J Neurol
DOI 10.1007/s00415-014-7651-5

ORIGINAL COMMUNICATION

Hamsi scoring in the prediction of unfavorable outcomes from tuberculous meningitis: results of Haydarpasa-II study

Hakan Erdem · Derya Ozturk-Engin · Hulya Tireli · Gamze Kilicoglu · Sylviane Defres · Serda Gulsun · Gonul Sengoz · Alexandru Crisan · Isik Somuncu Johansen · Asuman Inan · Mihai Nechifor · Akram Al-Mahdawi · Rok Civljak · Muge Ozguler · Branislava Savic · Nurgul Ceran · Bruno Cacopardo · Ayse Seza Inal · Mustafa Namiduru · Saim Dayan · Uner Kayabas · Emine Parlak · Ahmad Khalifa · Ebru Kursun · Oguz Resat Sipahi · Mucahit Yemisen · Ayhan Akbulut · Mehmet Bitirgen · Natasa Popovic · Bahar Kandemir · Catalina Luca · Mehmet Parlak · Jean Paul Stahl · Filiz Pehlivanoglu · Soline Simeon · Aysegul Ulu-Kilic · Kadriye Yasar · Gulden Yilmaz · Emel Yilmaz · Bojana Beovic · Melanie Catroux · Botond Lakatos · Mustafa Sunbul · Oral Oncul · Selma Alabay · Elif Sahin-Horasan · Sukran Kose · Ghaydaa Shehata · Katell Andre · Gorana Dragovac · Hanefi Cem Gul · Ahmet Karakas · Stéphane Chadapaud · Yves Hansmann · Arjan Harxhi · Valerija Kirova · Isabelle Masse-Chabredier · Serkan Oncu · Alper Sener · Recep Tekin · Nazif Elaldi · Ozcan Deveci · Hacer Deniz Ozkaya · Oguz Karabay · Seniha Senbayrak · Canan Agalar · Haluk Vahaboglu

Received: 14 October 2014 / Revised: 14 December 2014 / Accepted: 27 December 2014

Abstract Predicting unfavorable outcome is of paramount importance in clinical decision making. Accordingly, we designed this multinational study, which provided the largest case series of tuberculous meningitis (TBM). 43 centers from 14 countries (Albania, Croatia, Denmark, Egypt, France, Hungary, Iraq, Italy, Macedonia, Romania, Serbia, Slovenia, Syria, Turkey) submitted data of microbiologically confirmed TBM patients hospitalized between 2000 and 2012. Unfavorable outcome was defined as survival with significant sequela or death. In developing our index, binary logistic regression models were constructed via 200 replicates of database by bootstrap resampling methodology. The final model was built according to the selection frequencies of variables. The severity scale included variables with arbitrary scores proportional to predictive powers of terms in the final model. The final model was internally validated by bootstrap resampling. A total of 507 patients' data were submitted among which 165 had unfavorable outcome. Eighty-six patients died while 119 had different neurological sequelae in 79 (16 %) patients. The full model included 13

H. Erdem · O. Oncul
Department of Infectious Diseases and Clinical Microbiology, GATA Haydarpasa Training Hospital, Istanbul, Turkey

H. Erdem (✉)
Enfeksiyon Hastalıkları Servisi, GATA Haydarpasa AH, Uskudar, Istanbul, Turkey
e-mail: hakanerdem1969@yahoo.com

D. Ozturk-Engin · A. Inan · N. Ceran · S. Senbayrak
Department of Infectious Diseases and Clinical Microbiology, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey

H. Tireli
Department of Neurology, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey

G. Kilicoglu
Department of Radiology, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey

S. Defres
Institute of Infection & Global Health, University of Liverpool, Liverpool, UK

S. Defres
Tropical Infections Diseases Unit in Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, UK

S. Gulsun
Department of Infectious Diseases and Clinical Microbiology, Diyarbakir Training and Research Hospital, Diyarbakir, Turkey

G. Sengoz · F. Pehlivanoglu
Department of Infectious Diseases and Clinical Microbiology, Haseki Training and Research Hospital, Istanbul, Turkey

A. Crisan
Department of Infectious Diseases, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

Published online: 30 January 2015

variables. Age, nausea, vomiting, altered consciousness, hydrocephalus, vasculitis, immunosuppression, diabetes mellitus and neurological deficit remained in the final model. Scores 1–3 were assigned to the variables in the severity scale, which included scores of 1–6. The distribution of mortality for the scores 1–6 was 3.4, 8.2, 20.6, 31, 30 and 40.1 %, respectively. Altered consciousness, diabetes mellitus, immunosuppression, neurological deficits, hydrocephalus, and vasculitis predicted the unfavorable outcome in the scoring and the cumulative score provided a linear estimation of prognosis.

Keywords Tuberculosis · Meningitis · Death · Outcome · Sequelae

Introduction

Tuberculosis is a global health problem and is the most frequent cause of infection-related deaths just after HIV infection [9]. Mortality attributed to tuberculosis was reported to be 1.4 million in 2011 in the world [2]. Tuberculous meningitis (TBM), which is known to be the most severe form of tuberculosis [4], is detected in less than 1 % of all tuberculosis cases [7]. The outcome of the disease is quite problematic since half of patients either die or suffer from permanent squealae [4, 6]. Thus, predictive scoring of unfavorable outcome is of paramount importance in clinical decision making in TBM.

Various approaches in predicting the outcome in TBM have been proposed in the past. Radiological assessment [11, 16, 18, 19, 22], Glasgow coma scale (GCS) [16–18], electroencephalography [15, 17], motor and somatosensory evoked potentials [17] were studied individually to predict prognosis of the disease. Even APACHE II, a scoring system produced to measure the severity of disease for adult patients admitted to intensive care units, has been taken into consideration for the prediction of unfavorable outcome [5]. However, the most widely practiced among others is the British Medical Research Council (MRC) staging system which was developed in 1948 [1]. This system mainly considers the level of consciousness and neurological deficits and has been evaluated in various studies for the prediction of TBM prognosis [10–12, 16–18, 22]. Today, a reliable and consistent staging system is needed in medical practice. Therefore, an updated severity index using the parameters derived from sophisticated radio-diagnostic techniques and clinical parameters is of great significance in medical practice. Thus, we designed this multinational study to construct a steady model and a severity index based on the largest case series in the literature.

Methods

Study design and patient selection

Haydarpasa-II is a multicenter retrospective cohort study. It included 43 centers from 14 countries (Albania, Croatia, Denmark, Egypt, France, Hungary, Iraq, Italy, Macedonia, Romania, Serbia, Slovenia, Syria, and Turkey) which provided data from TBM patients hospitalized between

I. S. Johansen
Department of Infectious Diseases Q, Odense University Hospital, Odense, Denmark

M. Nechifor
Department of Pharmacology, Gr. T. Popa University of Medicine and Pharmacy, Iasi, Romania

A. Al-Mahdawi
Department of Neurology, Baghdad Teaching Hospital, Baghdad, Iraq

R. Civljak
Department of Infectious Diseases, Dr. Fran Mihaljevic University Hospital for Infectious Diseases, University of Zagreb School of Medicine, Zagreb, Croatia

M. Ozguler · A. Akbulut
Department of Infectious Diseases and Clinical Microbiology, Firat University School of Medicine, Elazig, Turkey

B. Savic
Institute of Microbiology and Immunology, National Reference Laboratory for Tuberculosis, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

B. Cacopardo
Section of Infectious Diseases, Department of Clinical and Molecular Biomedicine, University of Catania, Catania, Italy

A. S. Inal
Department of Infectious Diseases and Clinical Microbiology, Cukurova University School of Medicine, Adana, Turkey

M. Namiduru
Department of Infectious Diseases and Clinical Microbiology, Gaziantep University School of Medicine, Gaziantep, Turkey

S. Dayan · R. Tekin · O. Deveci
Department of Infectious Diseases and Clinical Microbiology, Dicle University School of Medicine, Diyarbakir, Turkey

U. Kayabas
Department of Infectious Diseases and Clinical Microbiology, Inonu University School of Medicine, Malatya, Turkey

E. Parlak · M. Parlak
Department of Infectious Diseases and Clinical Microbiology, Ataturk University School of Medicine, Erzurum, Turkey

2000 and 2012. Haydarpaşa-1 Study, which used the same database and evaluated the interrelations of microbiological tests, was published elsewhere [8]. A questionnaire was sent to participant centers, which finally submitted their databases in an excel file format. Finally, we formed A MS Windows® based computer database.

Adult (age over 14) TBM patients with microbiological confirmation were included in the study. At least one of the following tests on the CSF was mandatory for microbiological confirmation; a positive Ehrlich-Ziehl-Neelsen stain, positive *Mycobacterium tuberculosis* (Mtb) culture, or positive Mtb-PCR [4]. All the TBM cases included in this study were followed and treated in accordance with the centers' own policies. All epidemiological, clinical, laboratory, radiological and outcome data were retrieved from patient charts by the participant centers.

Definitions

Unfavorable outcome This term represents an outcome of either sequela or mortality. Sequelae were detected after the end of antibiotic treatment and defined as any dysfunction related to CNS that persisted during the follow-up period. These included motor deficit, cranial nerve palsy, ataxia, persisting unconscious state, seizures, difficulty with speech, hydrocephalus, diabetes insipidus, anal sphincter dysfunction, and coma.

Neurological deficit Patients with any cranial nerve palsy or motor deficit were classified in this category.

Motor deficit Hemiplegia-hemiparesis, paraplegia-paraparesis, and quadriplegia-quadriparesis were grouped together as motor deficit.

Cranial nerve palsy (CNP) CNP denotes paralysis of 3rd, 4th, 6th, 7th and 8th cranial nerves only. These are the common cranial nerves affected, and they are readily detected in medical practice.

Basal meningitis, hydrocephalus, tuberculoma, abscess, vasculitis and cerebritis were defined according to MRI or CT imaging findings.

Basal meningitis Meningitis detected at the base of the brain was recorded as basal meningitis.

Hydrocephalus Defined as the abnormal buildup of CSF in the ventricles of the brain, due to an altered CSF dynamics.

Tuberculoma A well-circumscribed mass detected in the cerebral hemispheres, cerebellum, brain stem, or perimeningeal spaces in due course of TBM was recorded as tuberculoma.

Vasculitis Since the classical histopathological change for vasculitis essentially consists of an inflammatory infiltrate within the vessel wall associated with destructive changes, occlusion and infarction [13], these radiological findings were grouped together in one bloc as vasculitis.

Cerebritis Inflammation of the cerebrum disclosed with radiological evaluations was recorded as cerebritis.

Immunosuppression Use of immunosuppressive drugs including corticosteroids for a number of conditions such as transplantation of any organ, connective tissue disorders, and malignancies was defined as immunosuppression. Alcoholism, HIV infection irrespective of CD4+ count and drug addiction were also included in this category.

Elapsed time Defined as the time period between the onset of symptoms and the start of anti-tuberculous treatment.

A. Khalifa
Department of Neurology, Damascus Hospital, Damascus, Syria

E. Kursun
Department of Infectious Diseases and Clinical Microbiology, Baskent University School of Medicine, Adana, Turkey

O. R. Sipahi
Department of Infectious Diseases and Clinical Microbiology, Ege University School of Medicine, Izmir, Turkey

M. Yemisen
Department of Infectious Diseases and Clinical Microbiology, Istanbul University Cerrahpasa School of Medicine, Istanbul, Turkey

M. Bitirgen · B. Kandemir
Department of Infectious Diseases and Clinical Microbiology, Necmettin Erbakan University School of Medicine, Konya, Turkey

N. Popovic
Clinic for Infectious and Tropical Diseases, Clinical Centre of Serbia, Belgrade, Serbia

C. Luca
Department of Infectious Diseases, Gr. T. Popa University of Medicine and Pharmacy, Iasi, Romania

J. P. Stahl
Department of Infectious Diseases, Joseph Fourier University and University Hospital of Grenoble, Grenoble, France

S. Simeon
Department of Infectious and Tropical Diseases, University Hospital of Pontchaillou, Rennes, France

A. Ulu-Kilic · S. Alabay
Department of Infectious Diseases and Clinical Microbiology, Erciyes University School of Medicine, Kayseri, Turkey

K. Yasar
Department of Infectious Diseases and Clinical Microbiology, Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey

G. Yilmaz
Department of Infectious Diseases and Clinical Microbiology, Ankara University School of Medicine, Ankara, Turkey

Stage of the disease The stage of the patients was determined according to traditional MRC system [1].

Statistical analysis

Statistical analysis was performed using the software package, Stata 12.1 (StataCorp® Texas, USA). In univariate analysis, categorical variables were compared by Pearson's Chi-squared test and were applied by Fisher's exact test, while continuous variables were compared by Student's t test or in a case of non-normal distribution compared by Wilcoxon rank-sum test. Normality was assessed by Shapiro–Wilk and Shapiro–Francia tests.

A total of 12 % (63 out of 507 patients) of observations in four (basal meningitis, hydrocephalus, abscess, vasculitis) variables were missing. These variables depended on CT or MRI examinations of CNS at admission. Since missing observations belong to patients without these tests at admission, missing observations for all these four variables belong to the same patients and 89 % were from three countries. These variables were significant candidates for the initial model. Logistic regression protocol drops missing observations in a list-wise fashion. Dropping 12 % off all other covariates might lead to biased estimates and so we decided to input these observations [14]. First, the missingness pattern was inspected and indicator variables were generated to further assess if the data are "missing completely at random". Depending on the relationship between missing values and other covariates including outcome, we concluded to input missing observations. Multiple Imputation (MI) using monotone-missing patterns was applied. Number of imputations was determined according to the Monte Carlo error estimates those ideally have to be less than 10 % of standard errors of related coefficients [23]. Eventually, we built up a multiple imputed data set and tested models with both complete cases and imputed data set.

Binary logistic regression model was constructed via a bootstrap resampling procedure described in detail elsewhere [20]. Briefly, each of 12 imputed data sets were replaced by resampling 200 times. The full model including all potential variables was tested across bootstrapped samples by means of logistic regression. In each bootstrap replication, significant variables were selected with backward elimination at a selection point of $\alpha = 0.05$. Since data vary between replicates, bootstrap inclusion frequencies of variables also vary, where weak predictors are found with less inclusion frequencies. Those variables that have more than 30 % inclusion frequency at least at half of the imputed data sets were included in the final model. The final model was tested with logistic regression analysis across imputed data sets and estimates were combined according to Rubin's rules (http://sutlib2.sut.ac.th/sut_contents/H112674.pdf). To test the significance of continuous predictors, multivariable fractional polynomial model selection procedure was applied. Global heuristic shrinkage factor was obtained by the average of heuristic shrinkage factors obtained from imputed data sets. The model was internally validated by bootstrapping [21].

According to the predictive powers of terms from the final model, scores were assigned to build a severity scale. Finally, this severity scale was tested on complete cases and imputed data set individually. Confidence intervals of c index, giving limits of the predictive accuracy, were generated by bootstrap sampling.

E. Yilmaz
Department of Infectious Diseases and Clinical Microbiology, Uludag University School of Medicine, Bursa, Turkey

B. Beovic
Department of Infectious Diseases, University Medical Centre, Ljubljana, Slovenia

M. Catroux
Department of Infectious Diseases, Poitiers University Hospital, Poitiers, France

B. Lakatos
Department of Infectious Diseases, Saint Laszlo Hospital, Budapest, Hungary

M. Sunbul
Department of Infectious Diseases and Clinical Microbiology, Ondokuz Mayis University School of Medicine, Samsun, Turkey

E. Sahin-Horasan
Department of Infectious Diseases and Clinical Microbiology, Mersin University School of Medicine, Mersin, Istanbul, Turkey

S. Kose
Department of Infectious Diseases and Clinical Microbiology, Tepecik Training and Research Hospital, Izmir, Turkey

G. Shehata
Department of Neurology and Psychiatry, Assiut University Hospital, Assiut, Egypt

K. Andre
Department of Infectious Diseases, Dax Hospital, Dax, France

G. Dragovac
Department of Prevention and Control of Diseases, Medical Faculty, IPH of Vojvodina, University of Novi Sad, Novi Sad, Serbia

H. C. Gul · A. Karakas
Department of Infectious Diseases and Clinical Microbiology, Gulhane Medical Academy, Ankara, Turkey

S. Chadapaud
Department of Infectious Diseases, Marie José Treffot Hospital, Hyeres, France

Results

Data for 507 patients were submitted from in Haydarpasa-2 study. Unfavorable outcome was detected in 165 of 507 patients. Eighty-six patients died and case-fatality rate for this cohort was 17 %. A total of 119 squealae were detected in 79 (16 %) patients. The squealae included motor deficit in 37 patients (7 %), cranial nerve palsy in 30 (6 %), ataxia in 11 (2 %), altered consciousness in 10 (2 %), seizures in 10 (2 %), difficulty with speech in nine (2 %), hydrocephalus in five (1 %), diabetes insipidus in four (1 %), anal sphincter dysfunction in two (0.3 %), coma in one (0.1 %).

Demographics and other factors with respect to outcome are presented in Table 1. Continuous variables such as age and elapsed time were non-normally distributed, and only age was found to be significant ($p < 0.001$). Among the other significant variables, neurological deficit represented motor deficit and/or cranial nerve palsy. Motor deficit and cranial nerve palsy were tested one by one and all together in the model. However, once the composite term neurological deficit was entered, motor deficit and central nerve palsy were both dropped from the model.

After reviewing all the data submitted, we detected that six variables were missing among 63 patients. These included the detection of basal meningitis, hydrocephalus, tuberculoma, abscess, vasculitis, and cerebritis. All of these variables are diagnosed by CT scan or MRI which means that missing data occurred when neuroimaging had not been performed. Missing data were mostly from three countries; 55.6 % (35/63) from Romania, 19 % (12/63) from Iraq and 14.3 % (9/63) from Turkey. More importantly, missing and non-missing data were concomitantly submitted from same centers thus indicating that a CT scan or MRI had been applied selectively. There was a significant relationship between missing data for these variables and favorable outcome which likely indicates that in these centers physicians probably do not request these tests for patients with mild disease. Therefore, the missingness might be missing at random (MAR) pattern, though we could not be certain that the missing data occurred missing not at random (MNAR). We imputed the missing variables and estimates were carried out on this data set and on the complete data set as well.

The 13 variables, indicated with asterisks in the right column of Table 1, were included in the full model. The global heuristic shrinkage factor was found to be 0.89 which indicated that over fitting of the model is not severe and might be omitted. Selection frequencies of variables in the final model are shown in Table 2. Selection frequencies of variables those not included in the final model were as follows; sphincter dysfunction, difficulty with speech, ataxia, and chronic renal disease were selected zero and abscess was selected two times during bootstrap sampling.

Among the selected variables, only age was a continuous variable. Estimates from the logistic regression failed to show a significant association between age and the outcome variable in its continuous form. Multivariable fractional polynomial model also failed to show any significant association between transformed forms of age and the outcome.

Y. Hansmann
Department of Infectious Diseases, University Hospital, Strasbourg, France

A. Harxhi
Service of Infectious Disease, University Hospital Center of Tirana, Tirana, Albania

V. Kirova
University Clinic for Infectious Diseases and Febrile Conditions, Skopje, Macedonia

I. Masse-Chabredier
Department of Infectious Diseases, Aurillac Hospital, Aurillac, France

S. Oncu
Department of Infectious Diseases and Clinical Microbiology, Adnan Menderes University School of Medicine, Aydin, Turkey

A. Sener
Department of Infectious Diseases and Clinical Microbiology, Onsekiz Mart University School of Medicine, Canakkale, Turkey

N. Elaldi
Department of Infectious Diseases and Clinical Microbiology, Cumhuriyet University School of Medicine, Sivas, Turkey

H. D. Ozkaya
Department of Infectious Diseases and Clinical Microbiology, Karsiyaka State Hospital, Izmir, Turkey

O. Karabay
Department of Infectious Diseases and Clinical Microbiology, Sakarya University School of Medicine, Sakarya, Turkey

C. Agalar
Department of Infectious Diseases and Clinical Microbiology, Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Turkey

H. Vahaboglu
Department of Infectious Diseases and Clinical Microbiology, Goztepe Training and Research Hospital, Medeniyet University, Istanbul, Turkey

Table 1 Demographics and risk variables recorded on admission

Factor[a]	*n* (%)		*p* value
	Favorable $n = 342$	Unfavorable $n = 165$	
Age (years), median (IQR)	34 (23.0, 46.0)	44 (28.0, 62.0)	<0.001*
Female gender	165 (48.2)	76 (46.1)	0.64
Altered consciousness	188 (55.0)	140 (84.8)	<0.001*
Nausea/vomiting	210 (61.4)	71 (43.0)	<0.001*
None	65 (19.0)	14 (8.5)	
Nausea vomiting only	89 (26.0)	11 (6.7)	
Altered consciousness only	67 (19.6)	80 (48.5)	
NV plus AC	121 (35.4)	60 (36.4)	
Neurological deficit	71 (20.8)	60 (36.4)	<0.001*
Motor neuron deficit	33 (9.6)	36 (21.8)	<0.001
Central Nerve Palsy	46 (13.5)	35 (21.2)	0.025
3rd Cranial nerve	16 (4.7)	12 (7.3)	0.23
4th Cranial nerve	7 (2.0)	7 (4.2)	0.16
6th Cranial nerve	23 (6.7)	13 (7.9)	0.64
7th Cranial nerve	9 (2.6)	14 (8.5)	0.003
8th Cranial nerve	5 (1.5)	3 (1.8)	0.76
Sphincter dysfunction	14 (4.1)	14 (8.5)	0.043*
Difficulty with speech	14 (4.1)	18 (10.9)	0.003*
Ataxia	6 (1.8)	7 (4.2)	0.097
Seizure	38 (11.1)	20 (12.1)	0.74*
Basal meningitis	62 (21.4)	36 (23.4)	0.63
Hydrocephalus	65 (22.4)	53 (34.4)	0.006*
Tuberculoma	70 (24.1)	44 (28.6)	0.31
Abscess	11 (3.8)	13 (8.4)	0.039*
Vasculitis	36 (12.4)	36 (23.4)	0.003*
Cerebritis	9 (3.1)	8 (5.2)	0.27
Chronic renal disease	4 (1.2)	8 (4.8)	0.011*
Chronic alcohol consumption	35 (10.2)	23 (13.9)	0.22
Immunosuppression	15 (4.4)	19 (11.5)	0.003*
Diabetes mellitus	15 (4.4)	28 (17.0)	<0.001*
Pregnancy	3 (0.9)	1 (0.6)	0.75
Stage of Disease			<0.001
Early	69 ()	6 ()	
Medium	181 ()	90 ()	
Advanced	92 ()	69 ()	
Elapsed time (days), median (IQR)	20 (10.0, 30.0)	20 (12.0, 34.0)	0.32

NV plus AC, nausea vomiting plus altered consciousness; Neurological deficit, any of central nerve palsy or motor neuron deficit; Elapsed time, days between the start of symptoms and institution of anti TB treatment

* Variables in the full model

Confidence intervals of coefficients obtained from the imputed data sets were not significantly different than those obtained from complete cases. Briefly, the confidence intervals obtained from the altered consciousness were significant with the highest coefficient of all the variables. However, it was not significant if the patient also presented with nausea and vomiting. We, therefore, assigned three points to this altered consciousness without nausea and vomiting and two points when nausea and vomiting accompany altered consciousness. Various ranks were assigned to predictors and those developed scales were tested in terms of predictive accuracy. Final scale giving higher area under the curve is presented in Table 3.

Next, we tested the predictive accuracy of clinical staging and compared to the severity index. In Table 4, the Severity scale and the Clinical staging with corresponding percentages of observed unfavorable outcome and adjusted predicted probabilities with standard errors are presented. In terms of predictive accuracy of clinical outcomes, the clinical staging system was inferior to the severity scale.

Table 2 The final model, selection frequencies of predictors and combined estimates from imputed data sets

	n	Coef	SE
Age	12	0.012	0.006
Nausea/Vomiting	12	−0.705	0.458
Altered consciousness	12	1.418	0.363**
AC/NV		0.849	0.355*
Hydrocephalus	12	0.644	0.256*
Vasculitis	11	0.628	0.312*
Immunosuppression	12	1.059	0.416*
Diabetes mellitus	12	1.072	0.390**
Neurological deficit	12	0.804	0.238**
Constant		−2.593	0.409**

n number of imputed data sets in which variable inclusion frequency is higher than 30% of bootstrap samples, *Coef* coefficients, *SE* Standard errors in parentheses, *AC/NV* altered consciousness plus nausea/vomiting (the interaction term)

** $p < 0.01$, * $p < 0.05$

Table 3 Severity scale

Altered consciousness	3
Altered consciousness plus nausea vomiting	−1
Diabetes mellitus	3
Immunosuppression	2
Neurological deficit[a]	1
Hydrocephalus	1
Vasculitis	1

[a] Central nerve palsy (any of 3rd, 4th, 6th, 7th or 8th nerve palsy) and/or motor neuron deficit

Table 4 "Severity scale" and "Clinical staging" with corresponding percentages of observed unfavorable outcome and adjusted predicted probabilities with standard errors

Severity scale	Observed unfavorable outcome (%)	Predicted probabilities % (SE)
≤1	9.03	9.01 (2.39)
2	19.59	19.49 (4.13)
3	37.57	37.35 (4.58)
4	54.06	53.78 (6.03)
5	61.35	61.30 (8.81)
≥6	73.85	73.66 (7.13)
Stage of disease		
Early	8	8.00 (3.13)
Medium	33.21	33.21 (2.86)
Advanced	42.86	42.86 (3.90)

This difference was significant (Fig. 1). When we compared the observed unfavorable outcome percentages by ranks, in the severity scale the relationship was almost linear. In contrast, the relationship between the clinical

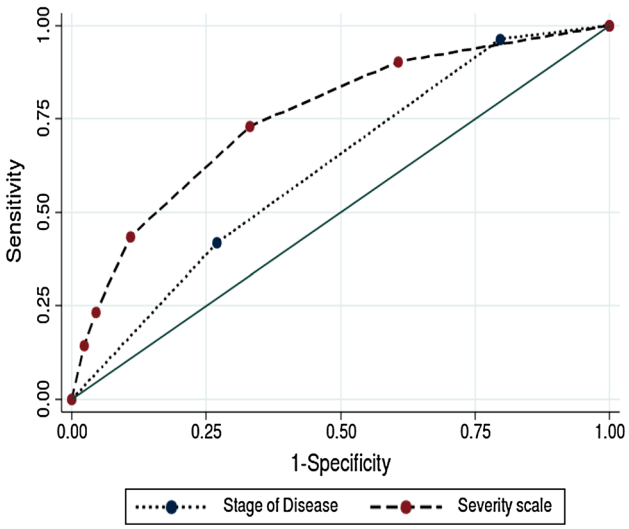

Fig. 1 Comparison of ROC curves

stages and outcome did not give a linear association. Medium and advanced levels of clinical stages presented similar outcome percentages which also discourage the use of clinical staging as a predictive scale (Fig. 2). In our database, observed mortality rates for the scores 1–6 were 3.4, 8.2, 20.6, 31, 30 and 40.1 %, respectively. On the other hand, mortality rates were 1.3 % for the early MRC stage, 18.1 % for the medium stage, and 22.4 % for the advanced stage.

Discussion

In this study, the largest retrospective cohort in the literature consisting of microbiologically confirmed cases, a severity index with acceptable predictive accuracy was developed by considering clinical findings, comorbidities, and CNS imaging findings all together. Our final model was highly stable as it provided similar estimates among complete cases and those with incomplete data sets and it was successfully validated by bootstrap estimation. Internal validation with bootstrapping has been reported to provide more reliable results compared to other methods such as split-sample analysis and cross-validation procedure [9]. Haydarpasa Meningitis Severity Index, HAMSI, developed by the aid of this logistic model gives a linear prediction for unfavorable outcome, which reflects the strength of the base model as well. This linear association between the ranks of the Severity Index and the outcome makes it more applicable in routine medical practice.

Traditionally, severity of TBM patients has been assessed by clinical staging developed in 1948 by the MRC, which solely depends on clinical assessment. Clinical parameters in staging systems are relatively subjective

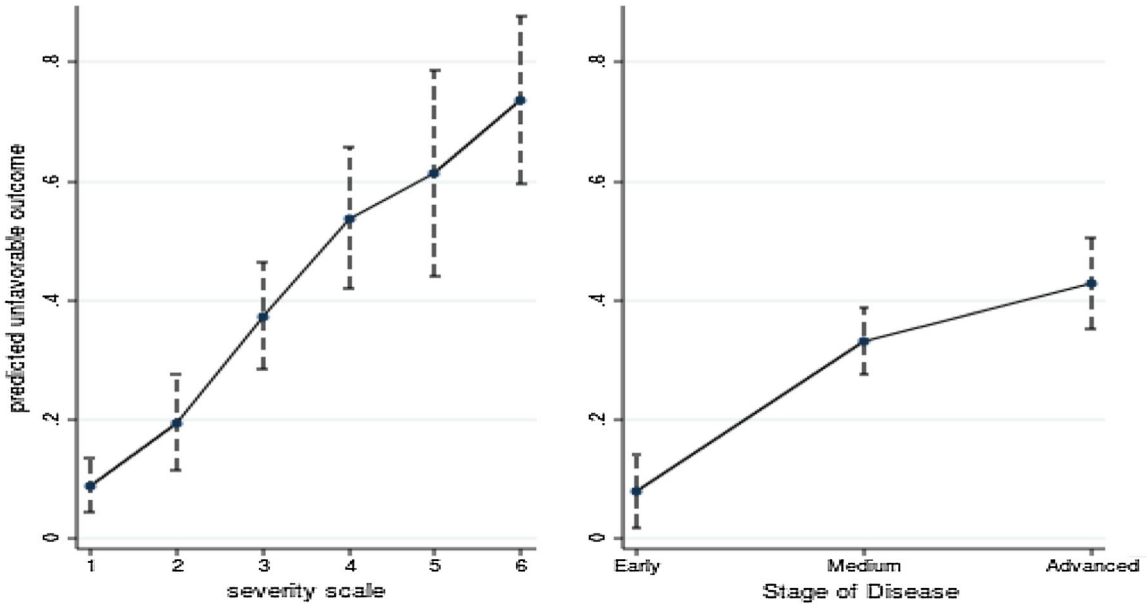

Fig. 2 Adjusted predictions and confidence intervals of scales

and somewhat vague by definition. The MRC categorizes patients as early, medium and advanced stages. Early stage indicates TBM patients with mainly non-specific symptoms, with little or no clinical signs of meningitis, no pareses, in good general condition, and fully conscious. Advanced-stage patients are extremely ill, deeply stuporous or comatosed, or with gross pareses while medium-stage patients are in a condition between the advanced and the early stages. Signs of meningeal irritation with or without slight clouding of consciousness with focal neurological signs such as cranial nerve palsies or hemiparesis are included in the medium stage [1]. On the other hand, the HAMSI scoring handles consciousness as fully conscious or altered mental status, which is a more straightforward classification. This simplified categorization of mental status might avoid the confusion arising among the medium-stage patients in the MRC clinical staging system. Although correlations between the unfavorable outcome and the stages of MRC system were noted in various studies [12, 16, 18], it did not provide satisfactory prediction to forecast outcome in other studies [5, 22, 24]. Accordingly, we could not show a reasonable association between the MRC scoring stage and unfavorable outcome in this study. On the other hand, integration of objective and measurable parameters into clinical parameters may increase the stability and the predictive accuracy of the prediction models. At this critical point, the question "can TBM clinical staging system developed by the British MRC in 1948 be improved" arises. In this context, we first tried to implant objective parameters such as radiological imaging and, comorbid conditions. Unfortunately, adding these parameters did not improve the predictive accuracy of the MRC clinical staging system. Consequently, MRC system is somewhat ill-defined or subjective by its nature. In addition, since when MRC defined clinical staging system at a time when sophisticated neuroimaging was not available and it was derived on a different population with less knowledge than now in the twenty-first century, it provided fairly rough estimates of unfavorable outcome, really no longer applicable today.

There have been other efforts to develop an improved severity index for TBM. In a recent relatively small study in which microbiological confirmation was established in less than half of the patients, impaired conscious, motor deficits, cerebral infarcts, and cisternal effacement were found to increase mortality [3]. The authors recommended a new staging system based on their findings. The first three parameters, impaired conscious, motor deficits, and infarcts, were shown to increase unfavorable outcome in our study, too. We also found that diabetes mellitus and hydrocephalus also affected prognosis.

According to our data, another significant point was that there was no relationship between the elapsed time from the onset of symptoms prior to treatment and outcome. This might be due to delayed diagnosis in mild cases. Another possibility is that, disease progression varies greatly among TBM patients. For example, patients at the early stages according to MRC system might not necessarily present to the hospital early. This point was underlined in the original study, too [1].

One of the limitations of this study was that GCS could not be provided due to missing data in hospital records. If

this study was prospectively planned and the data were collected, we would be able to apply GCS as measure of conscious. However, in a study of this type focusing on a quite rare disease, collecting data prospectively and reaching adequate case numbers would be practically impossible.

In conclusion, altered consciousness, diabetes mellitus, immunosuppression, neurological deficits, hydrocephalus, and vasculitis predicted the unfavorable outcome in HAMSI scoring and the cumulative score provided a linear estimation of prognosis. On the other hand, if a patient with altered consciousness can complain about nausea and vomiting, then this seemed to be a more favorable parameter on the outcome of the disease. This might represent a slight distortion of conscious compared to those patients who cannot complain about nausea due to deeper mental changes. Consequently, we provided a strong model in the prediction of TBM outcome and accordingly, HAMSI scoring should be validated subsequently in other cohorts.

Acknowledgments We would like to thank Patrick Royston, an honorary professor of statistics in the Department of Statistical Science at University College of London, for his guidance in statistics, and for the valuable contributions he made in reviewing the statistical method and results of the study.

Conflicts of interest We have no competing interests to declare.

Ethical standard The Institutional Review Board of Fatih Sultan Mehmet Training and Research Hospital in Istanbul approved the study protocol.

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