB, and systemic symptoms were general manifestations such as fever, night sweat and weight loss.

The adenosine deaminase (ADA) cutoff value was ≥40 IU/L in pleural effusion and ascites, ≥10 IU/L in cerebrospinal fluid and ≥36 IU/L in pericardial effusion.[23] Histopathological tests were considered positive when chronic granulomatous inflammation with caseous necrosis was detected, or consistent TB findings were confirmed by a pathologist.[24] Chest radiography (CXR), computed tomography (CT), and magnetic resonance imaging were positive when they revealed findings typical of active TB.[17] Positron emission tomography-CT was positive when findings led to a suspicion of TB infection.[25]

Statistical analysis

Continuous and categorical variables were compared using the Mann–Whitney test and Pearson's chi-square or Fisher's exact test, respectively. Spearman correlation was used to estimate the correlation coefficients (rho) and p-values. I considered $P < 0.05$ as significant. Variables with $P < 0.05$ in univariate analysis that had data from all subjects

were included in the multivariable analysis. Multivariable logistic regression using backward eliminations was conducted to estimate adjusted odds ratios (aORs) and 95% confidence intervals (95%CIs). Statistical analyses were performed using SPSS, version 25.0 (IBM Corp, Armonk, NY, USA).

RESULTS

General characteristics of EPTB

Baseline characteristics

I screened 687 patients and eventually enrolled 594. The median age was 58, and 51.3% of patients were female (Table 1). Patients with TB history were 8.8%, 27.1% visited the emergency room (ER), and 54.9% transferred. No comorbidities were found in 59.6% of patients; hypertension (24.9%), diabetes mellitus (13.8%), and solid malignancy (5.6%) were common underlying diseases. Patients with HIV infection was 0.8%. Localized and systemic symptoms were present in 77.6% and 30.0% of patients, respectively.

LN was the predominant EPTB location (n=168, 28.3%), followed by abdominal (n=109, 18.4%), disseminated (n=86, 14.5%), and musculo-skeletal TB (n=56, 9.4%) (Figure 2). Concurrent lung involvement with EPTB was observed in 17.8% of cases. Regarding treatment outcome, rates of success, default, and failure were 86.2%, 6.7%, and 0.5%, respectively. The all-cause mortality rate was 2.2%. The median pre-visit symptom duration was 22 days. The median duration from the first visit to diagnosis and TB medication was 9 and 19 days, respectively. The median interval between the date of diagnosis and TB-drug initiation was 4 days.

Table 1. Baseline characteristics of patients with extrapulmonary tuberculosis

Variables	Total n (%) (n=594)	Early diagnosis, n (%) (n=123)	Delayed diagnosis, n (%) (n=471)	P value
Age, years (median, range)	58 (16-93)	59 (19-93)	58 (16-93)	0.152
Gender, female	305 (51.3)	51 (41.5)	254 (53.9)	0.014
History of previous TB	52 (8.8)	6 (4.9)	46 (9.8)	0.088
Route of first visit				
Transferred	326 (54.9)	74 (60.2)	252 (53.5)	0.186
Outpatient clinic	433 (72.9)	49 (39.8)	384 (81.5)	<0.001
Emergency room	161 (27.1)	74 (60.2)	87 (18.5)	<0.001
Comorbidity				
None	354 (59.6)	59 (48.0)	295 (62.6)	0.003
Hypertension	148 (24.9)	43 (35.0)	105 (22.3)	0.004
Diabetes mellitus	82 (13.8)	20 (16.3)	62 (13.2)	0.375
Chronic liver disease	25 (4.2)	5 (4.1)	20 (4.2)	0.929
Cerebrovascular disease	18 (3.0)	7 (5.7)	11 (2.3)	0.072
Chronic kidney disease	30 (5.1)	6 (4.9)	24 (5.1)	0.922
Solid malignancy	33 (5.6)	6 (4.9)	27 (5.7)	0.713
Hematologic malignancy	7 (1.2)	1 (0.8)	6 (1.3)	1.000
Other immunosuppressive therapy	16 (2.7)	8 (6.5)	8 (1.7)	0.008
HIV-infected	5 (0.8)	3 (2.4)	2 (0.4)	0.063
Symptoms				
None	113 (19.0)	9 (7.3)	104 (22.1)	<0.001
Localized	461 (77.6)	109 (88.6)	352 (74.7)	0.001
Systemic	178 (30.0)	72 (58.5)	106 (22.5)	<0.001
Location of EPTB				
Lymph node	168 (28.3)	12 (9.8)	156 (33.1)	<0.001
Abdominal	109 (18.4)	5 (4.1)	104 (22.1)	<0.001
Disseminated	86 (14.5)	23 (18.7)	63 (13.4)	0.135
Musculo-skeletal	56 (9.4)	9 (7.3)	47 (10.0)	0.368

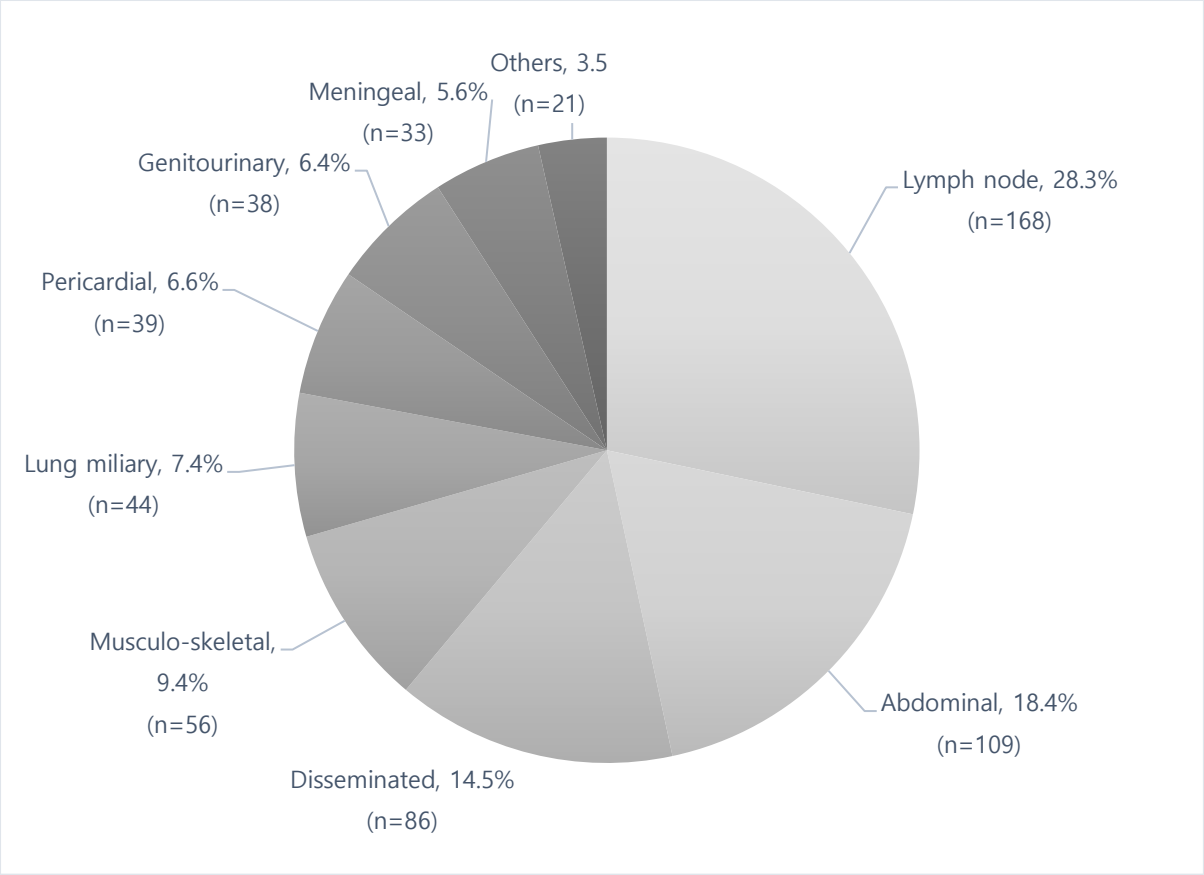
Lung miliary	44 (7.4)	30 (24.4)	14 (3.0)	<0001
Pericardial	39 (6.6)	18 (14.6)	21 (4.5)	<0.001
Genitourinary	38 (6.4)	3 (2.4)	35 (7.4)	0.044
Meningeal	33 (5.6)	22 (17.9)	11 (2.3)	<0.001
Others	21 (3.5)	1 (0.8)	20 (4.2)	0.095
Concurrent lung involvement[1]	106 (17.8)	49 (39.8)	57 (12.1)	<0.001
Expertise of department in charge				
Infection	69 (11.6)	24 (19.5)	45 (9.6)	0.002
Pulmonology	59 (9.9)	25 (20.3)	34 (7.2)	<0.001
Gastroenterology	122 (20.5)	8 (6.5)	114 (24.2)	<0.001
Other internal medicine	111 (18.7)	47 (38.2)	64 (13.6)	<0.001
Surgical department	233 (39.2)	19 (15.4)	214 (45.4)	<0.001
Final diagnosis				
Definite	235 (39.6)	53 (43.1)	182 (38.6)	0.369
Probable	219 (36.9)	50 (40.7)	169 (35.9)	0.329
Possible	140 (23.6)	20 (16.3)	120 (25.5)	0.032
Treatment outcome				
Success	512 (86.2)	105 (85.4)	407 (86.4)	0.765
Failure	3 (0.5)	0 (0.0)	3 (0.6)	1.000
Death	13 (2.2)	4 (3.3)	9 (1.9)	0.321
Default	40 (6.7)	8 (6.5)	32 (6.8)	0.909
Transferred	26 (4.4)	6 (4.9)	20 (4.2)	0.760
Duration, days (median, IQR)				
Onset of illness to first visit	22 (7-61)	13 (4-31)	30 (7-67)	<0.001
Onset of illness to diagnosis[2]	38 (18.00-97.5)	14 (6-32)	49 (26-116)	<0.001
Onset of illness to TB Mx	48 (24.0-106.5)	16.5 (7.75-34.00)	61 (35-121)	<0.001
First visit to diagnosis[2]	9 (2-27)	1 (0-3)	15 (6-32)	<0.001
First visit to TB Mx	19 (9-37)	3 (1-5)	25 (15-45)	<0.001
Diagnosis to TB Mx[2]	4 (0-11.25)	1 (0-3)	7 (0-14)	<0.001

[1]44 cases of lung miliary TB were included.

[2]Diagnosis date was defined as the date of acquisition of the specimen leading to the final diagnosis, or date of TB medication initiation in case of possible TB.

TB = tuberculosis; HIV = human immunodeficiency virus; EPTB = extrapulmonary tuberculosis; IQR = interquartile range; Mx = medication

Figure 2. Locations of extrapulmonary tuberculosis



Diagnostic tests

Diagnostic testing leading to final EPTB diagnosis revealed various performance results (Table 2). Positivity according to specimen type in each involved EPTB site was expressed as a range, and detailed data are presented in Table 3 and 4. In body fluid, AFB smear had a positivity of 6.1% (0.0–17.6%), MTB culture 23.2% (7.5–66.7%) in solid medium, and MTB 29.3% (5.7–59.4%) in liquid medium. In local tissue, positivity was 17.5% (7.3–31.6%), 36.6% (0.0–54.5%), and 42.9% (0.0–61.0%), respectively. MTB identification in solid medium (22 days, 25.5 days) occurred later than in liquid medium (18.5 days, 20.5 days) in body fluid and local tissue.

Among the NAA tests, the Xpert performed best in both body fluid (53.3%, 8/15) and local tissue specimens (90.0%, 9/10). The conventional and real-time MTB-PCR showed a positive rate of 56.9% (29.8-70.2%) and 50.6% (12.0-83.3%) in local tissue specimen. The ADA assay showed a positive rate of 86.6% (82.1–93.8%) and histopathological findings 31.6% (7.7–44.4%) (Table 3 & 4). Among 106 patients with lung involvement, 42.9% (39/91) were positive on CXR and 90.1% (91/101) on chest CT. Drug-susceptibility tests were performed on 29.3% (174/594) of patients: 122 on extrapulmonary specimens, such as body fluid or local tissue, and 52 on respiratory specimens. Mono-resistant TB (isoniazid, rifampicin, quinolones, injection drugs) was 8.6%, polyresistant TB (isoniazid, pyrazinamide, quinolones, injection drugs) was 2.3%, and multi-drug resistant (MDR) TB which was resistant to both isoniazid and rifampin was 0.6%. In mono-resistant TB and poly-resistant TB, 11 cases were resistant to isoniazid, 6 cases to injection drugs, 4 cases to quinolone,

and 1 case to rifampicin. Moreover, there was no significant difference in resistance rates between the extrapulmonary and respiratory specimens.

Factors associated with delayed diagnosis and treatment

Among the 594 patients, 123 were assigned to the early-diagnosis (group-1) and 471 to the delayed-diagnosis (group-2) groups. Univariable analysis showed that delayed diagnosis was significantly associated with female sex (P=0.014); first visit route via outpatient clinic (P<0.001); asymptomatic presentation (P<0.001); EPTB location of the LN, abdominal, and genitourinary system (P=0.044 for genitourinary system, P<0.001 for the rest); departments of gastroenterology and surgery (both P<0.001); and lower positive rates on CXR (P<0.001) (Table 1 & 2). Early diagnosis was significantly associated with first visit route via ER (P<0.001); localized and systemic symptoms (both P<0.001); hypertension (P=0.004); other immunosuppressive therapy (P=0.008); lung miliary, pericardial, and meningeal TB (all P<0.001); concurrent EPTB with lung involvement (P<0.001); and departments of infection, pulmonology, and other internal medicine (P=0.002 for infection, P<0.001 for the rest). Delayed diagnosis and treatment of EPTB were also related to longer pre-visit symptom duration (P<0.001) and delayed sample acquisition (both P<0.001). Positivity of diagnostic tests showed no significant difference of performance between early and delayed groups.

Multivariable analysis showed that diagnosis was delayed in the outpatient clinic visits (aOR 2.323, 95%CI 1.320–4.087) compared with that in ER visits, diagnosis in department of gastroenterology (aOR 3.360, 95%CI 1.070–10.553) or surgery (aOR 3.113, 95%CI 1.385–

6.997) based on infection (Table 5). Diagnosis was advanced when other immunosuppressive therapies (aOR 0.269, 95%CI 0.077–0.943) and disseminated TB (aOR 0.306, 95%CI 0.131–0.714), lung miliary TB (aOR 0.101, 95%CI 0.038–0.272), pericardial TB (aOR 0.135, 95%CI 0.042–0.438), and meningeal TB (aOR 0.066, 95%CI 0.020–0.224) based on LN TB were present.

Outpatient-clinic visits showed similar trends in group-2 and ER in group-1 (Table 6). Asymptomatic patients tended to visit the outpatient clinic (P<0.001). On the other hand, patients with symptoms tended to visit the ER, especially when systemic symptoms (P<0.001). Treatment outcomes were more successful for outpatient-clinic visitors, and failure or death was more frequent in the ER group (P=0.020 for failure, P<0.001 for the rest). Pre-visit symptom duration and time taken to acquire samples were longer in patients visiting the outpatient clinic (P=0.095 for local tissue, P<0.001 for the rest). The times to sample acquisition and anti-TB medication showed significantly positive correlation (rho=0.679, P<0.001 for body fluid; rho=0.682, P<0.001 for local tissue).

Table 2. Diagnostic tests of extrapulmonary tuberculosis

Variables[1]	Total n (%) (n=594)	Early diagnosis, n (%) (n=123)	Delayed diagnosis, n (%) (n=471)	P value
Body fluid	176 (29.6)	67 (54.5)	109 (23.1)	<0.001
AFB smear	10/164 (6.1)	3/64 (4.7)	7/100 (7.0)	0.742
MTB culture, solid	38/164 (23.2)	11/64 (17.2)	27/100 (27.0)	0.146
MTB culture, liquid	44/150 (29.3)	14/59 (23.7)	30/91 (33.0)	0.225
Conventional MTB-PCR	1/18 (5.6)	1/10 (10.0)	0/8 (0.0)	1.000
Real-time MTB-PCR	23/119 (19.3)	8/46 (17.4)	15/73 (20.5)	0.671
Xpert® MTB/RIF assay[2]	8/15 (53.3)	1/3 (33.3)	7/12 (58.3)	0.569
ADA assay	103/119 (86.6)	52/58 (89.7)	51/61 (83.6)	0.334
Duration, days (median, IQR)				
: until sample acquisition	4 (1-13.75)	1 (0-2)	8 (2-29)	<0.001
: until MTB in solid culture	22 (19-36)	21 (18-36)	22 (20-36)	0.546
: until MTB in liquid culture	18.5 (14.25-26)	18.5 (13-29)	19 (14.75-24)	0.850
Local tissue	428 (72.1)	38 (30.9)	390 (82.8)	<0.001
AFB smear	48/275 (17.5)	5/24 (20.8)	43/251 (17.1)	0.583
MTB culture, solid	71/194 (36.6)	8/20 (40.0)	63/174 (36.2)	0.739
MTB culture, liquid	78/182 (42.9)	7/18 (38.9)	71/164 (43.3)	0.720
Conventional MTB-PCR	124/218 (56.9)	12/17 (70.6)	112/201 (55.7)	0.235
Real-time MTB-PCR	79/156 (50.6)	7/17 (41.2)	72/139 (51.8)	0.408
Xpert MTB/RIF assay[2]	9/10 (90.0)	2/2 (100)	7/8 (87.5)	1.000
Histopathologic findings	131/415 (31.6)	7/36 (19.4)	124/379 (32.7)	0.102
Duration, days (median, IQR)				
: until sample acquisition	10 (3-24)	2 (1-4)	11 (4-26)	<0.001
: until MTB in solid culture	25.5 (20-34)	27 (21-38)	25 (19-34)	0.487
: until MTB in liquid culture	20.5 (17-24)	21 (18-27)	20 (17-24)	0.545
Radiologic tests				
Chest x-ray	36/492 (7.3)	25/109 (22.9)	11/383 (2.9)	<0.001
CT scan	262/478 (54.8)	68/110 (61.8)	194/368 (52.7)	0.092

MRI	62/113 (54.9)	26/40 (65.0)	36/73 (49.3)	0.109
PET-CT scan	44/55 (80.0)	2/4 (50.0)	42/51 (82.4)	0.175
Drug susceptibility[3]				
Mono-resistant	15/174 (8.6)	3/48 (6.3)	12/126 (9.5)	0.763
Polyresistant	4/174 (2.3)	2/48 (4.2)	2/126 (1.6)	0.305
Multi-drug resistant	1/174 (0.6)	1/48 (2.1)	0/126 (0.0)	0.276

[1]All fraction values are the proportion of positives among the cases where each test was done.

[2]It was analyzed including only the data of the four institutions performed Xpert® MTB/RIF assay for diagnosis of extrapulmonary tuberculosis.

[3]It was performed using respiratory, body fluid, and local tissue specimen

AFB = acid-fast bacilli; MTB = *Mycobacterium tuberculosis*; PCR = polymerase chain reaction; RFP = rifampin; ADA = adenosine deaminase; IQR = interquartile range; CT = computed tomography; MRI = magnetic resonance imaging; PET-CT = positron emission tomography-computed tomography.

Table 3. Diagnostic tests of body fluid in extrapulmonary tuberculosis according to the sample type

Variables[1]	pleural effusion (n=7)	Ascites (n=33)	CSF (n=41)	Urine (n=34)	Pericardial effusion (n=40)	Joint fluid (n=9)	Others (n=12)
AFB smear, fraction (%)	0/7 (0.0)	1/30 (3.3)	1/40 (2.5)	6/34 (17.6)	0/40 (0.0)	1/6 (16.7)	1/7 (14.3)
MTB culture, solid, fraction (%)	1/7 (14.3)	4/30 (13.3)	5/40 (12.5)	18/34 (52.9)	3/40 (7.5)	4/6 (66.7)	3/7 (42.9)
MTB culture, liquid, fraction (%)	2/7 (28.6)	6/25 (24.0)	8/38 (21.1)	19/32 (59.4)	2/35 (5.7)	3/6 (50.0)	4/7 (57.1)
conventional MTB-PCR, fraction (%)	0/1 (0.0)	0/3 (0.0)	0/5 (0.0)	-	0/8 (0.0)	-	1/1 (100)
real-time MTB-PCR, fraction (%)	0/4 (0.0)	0/18 (0.0)	4/29 (13.8)	9/25 (36.0)	0/27 (0.0)	5/8 (62.5)	5/8 (62.5)
Xpert® MTB/RIF assay[2], fraction (%)	-	2/6 (33.3)	2/3 (66.7)	3/4 (75.0)	-	1/1 (100)	0/1 (0.0)
ADA assay, fraction (%)	6/7 (85.7)	30/32 (93.8)	35/41 (85.4)	-	32/39 (82.1)	-	-
Duration, days (median)							
: until sample acquisition	4	3	1	20	2.5	2	7
: until MTB in solid culture	15[3]	28.5	19	22	27[3]	35.5	20[3]
: until MTB in liquid culture	23.5[3]	30.5	19	15	19.5[3]	16[3]	28

[1]All fraction values are the proportion of positives among the cases where each test was done.

[2]It was analyzed including only the data of the four institutions performed Xpert® MTB/RIF assay for diagnosis of extrapulmonary tuberculosis.

[3]It was expressed as the mean, because the corresponding cases are less than four

CSF = cerebrospinal fluid; AFB = acid-fast bacilli; MTB = *Mycobacterium tuberculosis*; PCR = polymerase chain reaction; RFP = rifampin; ADA = adenosine deaminase; IQR = interquartile range

Table 4. Diagnostic tests of local tissue in extrapulmonary tuberculosis according to the sample type

Variables[1]	Lymph node (n=194)	Bone/joint (n=58)	Gastro-intestine (n=91)	Peritoneum (n=24)	Genitourinary system (n=27)	Others (n=34)
AFB smear, fraction (%)	23/125 (18.4)	9/49 (18.4)	4/55 (7.3)	4/15 (26.7)	2/12 (16.7)	6/19 (31.6)
MTB culture, solid, fraction (%)	28/89 (31.5)	24/44 (54.5)	12/41 (29.3)	0/3 (0.0)	2/4 (50.0)	5/13 (38.5)
MTB culture, liquid, fraction (%)	33/79 (41.8)	25/41 (61.0)	14/42 (33.3)	0/3 (0.0)	1/4 (25.0)	5/13 (38.5)
conventional MTB-PCR, fraction (%)	66/94 (70.2)	21/32 (65.6)	14/47 (29.8)	7/14 (50.0)	8/15 (53.3)	8/16 (50.0)
real-time MTB-PCR, fraction (%)	50/79 (63.3)	15/30 (50.0)	3/25 (12.0)	4/5 (80.0)	5/6 (83.3)	2/11 (18.2)
Xpert® MTB/RIF assay[2], fraction (%)	6/6 (100)	3/3 (100)	-	-	-	0/1 (0.0)
Histopathologic findings, fraction (%)	82/186 (44.1)	18/55 (32.7)	7/91 (7.7)	7/24 (29.2)	12/27 (44.4)	5/32 (15.6)
Duration, days (median)						
: until sample acquisition	8	10.5	8	11	17	12
: until MTB in solid culture	29	21.5	23	-	31[3]	21
: until MTB in liquid culture	21	18	23	-	21[3]	17

[1]All fraction values are the proportion of positives among the cases where each test was done.

[2]It was analyzed including only the data of the four institutions performed Xpert® MTB/RIF assay for diagnosis of extrapulmonary tuberculosis.

[3]It was expressed as the mean, because the corresponding cases are less than four.

AFB = acid-fast bacilli; MTB = *Mycobacterium tuberculosis*; PCR = polymerase chain reaction; RFP = rifampin; IQR = interquartile range

Table 5. Factors associated with delayed diagnosis and treatment of extrapulmonary tuberculosis by multivariable logistic regression analysis

Variables	Adjusted odds ratio (95% confidence interval)	P value
Other immunosuppressive therapy	0.269 (0.077 – 0.943)	0.040
Route of first visit		
Emergency room	Reference	
Outpatient clinic	2.323 (1.320 – 4.087)	0.003
Location of EPTB		
Lymph node	Reference	
Abdominal	1.375 (0.365 - 5.177)	0.638
Disseminated	0.306 (0.131 - 0.714)	0.006
Musculo-skeletal	0.419 (0.158 - 1.115)	0.081
Lung miliary	0.101 (0.038 - 0.272)	<0.001
Pericardial	0.135 (0.042 - 0.438)	0.001
Genitourinary	0.658 (0.168 - 2.577)	0.548
Meningeal	0.066 (0.020 - 0.224)	<0.001
Others	1.747 (0.199 – 15.301)	0.615
Expertise of department in charge		
Infection	Reference	
Pulmonology	0.922 (0.383 - 2.216)	0.855
Gastroenterology	3.360 (1.070 - 10.553)	0.038
Other internal medicine	2.261 (0.883 - 5.791)	0.089
Surgical departments	3.113 (1.385 – 6.997)	0.006

EPTB = extrapulmonary tuberculosis

Table 6. Characteristics of patients with extrapulmonary tuberculosis by the route of first visit, emergency room versus outpatient clinic

Variables	Emergency room, n (%) (n=161)	Outpatient clinic, n (%) (n=433)	P value
Symptoms			
None	6 (3.7)	107 (24.7)	<0.001
Localized	146 (90.7)	315 (72.7)	<0.001
Systemic	99 (61.5)	79 (18.2)	<0.001
Location of EPTB			
Lymph node	7 (4.3)	161 (37.2)	<0.001
Abdominal	22 (13.7)	87 (20.1)	0.072
Disseminated	26 (16.1)	60 (13.9)	0.480
Musculo-skeletal	16 (9.9)	40 (9.2)	0.795
Lung miliary	29 (18.0)	15 (3.5)	<0.001
Pericardial	26 (16.1)	13 (3.0)	<0.001
Genitourinary	4 (2.5)	34 (7.9)	0.017
Meningeal	30 (18.6)	3 (0.7)	<0.001
Others	1 (0.6)	20 (4.6)	0.019
Expertise of department in charge			
Infection	24 (14.9)	45 (10.4)	0.127
Pulmonology	19 (11.8)	40 (9.2)	0.353
Gastroenterology	21 (13.0)	101 (23.3)	0.006
Other internal medicine	69 (42.9)	42 (9.7)	<0.001
Surgical departments	28 (17.4)	205 (47.3)	<0.001
Treatment outcome			
Success	124 (77.0)	388 (89.6)	<0.001
Failure	3 (1.9)	0 (0.0)	0.020
Death	10 (6.2)	3 (0.7)	<0.001
Default	14 (8.7)	26 (6.0)	0.245
Transferred	10 (6.2)	16 (3.7)	0.183
Duration, days (median, IQR)			

First visit to body fluid acquisition	1 (0-5)	11.5 (2.75-32.50)	<0.001
First visit to local tissue acquisition	8 (2.25-14.75)	10.5 (3.00-25.75)	0.095
Onset of illness to first visit	10 (3-30)	31 (10.00-91.25)	<0.001
Onset of illness to diagnosis[1]	21 (12-47)	54 (27.00-122.25)	<0.001
Onset of illness to TB Mx	27 (12-47)	65.5 (34.00-127.25)	<0.001
First visit to diagnosis[1]	3 (1-9)	14 (4-32)	<0.001
First visit to TB Mx	8 (3-19)	24 (14-44)	<0.001
Diagnosis to TB Mx[1]	2 (0-7)	6 (0-13)	0.012

[1]Diagnosis date was defined as the date of acquisition of the specimen leading to the final diagnosis, or date of TB medication initiation in case of possible TB.

EPTB = extrapulmonary tuberculosis, IQR = interquartile range; Mx = medication

Discussion

The predominant EPTB location was LN or pleural TB in previous studies, and LN TB was the predominant form in this study.[2, 3] In South Korea's annual TB report, the invasion sites of tuberculosis were marked as duplicate and EPTB with lung involvement was classified as PTB. Distribution of EPTB sites was similar after adjustment of the study data to conform to national data (study data vs. national data: 36.4% vs. 33.9% in LN TB, 24.3% vs. 27.2% in abdominal TB, and 11.7% vs. 10.8% in skeletal TB).[5] Chest CT was more than twice as positive as CXR in detecting lung involvement in this study. Lung involvement findings were important TB clues; hence, chest CT is recommended in patients suspected to have TB with negative CXR. The MDR-TB proportion of EPTB was 0.6%, which was lower than 0.9–17.2% in previous studies.[2, 3, 6] It was lower than the MDR-TB rate of PTB in domestic studies (4.5% or 8.7%).[26, 27] Isoniazid resistance rate, the most common drug resistance as per previous studies, was low as 6.9% (12/174) in this study, which collected data within the last 3 years.[27, 28] Therefore, it is justified to continue including isoniazid in the initial EPTB-treatment regimen in South Korea.

Several factors significantly influenced timely EPTB diagnosis and treatment. Patients receiving other immunosuppressive therapies were associated with early diagnosis, possibly due to the presence of systemic symptoms (62.5%, 10/16) in patients undergoing other immunosuppressive therapy, which was much higher than that in all patients (30%, 178/594). Diagnosis and treatment timing for each EPTB site was related to the presence of symptoms and first visit route. Differences in the diagnosis department were due to

the relationship between the main department and EPTB location. 31.8% (14/44) and 43.2% (19/44) of lung miliary TB were diagnosed at division of infection and pulmonology, respectively. 94.9% (37/39) of pericardial TB and 87.9% (29/33) of meningeal TB were diagnosed at other internal medicine. 92.1% (35/38) of genitourinary TB, 76.8% (43/56) of musculo-skeletal TB, and 63.7% (107/168) of LN TB were diagnosed at surgical department, and 84.4% (92/109) of abdominal TB were diagnosed at division of gastroenterology. Since the surgical and gastroenterology departments are major factors in delayed diagnosis, a system is needed to strengthen medical decisions and accelerate diagnostic procedures, such as early consultation with TB experts or increasing the speed of work-up through hospitalization for outpatients.

58.5% (48/82) of intestinal TB, mainly diagnosed at division of gastroenterology, was found by chance in colonoscopy for health screening without clinical manifestation and 60.1% (50/82) was clinically diagnosed without microbiologic, histopathologic, molecule-genetic evidence. It was reported 28.8% to 48.2% of intestinal TB was diagnosed by therapeutic anti-TB trial for distinguishing it from Crohn's disease.[29, 30] Therefore, when diagnosing intestinal TB in gastroenterology, the actively applying therapeutic anti-TB trial might advance the diagnosis.

Visiting the outpatient clinic was an important factor with high OR in multivariable analysis, reflecting most characteristics of delayed diagnosis. Pre-visit symptom duration was longer and asymptomatic case frequency was higher in outpatient clinic visits, possibly due to absent symptoms or insidious onset, causing patients to visit the outpatient clinic

of the medical center later. Sample acquisition was delayed, especially for body fluid specimens of patients visiting the outpatient clinic, possibly due to long follow-up intervals in outpatient clinic-based diagnosis. The higher mortality rate in patients visiting the ER was considered because EPTB sites with high mortality rates, such as lung miliary or meningeal TB, were more likely to visit the ER.[4, 12] Unlike other factors related to delayed EPTB diagnosis and treatment, such as comorbidity or EPTB location, clinical practice by departments and delayed sample acquisition by the visit route were correctable factors. Hence, a team-approach system, especially in non TB-specialized departments, and prompt specimen acquisition at outpatient clinics, even in patients with no or mild symptoms, would accelerate EPTB diagnosis and treatment.

Contrary to the expectation that rapid tests such as NAA tests could advance the time of diagnosis and treatment of EPTB, there was no difference in positive rates between early/delayed groups. This might be because Xpert was not performed widely in diagnosis of EPTB, so it would be helpful if there was a version that could easily apply Xpert to tissue specimens of EPTB. The result that positivity of the diagnostic tests does not differ for group means that there was no significant difference in the microbiologic characteristics of TB itself, between groups. Therefore, the difference in timing of diagnosis and treatment was determined by the presence of overt symptomatic manifestations, the pattern of patient visits to the medical center and the expertise of the clinician on TB.

This study had a few limitations. First, the study was retrospective and had a relatively

small sample size. However, I attempted to minimize retrospective study errors by collecting objective data based on clear definitions. Additionally, I attempted to reduce selection bias through a multiple-center approach and limited the research period to 2 years to reduce the effects of diagnostic technology advancements. Second, I arbitrarily set 7 days as the basis for group categorization. It was considered as a reasonable period because the median duration from the first visit to TB diagnosis was 9 days on analyzing the entire data, and it usually took a week to obtain histopathological results, the most time-consuming laboratory-test results. Third, treatment outcome showed no significant differences between groups. It might be because complication rate, social burden from patients with sequalae, and disease cost were not included in the treatment outcome investigated in this study.

In conclusion, EPTB diagnosis and treatment timing was determined by symptom manifestations, promptness of sample acquisition, route of patient visits, and clinicians' TB expertise. Therefore, it is necessary to establish a clinical system that promptly acquires diagnostic samples, and reinforcing consultation and collaboration with TB specialists to reduce complications and socioeconomic burden through earlier diagnosis of EPTB.

Acknowledgments

There was no conflict of interest.

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국문 초록

배경

전체 결핵감염 중 폐외결핵이 차지하는 비율은 증가하고 있다. 폐외결핵은 결핵 관련 사망, 합병증, 후유증, 그리고 장애의 증가에 상당히 기여한다. 폐외결핵은 폐결핵보다 진단하기 어렵다. 폐외결핵 진단 및 치료의 지연은 합병증과 평생 지속될 후유증 및 사회경제적 부담의 증가를 야기할 수 있다. 교정 가능한 요인을 교정하여 진단 시기를 앞당기기 위해 폐외결핵의 진단을 지연시키는 위험인자를 밝히고자 한다.

방법

2017년 1월부터 2018년 12월 사이에 국내 11개 종합병원에서 새롭게 진단된 폐외결핵 환자들이 후향적으로 연구에 포함되었다. 폐외결핵의 최근 역학과 환자들의 기본적인 특성을 기술하였다. 연구대상자는 의료기관 첫 방문부터 항결핵제 투여까지의 기간을 기준으로 조기진단군 (7일 이하) 과 지연진단군 (7일 초과)으로 나뉘었다. 폐외결핵의 진단 및 치료 지연의 위험인자를 찾기 위해 그룹간 단변수, 다변수 분석을 시행하였다.

결과

최종적으로 594명의 환자가 연구에 포함되었다. 림프절 결핵 (28.3%) 이 가장 흔하였고, 복부 결핵 (18.4%), 파종성 결핵 (14.5%) 순으로 뒤를 이었다. 폐침범이 동반된 경우는 17.8% 였다. 치료의 성공과 실패는 각각 86.2%, 0.5% 였고, 사망률은 2.2% 였다. 의료기관 방문 전 증상의 지속기간은 중위수 22일이었다. 의료기관 첫 방문부터 진단적 검사의 시행까지는 중위수 9일이 걸렸고, 항결핵제의 투여까지는 중위수 19일이 소요되었다. 진

단적 검사의 양성률은 두 그룹간 유의미한 차이를 보이지 않았다. 면역억제제를 복용중인 환자 (교차비: 0.269, 95% 신뢰구간: 0.077–0.943)에서 증상의 급성 발현, 파종성 결핵 (교차비: 0.306, 95% 신뢰구간: 0.131-0.714), 결핵심장막염 (교차비: 0.135, 95% 신뢰구간: 0.042–0.438), 결핵수막염 (교차비: 0.066, 95% 신뢰구간: 0.020–0.224)은 조기진단과 관련이 있었다. 지연진단은 첫 방문 시 외래로 방문한 경우 (교차비: 2.323, 95% 신뢰구간: 1.320–4.087), 검체 채취의 지연, 감염내과나 호흡기내과와 같은 결핵 전문 진료과에서 진단받지 않은 경우(위장관내과의 교차비: 3.360, 95% 신뢰구간: 1.070–10.553, 외과계 진료과의 교차비: 3.113, 95% 신뢰구간: 1.385–6.997)와 관련되어 있었다.

결론

폐외결핵의 진단 및 치료의 지연은 결핵균의 미생물학적 특성의 차이가 아닌, 임상 증상의 급성발현, 검체 채취의 신속성, 환자의 의료기관 방문 경로와 결핵에 대한 진료과의 전문성과 관련되어 있었다. 그러므로 폐외결핵을 더 신속하게 진단하여 합병증 및 사회경제적 부담을 줄이기 위해서는, 진단적 검체를 신속하게 얻을 수 있는 진료시스템 및 결핵 전문가와의 협진을 강화하는 것이 필요하다.

주요어 : 폐외결핵, 지연진단, 위험인자, 임상적 특성

학 번 : 2019-20529