ORIGINAL ARTICLE

BACES Score for Predicting Mortality in Nontuberculous Mycobacterial Pulmonary Disease

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Abstract

Rationale: Because the prognosis of nontuberculous mycobacterial pulmonary disease varies, a scoring system predicting mortality is needed.

Objectives: We aimed to develop a novel scoring system to predict mortality among patients with nontuberculous mycobacterial pulmonary disease.

Methods: We included patients age ⩾20 years with newly diagnosed nontuberculous mycobacterial pulmonary disease, with *Mycobacterium avium*, *M. intracellulare*, *M. abscessus* subsp. *abscessus*, or *M. abscessus* subsp. *massiliense*. Cox proportional hazards models were used to identify predictors of mortality in a derivation cohort, and a scoring system was developed. It was validated in an independent prospective cohort.

Measurements and Main Results: A total 1,181 and 377 patients were included in the derivation and validation cohorts, respectively. In the final model, body mass index <18.5 kg/m^2 (1 point), age ⩾65 years (1 point), presence of cavity (1 point), elevated erythrocyte sedimentation rate (1 point), and male sex (1 point) were selected as predictors for mortality. We named this novel scoring system BACES (body mass index, age, cavity, erythrocyte sedimentation rate, and sex). Harrell's C-index for the BACES score was 0.812 (95% confidence interval, 0.786–0.837) in the derivation cohort and 0.854 (95% confidence interval, 0.797–0.911) in the validation cohort, indicating excellent discrimination performance. The estimated 5-year risk of mortality was 1.2% with BACES score 0 and 82.9% with BACES score 5.

Conclusions: We developed the BACES score, which could accurately predict mortality among patients with nontuberculous mycobacterial pulmonary disease caused by *M. avium*, *M. intracellulare*, *M. abscessus* subsp. *abscessus*, or *M. abscessus* subsp. *massiliense*.

Keywords: nontuberculous mycobacteria; mortality; cohort studies; predictive value of tests

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Data analyzed are restricted, as they include identifiers and cannot be shared in their current form. However, the data can be provided as a deidentified data set with a reasonable request after Institutional Review Board approval of both institutions (Seoul National University Hospital and Samsung Medical Center).

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At a Glance Commentary

Scientific Knowledge on the Subject: Although several predictors for mortality have been proposed among patients with nontuberculous mycobacterial pulmonary disease (NTM-PD), a scoring system to accurately predict mortality is not yet available.

What This Study Adds to the Field: In this study, we derive and validate a mortality prediction score for NTM-PD. Using a derivation cohort of 1,181 patients with NTM-PD, body mass index <18.5 kg/m^2, age ≥ 65 years, presence of cavity on computed tomography, elevated erythrocyte sedimentation rate (>15 mm/h in men and 20 mm/h in women), and male sex were predictors for shorter time to death. One point was assigned to each variable, and the scoring system was named the BACES (body mass index, age, cavity, erythrocyte sedimentation rate, sex) score. The BACES score was validated in an independent cohort of 377 patients with NTM-PD, with excellent discrimination performance (Harrell's C-index = 0.854).

Nontuberculous mycobacteria (NTM) are ubiquitously present in the environment, including water, soil, and dust (1). They can cause pulmonary disease (PD), a chronic progressive disease, the burden of which has increased rapidly worldwide during the past decade (2, 3). *Mycobacterium avium* complex (MAC) is the most commonly encountered species, followed by *M. abscessus* species in East Asia and North America (1).

The clinical course of NTM-PD varies widely. In noncavitary nodular bronchiectatic NTM-PD, spontaneous sputum conversion occurs in 34–52% of patients in whom antibiotics were not used, whereas about 60% of patients require antibiotic treatment owing to disease progression (4, 5). According to a recent meta-analysis, the treatment success rate for MAC-PD is 65.6% for treatment-naive patients and 58.0% for patients with a history of treatment (6). The treatment success rates for *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense* are 33.0% and 56.7%, respectively (7). Even after achieving culture conversion, relapse and reinfection frequently occur (8, 9). With this heterogeneity of clinical course, the decision to start antibiotic treatment is largely based on the experience and preference of the duty physician (10).

Some demographic and clinical characteristics have been suggested as prognostic factors for patients with NTM-PD. Male sex, older age, lower body mass index (BMI), presence of fibrocavitary disease, and comorbidities are known risk factors for all-cause mortality (11–13). Risk stratification for long-term prognosis based on patients' characteristics may guide the identification of patients who may benefit from antibiotic therapy (10).

The aim of this study was to develop and validate a scoring system for classifying patients with NTM-PD based on mortality risk, using two NTM-PD cohorts in South Korea.

Methods

Study Cohorts

The data used in our study were derived from independent cohorts of two tertiary referral centers in Seoul, South Korea. In the derivation cohort, patients with NTM-PD were enrolled between July 14, 1997, and December 31, 2013, at Samsung Medical Center (ClinicalTrials.gov identifier: NCT00970801) (9, 14). Data from July 14, 1997, to December 31, 2007, were obtained retrospectively, and data after January 1, 2008, were collected prospectively with informed consent. Patients were followed up until June 30, 2017. The validation cohort consists of patients with NTM-PD prospectively enrolled from July 1, 2011, at Seoul National University Hospital (ClinicalTrials.gov identifier: NCT01616745) (15, 16). In both cohorts, clinical variables were collected through interviews or questionnaires, and the results of laboratory tests were retrieved from electronic health records. These were periodically uploaded to an online database. Informed consent was obtained from all participants. As this is an ongoing cohort, patients enrolled until October 28, 2019, were included, and data retrieval was performed on December 19, 2019. The date of death was confirmed using the database of the National Health Insurance Service (Samsung Medical Center Cohort) or the Ministry of the Interior and Safety (Seoul National University Hospital Cohort), South Korea.

The diagnosis of NTM-PD was made based on the criteria of the 2007 American Thoracic Society and the Infectious Diseases Society of America or 2017 British Thoracic Society official statements (17, 18). Patients were treated according to the recent guideline available at the time of management (17, 18). We included patients with newly diagnosed NTM-PD and excluded those with relatively rare NTM species other than four most common NTM species in South Korea, *M. avium*, *M. intracellulare*, *M. abscessus* subsp. *abscessus*, and *M. abscessus* subsp. *massiliense*, to reduce heterogeneity. We also excluded patients with radiographic lesions that could not be classified into one of three categories (noncavitary nodular bronchiectatic, cavitary nodular bronchiectatic, or fibrocavitary forms) (9), missing laboratory values of erythrocyte sedimentation rate (ESR), or unavailable death certificate. This study was approved by the Institutional Review Board of Seoul National University Hospital (protocol number: 1911–145–1081) and Samsung Medical Center (protocol number: 158–346).

Data Extraction

Shared variables between the two cohorts were identified. Age and BMI at diagnosis, sex, causative NTM species, acid-fast bacillus (AFB) smear of a respiratory specimen, and history of tuberculosis were included. In both cohorts, two independent pulmonary physicians reviewed the computed tomography (CT) scans referring to the interpretation of chest radiologists. Radiographic type was classified into three categories according to the chest CT findings: noncavitary nodular bronchiectatic, cavitary nodular bronchiectatic, and fibrocavitary forms (9). Any discrepancies between the reviewers were resolved in discussion. Cavity was considered present with either the cavitary bronchiectatic or fibrocavitary form. Subjective symptoms of cough, sputum, and hemoptysis were excluded because these were assessed differently between the two cohorts. Duration of follow-up was calculated according to the most recent hospital visit or date of death. Continuous variables were dichotomized according to the following clinically significant cutoff values:

age ⩾65 and <65 years and BMI ⩾18.5 kg/m^2 and <18.5 kg/m^2. Laboratory ESR findings were considered elevated with values more than 15 mm/h in men and 20 mm/h in women (19).

Construction of the Scoring System

Construction of the scoring system proposed in this study was based on the methods described by Sullivan and colleagues and Leisman and colleagues (20, 21). Survival analysis using Cox proportional hazards regression was performed using variables considered clinically relevant to the innate aspects of NTM-PD: age, sex, BMI, smoking history, history of tuberculosis, AFB smear positivity at diagnosis, mycobacterial species, ESR, and presence of cavity. Variables that were irrelevant to the status of NTM-PD itself were not considered in the model, such as underlying comorbidities. We considered variables significant at a value of 0.2 in univariable analysis as candidates in the multivariable analysis. The final prediction model was obtained using a stepwise method. The β-coefficients of the variables included in the final multivariate model were rounded to integers, and the integers were considered points assigned to each variable. The proportional hazard assumption was examined by visual assessment of log–log survival curves against time, and there was no violation for this assumption.

Score Validation

Validation of the derived scoring system was based on the methods proposed by Royston and colleagues and Leisman and colleagues (21, 22). The discrimination performance of the score was assessed using Harrell's C-statistic for internal and external validation; the degree of optimism, which reflects overfitting, was calculated using 200-fold bootstrap resampling iterations in the internal validation. Kaplan-Meier curves were drawn for three risk groups according to their calculated scores and compared with the estimated probability of survival according to the scoring system.

Other Statistical Considerations

Baseline characteristics of participants were summarized as counts and proportions for categorical variables and median with interquartile range (IQR) for continuous variables. Estimated probability of death was calculated using the following formula, after Cox regression, where S_0 is the estimated survival at time t with score of 0:

$$\text{Probability of death at time } t = 1 - S_0(t)^{\exp(\text{score})}.$$

Probability of survival and the Harrell's C-index were calculated using the "rms" package in R version 3.6.2 (The R Foundation for Statistical Computing). Additional statistical analysis and figure creation were done using Stata version 16.0 (StataCorp LLC).

Our study was performed in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement (23). The checklist is available in File E1 of the online supplement.

Results

Patient Characteristics

After exclusion of patients according to the criteria described above, 1,181 and 377 patients were included in the derivation and validation cohorts, respectively (*see* Figure E1). Compared with patients in the derivation cohort, those in the validation cohort had older age (median, 63 [IQR, 56–70] vs. 60 [IQR, 51–68] yr; $P < 0.001$), higher BMI (median, 20.9 [IQR, 19.4–22.5] vs. 20.5 [IQR, 18.7–22.3] kg/m^2; $P = 0.004$), and lower ESR (median, 20 [IQR, 12–33] vs. 29 [IQR, 16–52] mm/h; $P < 0.001$). The validation cohort also had fewer patients with positive results of an AFB smear (18.7% vs. 52.0%; $P < 0.001$), cavity on chest CT (23.5% vs. 30.8%; $P = 0.007$), treatment initiation (37.9% vs. 66.0%; $P < 0.001$), and mortality (6.9% vs. 21.0%; $P < 0.001$). Patients in the validation cohort were followed up for shorter periods than those in the derivation cohort (median, 4.9 yr [IQR, 3.2–7.1] vs. 6.8 years [IQR, 4.7–9.7]; $P < 0.001$). Sex, smoking status, history of tuberculosis, and mycobacterial

Table 1. Characteristics of Patients Included in the Derivation and Validation Cohorts

Variables	Total Patients (*N = 1,558*)	Derivation Cohort (*n = 1,181*)	Validation Cohort (*n = 377*)	*P* Value
Age, yr	61 (52–69)	60 (51–68)	63 (56–70)	<0.001
Sex, M	561 (36.0)	438 (37.1)	123 (32.6)	0.116
Body mass index, kg/m^2	20.6 (18.8–22.3)	20.5 (18.7–22.3)	20.9 (19.4–22.5)	0.004
Ever-smoker*	390 (25.0)	302 (25.6)	88 (23.3)	0.384
History of tuberculosis	629 (40.6)	489 (41.4)	140 (37.4)	0.223
Acid-fast bacillus smear positivity	684 (44.0)	614 (52.0)	70 (18.7)	<0.001
Mycobacterial species				0.302
M. avium	663 (42.6)	499 (42.3)	164 (43.5)	
M. intracellulare	549 (35.2)	412 (34.9)	137 (36.3)	
M. abscessus subsp. *abscessus*	54 (9.9)	114 (9.7)	40 (10.6)	
M. abscessus subsp. *massiliense*	192 (12.3)	156 (13.2)	36 (9.6)	
Erythrocyte sedimentation rate, mm/h	27 (15–47)	29 (16–52)	20 (12–33)	<0.001
Cavity on chest computed tomography	453 (29.1)	364 (30.8)	89 (23.6)	0.007
Follow-up duration, yr	6.2 (4.2–8.9)	6.8 (4.7–9.7)	4.9 (3.2–7.1)	<0.001
Treatment initiation	922 (59.2)	779 (66.0)	143 (37.9)	<0.001
Death during follow-up	274 (17.6)	248 (21.0)	26 (6.9)	<0.001

Numbers are presented as numbers (percentages) or median (interquartile range).
*Includes current and former smokers.

Table 2. Factors Associated with Time to Mortality among Patients with Nontuberculous Mycobacterial Pulmonary Disease in the Derivation Cohort

Variables	Unadjusted HR	Adjusted HR in the Final Model	β Coefficient in the Final Model	Score
Age ⩾65 yr	4.42 (3.39–5.75)	3.31 (2.52–4.36)	1.20	1
Sex, M	3.56 (2.75–4.61)	2.29 (1.75–3.00)	0.83	1
Body mass index, <18.5 kg/m^2	3.53 (2.75–4.53)	2.25 (1.73–2.91)	0.81	1
Ever-smoker*	2.77 (2.15–3.56)	—	—	—
History of tuberculosis	2.25 (1.74–2.90)	—	—	—
Acid-fast bacillus smear positivity	2.43 (1.85–3.20)	1.38 (1.03–1.86)	0.32	0
Mycobacterial species				
M. avium	Reference	—	—	—
M. intracellulare	2.13 (1.60–2.83)	—	—	—
M. abscessus subsp. *abscessus*	1.41 (0.90–2.21)	—	—	—
M. abscessus subsp. *massiliense*	0.84 (0.52–1.35)	—	—	—
Elevated erythrocyte sedimentation rate†	3.88 (2.63–5.72)	2.38 (1.60–3.54)	0.87	1
Cavity on chest computed tomography	2.62 (2.82–4.66)	2.41 (1.82–3.18)	0.88	1

Definition of abbreviation: HR = hazard ratio.
Numbers are presented as HR (95% confidence interval), unless otherwise specified.
*Includes current and former smokers.
†Men >15 mm/h, women >20 mm/h.

species of NTM-PD were not different between the two cohorts (Table 1).

Predictors of Mortality

In univariate Cox regression analysis, all variables (age ⩾65 yr, sex, BMI <18.5 kg/m^2, smoking history, history of tuberculosis, AFB smear positivity at diagnosis, mycobacterial species, elevated ESR, and presence of cavity) were associated with the time to death. After multivariable analysis, smoking history, history of tuberculosis, and mycobacterial species did not maintain statistical significance. In the final prediction model, the variables age ⩾65 years (hazard ratio [HR], 3.31; 95% confidence interval [CI], 2.52–4.36), male sex (HR, 2.29; 95% CI, 1.75–3.00), BMI <18.5 kg/m^2 (HR, 2.25; 95% CI, 1.73–2.91), AFB smear positivity (HR, 1.38; 95% CI, 1.03–1.86), elevated ESR (HR, 2.38; 95% CI, 1.60–3.54), and presence of cavity (HR, 2.41; 95% CI, 1.82–3.18) remained significant. The β coefficients were as follows: age ⩾65 years, 1.20; male sex, 0.83; BMI <18.5 kg/m^2, 0.81; AFB smear positivity, 0.32; elevated ESR, 0.87; and presence of cavity, 0.88. These were all rounded to integers, and a point of 1 was assigned to age ⩾65 years, male sex, BMI <18.5 kg/m^2, elevated ESR, and presence of cavity. The score for AFB smear positivity was rounded down to 0 because the coefficient was 0.32; therefore, AFB smear results were excluded in the final scoring system (Table 2). The distribution of the scores are shown in Figure 1. We named this scoring system BACES (BMI, age, cavity, ESR, and sex).

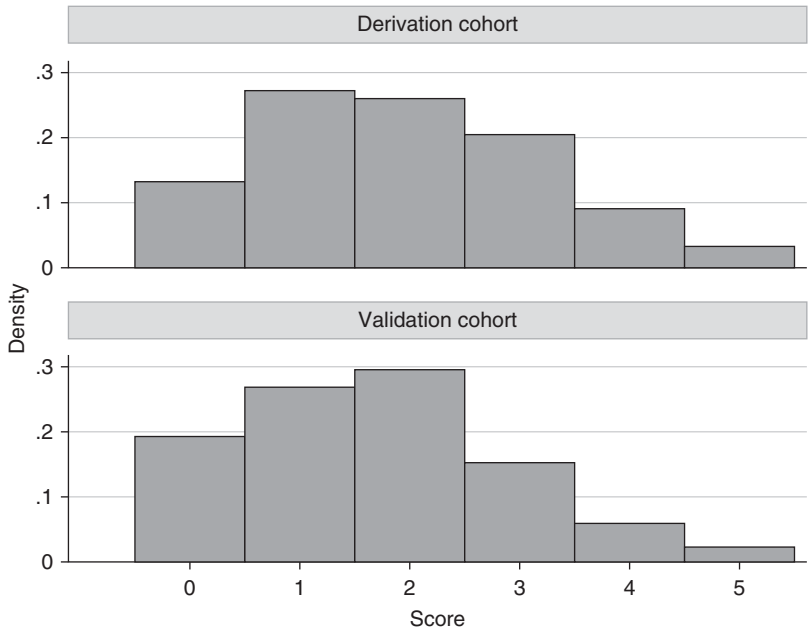

Figure 1. Histogram of the BACES (body mass index, age, cavity, erythrocyte sedimentation rate, and sex) score for nontuberculous mycobacterial pulmonary disease in the two study cohorts.

Performance and Calibration of the BACES Score

Harrell's C-index, an index of discrimination performance, for the BACES score was calculated for both cohorts. This was 0.812 (95% CI, 0.786–0.837) in the derivation cohort, and the degree of optimism was calculated as −0.003; therefore, the risk of overfitting was assumed to be negligible. In the validation cohort, Harrell's C-index was 0.854 (95% CI, 0.797–0.911), indicating excellent discrimination performance. When the scores were organized into three risk groups (scores 4–5, 2–3, and 0–1), the estimated

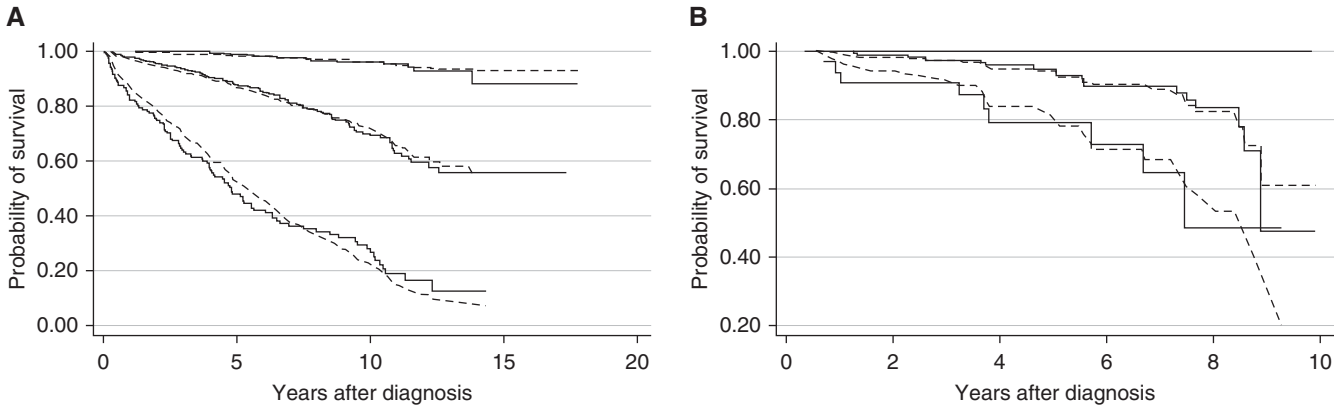

Figure 2. (*A* and *B*) Calibration plot of survival probabilities in the derivation cohort (*A*) and validation cohort (*B*), according to three risk groups: high (BACES [body mass index, age, cavity, erythrocyte sedimentation rate, and sex] scores 4–5), moderate (BACES scores 2–3), and low (BACES scores 0–1). Solid lines indicate Kaplan-Meier estimates of survival probability. Dashed lines indicate estimated survival probabilities according to the Cox proportional hazards model.

and observed probability of survival correlated appropriately (Figure 2).

Estimated Survival according to BACES Score

The estimated 5-year probability of death based on the BACES score was as follows; 1.2% for a score of 0, 3.2% for a score of 1, 8.4% for a score of 2, 21.3% for a score of 3, 47.8% for a score of 4, and 82.9% for a score of 5 (Figure 3).

Discussion

NTM-PD is a heterogeneous disease in terms of progression and treatment response. For clinicians, decisions about whom to treat, when to treat, and how to treat are very difficult (17, 18). In this study, we developed a new scoring system, the BACES score, to stratify the risk of mortality based on five variables at the time of NTM-PD diagnosis: BMI, age, presence of cavity, ESR, and male sex. The BACES score was developed using a cohort of 1,181 patients with NTM-PD (*M. avium*, *M. intracellulare*, *M. abscessus* subsp. *abscessus*, and *M. abscessus* subsp. *massiliense*) and validated with a separate prospective cohort of 377 patients with the same NTM species.

Five variables adopted in the BACES score (BMI, age, cavity, ESR, and sex) have been proposed as prognostic factors in previous studies among different populations (11–13, 24, 25). In addition, a Japanese group designed a prognostic scoring model using some of these variables for patients with NTM-PD (26). To predict all-cause mortality, they included male sex, age $\geqslant$70 years, presence of malignancy, BMI $<$18.5 kg/m^2, lymphocyte count $<$1000 cells/μl, serum albumin $<$3.5 g/dl, and fibrocavitary disease. Although the model was persuasive, it was developed using a retrospective cohort with a moderate number ($n = 486$) of patients. Most importantly, the model only included patients with MAC-PD but not *M. abscessus* PD, which is more difficult to treat and the second most common species of NTM in East Asia and North America (1).

Although treatment outcomes of PD caused by *M. abscessus*, especially *M. abscessus* subsp. *abscessus*, are much worse than those of MAC-PD (6, 7, 16, 27), the species of NTM was not included in our scoring system. The results of previous studies investigating the impact of NTM species on mortality have been controversial. Several studies have suggested that patients with certain species of NTM have better survival than those in which other species are involved (11, 28); however, other studies have refuted these observations (13, 25, 29, 30). The results of our study, based on two large independent cohorts of NTM-PD, did not support the association between NTM species and mortality. Consequently, NTM species was not included in the scoring system.

Previous analyses based on our derivation cohort have reported that patients

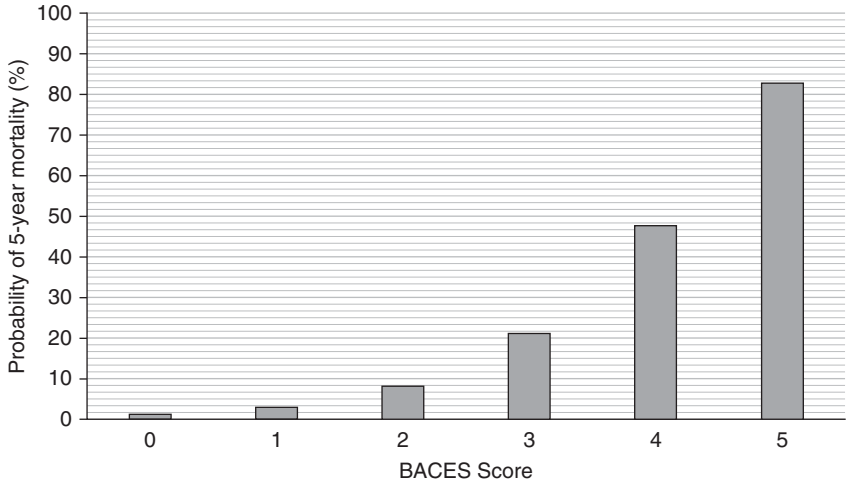

Figure 3. Estimated probability of 5-year mortality in patients with nontuberculous mycobacterial pulmonary disease, according to BACES (body mass index, age, cavity, erythrocyte sedimentation rate, and sex) score.

with *M. intracellulare* or *M. abscessus* subsp. *abscessus* had higher mortality rates than patients with *M. avium* (14). The difference in our scoring system might arise from the fact that the current analysis did not take into account the initiation of treatment or comorbidities including pulmonary aspergillosis, malignancy, and chronic heart or liver disease. Given that the BACES scoring system showed excellent discrimination performance, we can assume that the role of NTM species in predicting mortality is limited.

Although both cohorts analyzed in this study were based on hospitals in the same city, Seoul, South Korea, the characteristics of patients differed in some respects. Patients in the derivation cohort were younger but presented more severe forms of the disease; they had lower BMI, more frequent AFB smear positivity and cavity, and higher ESR. Consequently, the mortality rate was higher in the derivation cohort (21% during 6.8 yr of follow-up) than in the validation cohort (6.9% during 4.9 yr of follow-up). Despite these differences, the BACES score showed excellent discrimination performance in the validation cohort as well as in the derivation cohort. This observation suggests that the BACES score could be applied in patients with NTM-PD from other geographic regions with different demographic and clinical characteristics.

Although future studies are needed to validate the accuracy of the BACES score for patients with NTM-PD in other clinical settings, it has the potential for several applications. First, the BACES score can be used to assist in the initial assessment of the patient and to guide whether the patient can be observed for a time or whether treatment should be initiated immediately. For example, patients with scores 0–1 can be observed without treatment, those with scores 2–3 can be treated only if symptomatic, and treatment should be initiated for those with scores 4–5. Second, the treatment regimen could be decided using the BACES score. It is currently recommended that the regimen for MAC-PD and *M. abscessus* PD be selected according to "severity" of the disease. For example, aminoglycoside should be considered with daily oral antibiotics for patients with MAC-PD and severe disease (i.e., AFB smear positivity, radiological evidence of lung cavitation, and severe infection or severe symptoms and signs of systemic illness). However, the assessment of severity is quite comprehensive and may vary among medical professionals (17, 18). Thus, the BACES score could guide decisions regarding the most appropriate treatment regimen.

To correctly interpret the results of this study, several limitations should be acknowledged. First, although the BACES score was derived and validated using separate cohorts with different baseline characteristics, these cohorts were from the same country. The BACES score should be validated in different ethnic and regional groups. Second, we only included patients with MAC and *M. abscessus* species, which are the two most common NTM species in East Asia and North America. However, in some regions, *M. kansasii* is the second most common species (1). The performance of the BACES scores for patients with NTM other than MAC and *M. abscessus* species should be validated in future studies.

In conclusion, we developed the BACES score, a simple and intuitive scoring system, to predict the risk of mortality among patients with NTM-PD caused by *M. avium*, *M. intracellulare*, *M. abscessus* subsp. *abscessus*, or *M. abscessus* subsp. *massiliense*. This scoring system showed an excellent capacity to predict mortality. Future studies are needed to validate the BACES score in various ethnic groups and for other clinical applications. ■

Author disclosures are available with the text of this article at wwwatsjournals.org.

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