



Clinical significance of Glasgow Prognostic Score in patients with tuberculous pleurisy

Hye Seon Kang¹, Hwa Young Lee¹, Jung Im Jung², Ju Sang Kim¹, Yong Hyun Kim¹, Seung Joon Kim¹, Seok Chan Kim¹, Soon Seog Kwon¹, Young Kyoon Kim¹, Ji Young Kang¹

¹Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, College of Medicine, ²Department of Radiology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Contributions: (I) Conception and design: HS Kang, JY Kang; (II) Administrative support: JI Jung, JS Kim, YH Kim; (III) Provision of study materials or patients: SJ Kim, SC Kim, SS Kwon, YK Kim; (IV) Collection and assembly of data: HS Kang, HY Lee, JY Kang; (V) Data analysis and interpretation: JS Kim, YH Kim, JY Kang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ji Young Kang, MD, PhD. Division of Pulmonology, Allergy and Critical Care Medicine, Department of Internal medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-Daero, Seocho-Gu, Seoul 06591, Republic of Korea. Email: rkdwldud@catholic.ac.kr.

Background: The Glasgow Prognostic Score (GPS) reflects the host systemic inflammatory response and is a validated, independent prognostic factor for various malignancies. We investigated the clinical significance of the GPS in patients with tuberculosis (TB) pleurisy, focusing on treatment outcomes including paradoxical response (PR).

Methods: This was a retrospective study performed between January 2010 and December 2015 in two referral and university hospitals in South Korea, with intermediate incidences of TB. In all, 462 patients with TB pleurisy were registered in the study. The patients were classified into three groups based on GPS score, as follows: (I) GPS of 2, elevated CRP level (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL); (II) GPS of 1, elevated CRP level or hypoalbuminemia; and (III) GPS of 0, neither elevated CRP level nor hypoalbuminemia.

Results: A total of 367 patients with TB pleurisy were finally included. PR occurred in 102 (27.8%) patients after a mean of 75 days following initiation of anti-TB treatment. The proportion of PR occurrence was significantly lower in the GPS 2 group ($P=0.007$). Successful treatment outcomes including cure and completion were also significantly lower in the GPS 2 group ($P=0.001$), while all-cause mortality and TB-specific mortality were higher in the GPS 2 group ($P=0.001$ and <0.001 , respectively). Old age over than 65 years old was an independent predicting factor for high mortality and lower PR occurrence. However, the TB relapse rate was not different among the three GPS groups.

Conclusions: Higher GPS value and elderly age were identified as prognostic factors for poor outcomes in TB pleurisy and as predicting factors for lower PR occurrence. More prospective studies are needed to clarify the utility of GPS in patients with TB pleurisy.

Keywords: Albumin; C-reactive protein (CRP); age; tuberculous pleurisy

Submitted Apr 25, 2018. Accepted for publication Sep 27, 2018.

doi: 10.21037/jtd.2018.10.02

View this article at: <http://dx.doi.org/10.21037/jtd.2018.10.02>

Introduction

According to the World Health Organization, an estimated 10.4 million new cases of tuberculosis (TB) developed and 1.3 million people died from the disease worldwide in 2016 (1).

Among the types of TB, extrapulmonary TB is difficult to diagnose early due to variable manifestations, and it remains a challenging task to collect the necessary samples in patients. TB pleurisy is the second most common extra-

pulmonary infection globally and the most common one in South Korea (2,3). In South Korea, 2,237 new tuberculous pleurisy cases were reported in 2017, which accounted for 7.9% of the 28,161 new TB cases and 38.3% of the 5,847 extrapulmonary TB cases. The incidence rate of total TB cases was 70.4 per 100,000 populations, a decreasing pattern over the 7 year. The multi-drug resistant TB and extensively-drug resistant TB were reported as 689 and 55 cases, respectively with a corresponding prevalence rate of 2.0% and 0.2% in 2017 (4).

Identifying the poor prognostic factors in TB is important, because personalized targeting of care in high-risk groups could improve clinical outcomes. In pulmonary TB (PTB), poor prognostic factors include co-infection with human immunodeficiency virus (HIV), sputum non-conversion at the end of the second month, lower body mass index (BMI), and elderly age (5-10). However, with regard to TB pleurisy, there have been few reports published to date to verify poor prognostic factors such as delayed treatment, pulmonary involvement, or presence of *Mycobacterium TB* (*M. TB*) in the effusion (11-13).

With exposure to mycobacterial antigens, the immune system is activated, and the resultant inflammatory process cascades into TB pleurisy (14,15). C-reactive protein (CRP) is an acute-phase protein and indicates systemic inflammatory activity in PTB (16-19). CRP is associated with *M. TB* loads and host immune response and is decreased by anti-TB treatment (20-22). Also, serum albumin, a negative acute-phase protein, which is used as a marker of inflammation and reflects body mass or malnutrition, is associated with poor outcomes in smear-positive PTB patients (23,24).

The Glasgow Prognostic Score (GPS) is an inflammation-based prognostic scoring system that considers albumin and CRP levels. Recent studies have shown that the GPS represents prognostic factors reliably in patients with various malignancies and acute exacerbation of idiopathic pulmonary fibrosis (25-29). However, to our knowledge, the prognostic value of the GPS in TB pleurisy has never been investigated.

Paradoxical response (PR) is a common phenomenon not only in HIV-positive patients, but also in HIV-negative subjects during TB treatment (30,31). However, despite the good prognosis of PR, physicians may remain challenged because there are some similar situations that can present and confound evaluation, such as combined infection or poor disease control due to noncompliance or drug resistance. Thus, it may be helpful in practice to identify

vulnerable patients in whom PR occurs frequently.

In the present study, we evaluated the clinical significance of GPS in patients with TB pleurisy, focusing particularly on treatment outcomes including PR.

Methods

This was a retrospective study conducted in Seoul St. Mary's Hospital and Bucheon St. Mary's Hospital, which are referral and university hospitals in South Korea, identified as having intermediate incidences of TB between January 2010 and December 2015. The study was approved by the institutional review boards of the participating centers (approval No. XC18RCDI0002). The requirement for informed patient consent was waived by the boards.

Patients

Patients who were older than 18 years and who had been diagnosed with TB pleurisy were included in our analysis. The serostatus of HIV was tested in all participants. A diagnosis of TB pleurisy was made based on microbiologic evidence of the existence of *M. TB* or positivity for *M. TB* polymerase chain reaction (PCR) in sputum, pleural fluid, or pleural biopsy specimens. Other supporting evidence in diagnosing the disease included the demonstration of TB granulomas with or without caseous necrosis in the pleural tissue or an elevated ADA level that exceeded 40 U/L with lymphocyte-predominant (>50% of white blood cells in the pleural fluid) exudate in the pleural fluid and clinical improvement after standard anti-TB therapy (14,32). Subjects who demonstrated pulmonary involvement were included, while those who presented with TB empyema with pus-like pleural fluid were excluded. Also, those who defaulted during follow-up were not included in the final analysis. The follow-up period ended on December 31, 2017.

Data

We extracted the following data from patient medical records: patient demographics; smoking and past TB history; comorbid diseases; subjective symptoms; laboratory data (pleural effusion analysis, albumin, and CRP levels in serum); microbiologic assays of TB; drug susceptibility test of *M. TB*; radiologic findings including the sites of pleural effusion and combined PTB; histologic examination in pleural tissue; occurrence of PR; and treatment outcomes.

Acid-fast bacilli (AFB) culture was performed using both

Ogawa solid media and mycobacteria growth indicator tube (MGIT) liquid media. Drug sensitivity test was performed using the absolute concentration method with the Ogawa media and BACTEC™ MGIT™ 960 system (Becton Dickinson Sparks, Glencoe, MD, USA) with liquid media. TB PCR was performed using the AdvanSure TB/non-tuberculous mycobacterium PCR (LG Life Sciences, Seoul, South Korea) or the Xpert *M. TB*/resistance to rifampin assay (Cepheid, Sunnyvale, CA, USA). PR was defined as a worsening of clinical or radiological findings at two weeks after the initiation of anti-TB treatment in the absence of evidence of disease relapse or the presence of another diagnosis (33). PR was evaluated by two clinicians and one radiologist. The treatment outcomes were categorized into two groups: (I) successful outcomes, such as if TB patients were cured or completed treatment; and (II) unsuccessful outcomes, such as if treatment resulted in treatment failure, default on follow-up, or death. Mortality was classified as TB-specific or non-TB-specific death. Relapse was defined as a TB patient who was declared cured or who had completed treatment as determined by a physician, but who was diagnosed with a recurrent episode of TB during the follow-up period. Following evaluation, the patients were classified into three groups based on GPS score, as follows: (I) GPS of 2, elevated CRP level (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL); (II) GPS of 1, elevated CRP level or hypoalbuminemia; and (III) GPS of 0, neither elevated CRP level nor hypoalbuminemia (34,35). The value of serum CRP concentration was measured within 1 week before anti-TB treatment. In our study, CRP was measured by different methods depending on the institutions because two institutions have registered patients. In one institution, high sensitivity CRP (hs-CRP) was measured, while in others, CRP was measured. Hs-CRP levels were measured using a latex immunoassay method with the commercial kits LT CRP-HS II (Wako Pure Chemical Industries, Ltd., Osaka, Japan). Serum CRP levels were measured using immunoturbidimetric assays (CRPL3, Roche, Diagnostics, Indianapolis, IN, USA). In the case of high-sensitivity CRP, upper range of normal value is 0.47 mg/dL, and that for CRP is 5 mg/L. In various clinical conditions, significant correlation was noted between hs-CRP and standard CRP assay after unit conversion (36-38).

Statistical analysis

Baseline demographics and clinical outcomes were compared among the participants according to GPS criteria. We used

Pearson's Chi-square test to compare discrete variables and Student's *t*-test or analysis of variance to compare continuous variables. Hazard ratios and corresponding 95% confidence intervals (CIs) were calculated for predictors that were significant in the multivariate analysis. A two-sided *P* value <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS for Windows software (ver. 20.0; IBM Corp., Armonk, NY, USA).

Results

Overall, 462 patients were diagnosed with TB pleurisy, of whom 95 met the exclusion criteria; specifically, these individuals defaulted on follow-up, were transferred to another medical center, or demonstrated a lack of measurements of albumin or CRP level. Thus, 367 patients were finally included in our analysis. The mean age of the included subjects was 40.5 years (range, 19–97 years), and 56.9% of them were male. Of these patients, 119 (32.4%), 198 (54.0%), and 50 (13.6%) patients were classified into the GPS 0, GPS 1, and GPS 2 groups, respectively. The total follow-up time was 20.6 person-months.

Baseline characteristics and comparisons between the groups are demonstrated in *Table 1*. Mean age and proportion of diabetes mellitus (DM) were higher in the GPS 2 group ($P<0.001$ and $P=0.043$, respectively). The proportions of male gender, smoking history, presence of underlying disease other than DM, history of TB, presenting symptoms, and effusion sites were not different among the three groups (*Table 1*).

The yields of microbiology and pleural biopsy in the diagnosis of TB pleurisy and laboratory findings according to GPS group are summarized in *Table 2*. Among the 367 patients with TB pleurisy, 132 (36.0%) showed culture positivity for *M. TB* in the effusion. In the 235 patients with negative effusion cultures, 70 had positive sputum cultures. The combined diagnostic yields including AFB culture, smear, and TB PCR were 39.8% and 38.4% for the effusion and sputum, respectively. A combination of the effusion and sputum microbiologic results showed a diagnostic sensitivity of 59.1%. The diagnostic yield was 44.4% (55/124) for histologic confirmation of pleural biopsies. However, these diagnostic results did not differ among the three GPS groups.

In analysis of pleural fluid, the proportion of lymphocytes in inflammatory cells was higher and that of eosinophil was lower in the GPS 2 group compared with the other groups ($P=0.024$ and 0.005 , respectively). The level of protein was

Table 1 Baseline characteristics of patients with TB pleurisy

Variables	Total (N=367)	GPS 0 (n=119)	GPS 1 (n=198)	GPS 2 (n=50)	P value
Age (year)	49.5±21.5	46.0±19.4	48.9±21.3	60.1±23.9	<0.001
Males	209 (56.9)	65 (54.6)	118 (59.6)	26 (52.0)	0.515
BMI	21.6±3.3	21.9±2.8	21.5±3.7	20.8±3.2	0.158
Smoking					
Current smoker	78 (21.3)	20 (16.8)	49 (24.7)	9 (18.0)	0.205
Ex-smoker	45 (12.3)	11 (9.2)	31 (15.7)	3 (6.0)	0.084
PYs	23.9±20.4	20.6±17.2	24.6±21.7	28.2±20.2	0.509
Underlying disease					
DM	29 (7.9)	4 (3.4)	18 (9.1)	7 (14.0)	0.043
COPD	4 (1.1)	2 (1.7)	2 (1.0)	0 (0.0)	0.623
Other malignancy	11 (3.0)	3 (2.5)	7 (3.5)	1 (2.0)	0.794
LC	4 (1.1)	1 (0.8)	3 (1.5)	0 (0.0)	0.621
Autoimmune disease	4 (1.1)	1 (0.8)	3 (1.5)	0 (0.0)	0.621
Post-transplantation	1 (0.3)	1 (0.8)	0 (0.0)	0 (0.0)	0.352
ESRD	3 (0.8)	1 (0.8)	2 (1.0)	0 (0.0)	0.777
History of TB	50 (13.6)	12 (10.1)	28 (14.1)	10 (20.0)	0.219
Symptoms					
Dyspnea	142 (38.7)	38 (31.9)	84 (42.4)	20 (40.0)	0.175
Chest pain	176 (48.0)	61 (51.3)	95 (48.0)	20 (40.0)	0.409
Cough	73 (19.9)	28 (23.5)	31 (15.7)	14 (28.0)	0.071
Fever	48 (13.1)	12 (10.1)	27 (13.6)	9 (18.0)	0.357
General weakness	7 (1.9)	2 (1.7)	5 (2.5)	0 (0.0)	0.494
Weight loss	11 (3.0)	4 (3.4)	5 (2.5)	2 (4.0)	0.827
Hemoptysis	4 (1.1)	3 (2.5)	1 (0.5)	0 (0.0)	0.179
Effusion site					0.427
Right	225 (61.3)	76 (63.9)	118 (59.6)	31 (62.0)	
Left	135 (36.8)	43 (36.1)	74 (37.4)	18 (36.0)	
Bilateral	7 (1.9)	0 (0.0)	6 (3.0)	1 (2.0)	
Accompanied PTB	141 (38.4)	43 (36.1)	81 (40.9)	17 (34)	0.505

Data are presented as n (%) or mean ± SD. GPS, Glasgow Prognostic Score; BMI, body mass index; PYs, pack years; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; LC, liver cirrhosis; ESRD, end stage renal disease; TB, tuberculosis; PTB, pulmonary tuberculosis.

also lower in the GPS 2 group than in the other groups ($P<0.001$). Additionally, in serum analysis, the proportion of polymorphonuclear cells among white blood cells was higher and that of lymphocytes was lower in the GPS 2

group ($P<0.001$ and <0.001 , respectively). In all three GPS groups, the percentage of lymphocytes in the pleural fluid had an inverse correlation with that in the serum, reflecting a recruitment of inflammatory cells to the TB infection site

Table 2 Laboratory findings at the time of diagnosis of TB pleurisy according to GPS

Diagnostic procedures	Total (N=367)	GPS 0 (n=119)	GPS 1 (n=198)	GPS 2 (n=50)	P value
Pathologic diagnosis	55/124 (44.4)	7/19 (36.8)	38/84 (45.2)	10/17 (58.8)	0.451
Positive effusion <i>M. TB</i> culture	132 (36.0)	47 (39.5)	70 (35.4)	15 (30.0)	0.467
Positive pleural AFB stain	1 (0.3)	0 (0.0)	1 (0.5)	0 (0.0)	0.651
Pleural TB PCR	34 (9.3)	4 (3.4)	26 (13.1)	4 (8.0)	0.014
Positive AFB smear/culture/TB PCR	146 (39.8)	50 (42.0)	79 (39.9)	17 (34.0)	0.597
Negative effusion <i>M. TB</i> culture	232 (63.2)	71 (59.7)	126 (63.6)	35 (70.0)	0.467
Positive sputum AFB culture	70	18/71 (25.4)	42/126 (33.3)	10/35 (28.6)	0.459
Sputum AFB culture	128 (34.9)	41 (34.5)	72 (36.4)	15 (30.0)	0.663
Sputum AFB stain	2 (0.5)	1 (0.8)	1 (0.5)	0 (0.0)	0.792
Sputum TB PCR	60 (16.3)	13 (10.9)	40 (20.2)	7 (14.0)	0.078
Positive AFB smear/culture/TB PCR	141 (38.4)	43 (36.1)	81 (40.9)	17 (34.0)	0.505
Combination of effusion and sputum AFB smear/culture/TB PCR	217 (59.1)	66 (55.5)	124 (62.6)	27 (54.0)	0.275
Pleural fluid analysis					
pH		7.5±0.3	7.7±0.5	7.5±0.4	<0.001
WBC (×10 ³)		3,304.9±2,963.1	3,188.7±4,156.2	2,561.6±3,056.4	0.47
Segment neutrophil (%)		10.4±12.1	12.7±18.6	9.4±17.1	0.32
Lymphocyte (%)		73.3±19.3	78.1±21.3	82.2±18.9	0.024
Eosinophil (%)		2.4±7.8	0.5±3.6	0.1±0.3	0.005
Protein		5.2±0.6	5.1±0.6	4.7±0.9	<0.001
Glucose		86.4±33.9	91.5±39.9	97.4±43.8	0.227
LDH		916.8±454.7	1,081.8±1,354.2	1,084.9±1,385.7	0.443
ADA		112.4±36.1	107.3±32.2	112.9±27.8	0.319
Serum analysis					
WBC (×10 ³)		6,498.8±1,684.1	6,765.4±2,040.1	7,277.0±1,843.1	0.053
Segment neutrophil (%)		64.0±8.8	67.2±9.1	70.0±10.3	<0.001
Lymphocyte (%)		22.1±7.5	18.7±7.5	15.9±7.1	<0.001

Data are presented as n (%) or mean ± SD. TB, tuberculosis; GPS, Glasgow Prognostic Score; *M. TB*, *Mycobacterium tuberculosis*; AFB, Acid-Fast Bacilli; PCR, polymerase chain reaction; pH, potential of hydrogen; WBC, white blood cells; LDH, lactate dehydrogenase; ADA, adenosine deaminase.

from the systemic circulation (Table 2).

PR occurred in 102 (27.8%) patients after a mean of 75 days following initiation of anti-TB treatment. The proportion of PR occurrence was significantly lower in the GPS 2 group (P=0.007). In the patients with PR, 27 (26.5%) demonstrated accompanying complications such as peripleural abscess formation, though surgical

intervention was required in only four patients. We used the peripleural abscess as empyema encircling the pleura. Drug susceptibility testing was performed on 178 of 213 (83.6%) cultures positive for *M. TB*, and the results of this testing were as follows: 163 demonstrated all-drugs sensitivity, 8 demonstrated resistance to isoniazid, 2 demonstrated resistance to rifampin, 1 demonstrated resistance to

Table 3 Comparison of treatment outcomes according to GPS

Treatment outcomes	GPS 0 (n=119)	GPS 1 (n=198)	GPS 2 (n=50)	P value
PR	44 (37.0)	51 (25.8)	7 (14.0)	0.007
Time of PR occurrence	69.3±50.6	80.2±65.4	73.4±52.4	0.665
Complication*	11 (9.2)	15 (7.6)	1 (2.0)	0.459
Time of complication occurrence (days)	170.5±76.0	163.2±35.7	60.0±0.0	0.191
Surgical intervention**	2 (1.7)	2 (1.0)	0 (0.0)	0.625
Treatment duration, days	225.6±87.3	237.0±99.3	219.1±94.4	0.38
Treatment outcomes				
Cure	4 (3.4)	2 (1.0)	0 (0.0)	0.172
Complete	115 (96.6)	188 (94.9)	43 (86.0)	0.021
Cure + complete	119 (100.0)	190 (96.0)	43 (86.0)	<0.001
Unfavorable				
Failure	0 (0.0)	1 (0.5)	0 (0.0)	0.652
Default	0 (0.0)	1 (0.5)	0 (0.0)	0.652
Loss of follow up	0 (0.0)	1 (0.5)	2 (4.0)	0.024
Death				
TB-related	0 (0.0)	1 (0.5)	4 (8.0)	<0.001
Not TB related	0 (0.0)	4 (2.0)	1 (2.0)	0.296
Relapse rate	0 (0.0)	5 (2.5)	2 (4.0)	0.143

Data are presented as n (%) or mean ± SD. *, complications are peripleural abscess or lung infiltrations; **, surgical intervention includes drainage or decortication. GPS, Glasgow Prognostic Score; PR, paradoxical response; TB, tuberculosis.

pyrazinamide, 3 demonstrated multi-drug-resistant TB, and 1 demonstrated pre-extensively drug-resistant TB. The proportions of drug-resistant TB were not different depending on GPS group. The mean treatment duration was 7.7 months. Out of the 367 patients, 352 (95.9%) showed successful treatment outcomes, 10 (2.7%) died during treatment, and 7 (1.9%) had TB recurrence during the follow-up period. Successful treatment outcome was significantly lower in the GPS 2 group ($P<0.001$), and all-cause mortality and TB-specific mortality were higher in the GPS 2 group ($P=0.001$ and <0.001 , respectively). However, the TB relapse rate was not different among the three groups (Table 3).

In univariate analysis, elderly age ($P=0.002$), DM ($P=0.019$), and higher GPS value ($P=0.008$) were negative predicting factors for PR occurrence. In the multivariate analysis, elderly age [odds ratio (OR): 0.469, 95% CI: 0.259–0.850; $P=0.013$] and GPS of 2 (OR: 0.345, 95% CI: 0.140–0.847; $P=0.020$) were independent negative

predicting factors for PR occurrence (Table 4). For all-cause mortality, elderly age ($P=0.003$) and GPS of 2 ($P=0.003$) were prognostic factors for poor clinical outcomes in univariate analysis. In multivariate analysis, elderly age (OR: 20.328, 95% CI: 2.507–164.833, $P=0.005$) and GPS of 2 (OR: 4.813, 95% CI: 1.272–18.207, $P=0.021$) were also independent prognostic factors for all-cause mortality in TB pleurisy (Table 5).

Discussion

In the present study, we compared the clinical characteristics and treatment outcomes of TB pleurisy with respect to GPS value. According to our findings, the proportions of patients in the GPS 0, GPS 1, and GPS 2 groups were 119 (32.4%), 198 (54.0%), and 50 (13.6%), respectively. Regarding the total study cohort, PR and death occurred in 102 (27.8%) cases and 10 (2.7%) cases, respectively, with patients with GPS 2 having significantly lower PR occurrence (14.0%) and

Table 4 Univariate and multivariate analysis of predicting factors for paradoxical response in patients with TB pleurisy

Factor	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Older age (>65 years)	0.398	0.223–0.711	0.002	0.469	0.259–0.850	0.013
DM	0.175	0.041–0.749	0.019	0.232	0.053–1.013	0.052
GPS						
0	1.000	–	–	–	–	–
1	0.600	0.367–0.979	0.041	0.669	0.406–1.104	0.116
2	0.277	0.115–0.670	0.004	0.345	0.140–0.847	0.020
Positive pleural <i>M. TB</i> culture	1.016	0.631–1.637	0.947	–	–	–

OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; GPS, Glasgow Prognostic Score; *M. TB*, *Mycobacterium tuberculosis*.

Table 5 Univariate and multivariate analysis of risk factors for all-cause mortality in patients with TB pleurisy

Factor	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Older age (>65 years)	24.469	3.059–195.698	0.003	20.328	2.507–164.833	0.005
DM	1.306	0.160–10.680	0.803	–	–	–
GPS						
0, 1	1.000	–	–	1.000	–	–
2	6.933	1.931–24.896	0.003	4.813	1.272–18.207	0.021
Positive <i>M. TB</i> pleural culture	1.419	0.374–5.378	0.607	–	–	–

OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; GPS, Glasgow Prognostic Score; *M. TB*, *Mycobacterium tuberculosis*.

higher mortality rates (10%) than those with GPSs of 0 or 1.

One possible explanation for the association between mortality and higher GPS value is that host systemic inflammation and mycobacterial control are strongly related in patients with TB pleurisy. In previous clinical studies, CRP level was found to be significantly decreased after initiation of anti-TB therapy (22). High CRP level is associated with mycobacterial load, and sustained elevated level of CRP is related to delayed culture conversion after treatment. It has been suggested that *M. TB*-driven inflammatory tissue damage may trigger induction of CRP production (18). Lower levels of serum albumin have also been strongly associated with mortality in patients with severe TB (24,39). Tsukahara *et al.* reported that a prognostic nutritional index consisting of albumin and lymphocyte count is a relating factor for poor prognosis in smear-positive PTB (23). Taken together, the results indicate that, as the GPS consists of CRP level and albumin,

higher GPS values are associated with increased mortality.

In addition, the mean age was higher in the GPS 2 group. TB in the elderly is related to atypical clinical and radiologic features, so it is often associated with a delay in diagnosis, resulting in higher morbidity and mortality (40,41). Hypoalbuminemia is known to be more prevalent in elderly individuals who are frail compared with those who are healthy. In healthy elderly males, high CRP level and hypoalbuminemia increased the risk of early death (42). A higher GPS value was associated with elderly age in our study; however, elderly age and higher GPS values were independent predicting factors for mortality in patients with TB pleurisy.

Even though the exact mechanism remains uncertain, PR is known to be related to an enhanced immunological response to large amounts of tuberculo-protein release prompted by effective anti-TB treatment (43). HIV co-infection is a well-recognized risk factor for PR, usually

developed when concomitant anti-retroviral therapy is initiated. Some studies have reported that there are various risk factors that predict PR in patients with TB, including young age, positive TB culture, presence of lymph node disease, hypo/hyperalbuminemia, and lymphopenia (30,44-47). Also, anemia and the proportions of eosinophils and protein concentration in pleural fluid at the time of diagnosis is known to be associated with PR (30,45). Some researchers observed that, in HIV-co-infected TB patients, higher CRP level was related to the risk of developing PR (48,49). In our study, rather high number of PR was presented. In South Korea, two studies reported PR was developed with an incidence of 23% and 16% in HIV-negative patients with TB pleurisy, respectively. Our incidence of PR was higher than those with the past studies. In fact, most clinicians in our institutions followed up a chest X-ray at the initiation, 2 weeks or 1 months later, 2 months later of the anti-TB treatment during the intensive phase, with laboratory test including sputum studies, and then at monthly or bimonthly during the continuation phase until the treatment completion. This strategy to monitor TB patients might detect frequently asymptomatic or mild PR cases. We found that the GPS 2 group in our study demonstrated a lower PR occurrence compared with the GPS 0 and 1 groups. There are several explanations for these results. First, serum albumin is not simply a negative acute-phase protein, but also represents nutrition status. In an experimental TB model, the immune system in patients with malnutrition may lose control over *M. TB* because of the suppression of T-cells caused by decreasing lymphocyte stimulation, presence of T helper 1 cytokines, and elevated production of transforming growth factor- β (50). Therefore, in the present study, the presence of hypoalbuminemia, which indicates a decreased nutritional and immunologic status, may play a part in the lower occurrence of PR, reflecting the severity of systemic inflammation in the GPS 2 group. Second, the GPS 2 group contained a considerably higher number of elderly people than did the other two groups. In our study, elderly age was one of the factors associated with mortality and lower PR occurrence. In previous investigations, younger age was found to be predictive for PR (47,51). Aging is related to a decline in host defense mechanisms and altered immune function (52). Low PR occurrence in the elderly is possibly related to decreased immunologic status. However, to verify a possible relationship between the GPS and PR occurrence, further prospective studies

are necessary.

In the present study, we confirmed TB pleurisy in 59.5% (217/367) of participants according to the obtained microbiologic evidence. On the other hand, the percentage of cases diagnosed by only a compatible pathology via pleural biopsy was 44.3% (55/124). This high performance in diagnosing TB pleurisy by microbiologic results could be due to the introduction of an automated liquid culture system for *M. TB* and advanced TB PCR tests (13). These findings provide evidence that recent microbiologic study is comparably useful—as much so as an invasive histologic examination—in the diagnosis of TB pleurisy. In line with the higher detection of *M. TB* in pleural fluid than previously reported, Ruan *et al.* suggested that TB pleurisy is not a delayed hypersensitivity reaction to TB antigens, but rather a continuous spectrum of the disease that is initiated by a direct infection of *M. TB* in the pleural space and that evolves with a cascade of immunological responses (13). They also reported that patients with *M. TB* in the pleural fluid had a higher mortality rate than did those without it. However, we did not identify any association between positive culture for *M. TB* and death in the present study (data not shown). Our data imply that the more significant item to consider in the clinical outcome of TB pleurisy might be the host's inflammatory response to the pathogen rather than the existence of *M. TB*.

Our study had certain limitations. First, it is a retrospective study with inherent weakness. Nonetheless, it is a multi-center study that included a relatively large sample size and that provides valuable clinical information about the role of GPS in TB pleurisy. Second, GPS monitoring was not performed serially according to the time of PR occurrence and mortality. As we mentioned above, the consideration of inflammatory markers might be useful in evaluating treatment response in TB patients. Third, the association of GPS with mortality in TB pleurisy patients could be explained by unassessed confounding factors.

Despite these limitations, our study had a number of strengths. Although several studies exploring prognostic factors in patients with TB pleurisy have been performed, the prognostic value of GPS has not been previously investigated. Our study suggests that higher GPS value in the pretreatment phase is a poor prognostic factor for clinical outcomes and is related with lower PR occurrence. The GPS can be determined through a simple, easy, and inexpensive test and is a reliable marker of inflammatory activity. Therefore, the GPS could help clinicians in predicting the clinical course of patients with TB pleurisy

and assist them to more successfully manage high-risk populations.

In conclusion, higher GPS value and elderly age were identified as prognostic factors for poor outcomes in TB pleurisy and as predicting factors for lower PR occurrence. Additional prospective studies are needed to clarify the utility of GPS in patients with TB pleurisy.

Acknowledgements

Funding: This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI14C1234).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the institutional review boards of the participating centers (approval No. XC18RCDI0002). The requirement for informed patient consent was waived by the boards.

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Cite this article as: Kang HS, Lee HY, Jung JI, Kim JS, Kim YH, Kim SJ, Kim SC, Kwon SS, Kim YK, Kang JY. Clinical significance of Glasgow Prognostic Score in patients with tuberculous pleurisy. *J Thorac Dis* 2018;10(11):6077-6087. doi: 10.21037/jtd.2018.10.02