Meningitis With a Negative Cerebrospinal Fluid Gram Stain in Adults: Risk Classification for an Adverse Clinical Outcome

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Abstract

Objective: To derive and validate a risk score for an adverse clinical outcome in adults with meningitis and a negative cerebrospinal fluid (CSF) Gram stain.

Patients and Methods: We conducted a retrospective study of 567 adults from Houston, Texas, with meningitis evaluated between January 1, 2005, and January 1, 2010. The patients were divided into derivation (N=292) and validation (N=275) cohorts. An adverse clinical outcome was defined as a Glasgow Outcome Scale score of 4 or less.

Results: Of the 567 patients, 62 (11%) had an adverse clinical outcome. A predictive model was created using 3 baseline variables that were independently associated with an adverse clinical outcome ($P<.05$): age greater than 60 years, abnormal findings on neurologic examination (altered mental status, focal neurologic deficits, or seizures), and CSF glucose level of less than 2.4975 mmol/L (to convert CSF glucose to mmol/L, multiply by 0.05551). The model classified patients into 2 categories of risk for an adverse clinical outcome—derivation sample: low risk, 0.6% and high risk, 32.8%; $P<.001$; and validation sample: low risk, 0.5% and high risk, 21.1%; $P<.001$.

Conclusion: Adults with meningitis and a negative CSF Gram stain can be accurately stratified for the risk of an adverse clinical outcome using clinical variables available at presentation.

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Meningitis with a negative cerebrospinal fluid (CSF) Gram stain represents a diagnostic and therapeutic challenge. The sensitivity of the Gram stain in community-acquired bacterial meningitis ranges between 60% and 90% and varies by the concentration of the bacteria in the CSF, by the type of meningeal pathogen, and by the receipt of previous antibiotic therapy.¹ Most patients with this syndrome are admitted to the hospital and treated empirically with intravenous antibiotic therapy until CSF and blood culture results are negative, even though only a small minority have bacterial meningitis.² In the 1950s, epidemiological studies of aseptic meningitis established a major role for viral etiologies, especially enteroviruses.³ In the past 60 years, case reports have documented a wide array of infectious and noninfectious causes of meningitis because of an increasing immunosuppressed population, discovery of new infectious agents, and improvements in the field of diagnostic microbiology, virology, and neuroradiology.⁴ Physicians recognize that patients with meningitis and a negative Gram stain may have etiologies that require urgent therapy, but they are uncertain of the probability for an adverse clinical outcome (ACO) in an individual patient.^{2,4} Consequently, this dilemma has fostered costly diagnostic testing, unnecessary hospitalization, and empirical antimicrobial therapy for the

majority of the patients.^{2,4,5} The purpose of this observational study was to derive and validate a predictive model for an ACO in adults who present with meningitis and a negative Gram stain.

PATIENTS AND METHODS

Case Definition

A case was defined as an adult patient (age >16 y) with symptoms of community-acquired meningitis (fever, headache, stiff neck, altered mental status, or focal neurologic symptoms), a CSF leukocyte count greater than 5 cells/mm³ (to convert to 10⁹/L, multiply by 1), and a negative CSF Gram stain who presented to an emergency department (ED) between January 1, 2005, and January 1, 2010, at 8 Memorial Hermann Healthcare System hospitals in Houston, Texas, and surrounding areas. The derivation cohort of 292 patients was assembled from adults who presented to Memorial Hermann Texas Medical Center, Katy Hospital, or Memorial City Hospital. This cohort represented a more acutely ill and heterogeneous patient population because of Memorial Hermann's tertiary care referral status. The validation cohort of 275 patients was assembled from adults with meningitis presenting to one of the following Memorial Hermann hospitals that serve as community hospitals: Woodlands, Sugarland, North-

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west, Southwest, and Southeast hospitals. The study was approved by the University of Texas Health in Houston Committee for the Protection of Human Subjects and by the Memorial Hermann Hospital Research Review Committee.

Data Collection, Laboratory Testing, and Definition of Diagnostic Outcomes

Baseline patient characteristics were recorded at a specified “zero time,” defined as the time when the patient was in the ED. Sociodemographic data, comorbid conditions (measured by the Charlson Comorbidity Index⁶), immunocompetence, sick exposures, clinical features (including neurologic examination findings and Glasgow Coma Scale score⁷), laboratory results, and management decisions were recorded. The CSF Gram stains were performed on cytospin samples. Computed tomographic scans of the head and magnetic resonance images (MRI) of the brain were read by board-certified neuroradiology faculty at the various Memorial Hermann hospitals, and findings were classified as abnormal if any intracranial parenchymal abnormality was noted. Cerebral atrophy or concomitant sinusitis was not considered abnormal.

Etiologies were divided into 4 categories: unknown cause, untreatable cause, treatable but not urgent cause, and urgent treatable cause. Etiologies predetermined to represent urgent treatable causes included bacterial, fungal, or mycobacterial meningitis; herpes simplex virus, varicella zoster virus (VZV), or cytomegalovirus (CMV) meningoencephalitis; rickettsial meningoencephalitis; bacteremia; meningeal carcinomatosis; central nervous system vasculitis; parameningeal or intracranial mass le-

sions (eg, tumor, abscess); or intracranial hemorrhage.⁴ The primary study end point was the presence of an ACO. Patients' outcomes were assessed at the time of discharge from the hospital with use of the Glasgow Outcome Scale.⁸ In this scale, a score of 1 indicates death, a score of 2 indicates a vegetative state (inability to interact with the environment), a score of 3 indicates severe disability (unable to live independently but follows commands), a score of 4 indicates moderate disability (unable to return to work or school but able to live independently), and a score of 5 indicates mild or no disability (able to return to work or school). An ACO was defined as a Glasgow Outcome Scale score of 1 to 4.

Statistical Analyses

After a complete descriptive comparison of derivation and validation cohorts, baseline characteristics having a clinically plausible association with an ACO were examined in bivariate analysis. As a variable reduction strategy, only clinically cogent baseline variables showing a bivariate association ($P < .05$) were entered into a logistic regression model to verify independent associations with an ACO. Using the variables from the logistic regression analyses, we developed a predictive model that classified the patients into 2 levels of risk (low and high) for an ACO.

The Fisher exact test, χ^2 test, and t test were used in the bivariate analyses. To avoid overfitting in the regression modeling, no more than one variable was entered per 6 outcome events.⁹ Goodness-of-fit of the predictive model was determined using the Hosmer-Lemeshow test. Model calibration was assessed by comparing predicted and observed outcome rates in both cohorts, and the prediction accuracy was calculated using the concordance index (c-index).¹⁰ The model validity was tested in the validation sample. We used a complete case analysis with covariate adjustment to address missing data.¹¹

RESULTS

Cohort Assembly

After screening 747 patients with meningitis, we excluded 180 patients for the following reasons: positive Gram stain for yeast (61 patients) or bacteria (32 patients); presence of a ventricular peritoneal shunt (24 patients) or postcraniotomy meningitis (17 patients); patient received oral antibiotics before lumbar puncture, was treated with intravenous antibiotics for more than 48 hours, and had no identifiable etiology (32 patients); and incomplete medical records (14 patients). Therefore, a total of 567 patients were enrolled and divided into derivation (292 patients) and validation (275 patients) cohorts (Figure).

TABLE 1. Baseline Characteristics, Laboratory Results, and Follow-up of 567 Adults With Meningitis and a Negative Gram Stain^{a,b,c}

Variable	Derivation cohort (N=292) ^d	Validation cohort (N=275) ^d	P value ^e
Age (y)	37 (18-92)	35 (18-89)	.06
Female	154 (53)	158 (57)	.26
Race			.54
White	138 (47)	127 (46)	
African American	78 (27)	68 (25)	
Hispanic	66 (23)	73 (27)	
Asian	10 (3)	7 (3)	
Uninsured	84 (29)	90 (33)	.31
Coexisting medical conditions			
Charlson Comorbidity Index score >1	41 (14)	29 (11)	.20
Immunocompetence			
Immunosuppressed	32 (11)	30 (11)	.98
HIV/AIDS	23 (8)	21 (8)	.92
History of injection drug use	10 (3)	3 (1)	.06
Season			.69
Summer (June-August)	92 (32)	88 (32)	
Fall (September-November)	73 (25)	79 (29)	
Winter (December-February)	54 (18)	48 (17)	
Spring (March-May)	73 (25)	60 (22)	
Presenting history			
Headache	254 (87)	256 (93)	.01
Fever	191 (65)	172 (63)	.48
Stiff neck	136 (47)	110 (40)	.11
Photophobia	112 (38)	168 (61)	<.001
Respiratory symptoms	46 (16)	17 (6)	<.001
Seizure within 1 wk of presentation	19 (7)	6 (2)	.01
Duration of illness (d)	3 (1-30)	3 (0-30)	.08
Presenting signs			
Temperature >39°C	92 (32)	78 (28)	.41
Nuchal rigidity	79 (27)	81 (29)	.53
Reduced level of consciousness ^f	84 (29)	22 (8)	<.001
Focal neurologic deficits ^g	26 (9)	31 (11)	.35
Vesicular or petechial rash	7 (2)	3 (1)	.23
Laboratory results			
Serum leukocyte count (cells/ μ L)	8700 (1100-43,500)	8800 (900-42,000)	.43
CSF leukocyte count (cells/ μ L)	160 (6-44,040)	149 (6-21,000)	.94
CSF protein (mg/dL)	82 (22-706)	75 (18-659)	.13
CSF glucose (mg/dL)	57 (1-421)	56 (5-366)	.98
CSF ANC >500 cells/ μ L ^h	136 (47)	106 (39)	.36
CSF leukocyte count >1000 cells/ μ L	25 (9)	18 (7)	.58
Management decision			
Admission to the hospital	280 (96)	266 (97)	.60
Duration of hospitalization (d)	3 (0-47)	3 (1-35)	.14
Empirical antibiotic therapy	202 (69)	213 (77)	.03
Duration of antibiotic therapy (d)	2 (0-45)	2 (0-42)	.06

Continued on next page

TABLE 1. Continued

Variable	Derivation cohort (N=292) ^d	Validation cohort (N=275) ^d	P value ^e
Management decision, continued			
Empirical acyclovir therapy	88 (30)	67 (24)	.12
Head CT	258 (88)	254 (92)	.10
Abnormal ⁱ	22 (9)	14 (6)	.23
Brain MRI	129 (44)	99 (36)	.05
Abnormal ⁱ	47 (36)	30 (30)	.07
Clinical status at discharge			
Normal	249 (85)	258 (94)	<.001
Adverse clinical outcome ^k	43 (15)	17 (6)	<.001
Unknown etiology	205 (70)	202 (73)	.39

^aANC = absolute neutrophil count; CMV = cytomegalovirus; CSF = cerebrospinal fluid; CT = computed tomography; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; VZV = varicella zoster virus.

^bData are presented as number (percentage) or median (range).

^cSI conversion factors: To convert CSF protein to mg/L, multiply by 10; to convert CSF ANC to 10⁹/L, multiply by 0.001; to convert serum leukocyte count to 10⁹/L, multiply by 0.001; to convert CSF glucose to mmol/L, multiply by 0.05551.

^dMissing data were analyzed as a complete case analysis.

^eP value comparing derivation and validation cohorts.

^fDisorientation or Glasgow Coma Scale score <15.

^gFocal motor deficit, cranial nerve abnormality, or aphasia.

^hCSF ANC was calculated as the multiplication of the CSF leukocyte count and the neutrophilic percentage of the CSF differential.

ⁱFocal (ie, mass lesions, strokes, or bleeds) or nonfocal (ie, hydrocephalus, white matter changes) intracranial abnormalities.

^jMass lesions, strokes, hypodensities, meningeal enhancement, bleeds, white matter abnormalities.

^kGlasgow Outcome Scale score of 1-4.⁹ In the derivation cohort, 5 patients had a score of 1 (death), 20 had a score of 3 (severe disability), and 18 had a score of 4 (moderate disability). In the validation cohort, 2 patients had a score of 1 (death), 1 had a score of 2 (vegetative state), 11 had a score of 3 (severe disability), and 3 had a score of 4 (moderate disability). A total of 7 patients died: 2 from encephalitis of unknown etiology and 1 each from methicillin-sensitive *Staphylococcus aureus* bacteremia and meningitis, CMV encephalitis, VZV encephalitis, central nervous system lymphoma, and *Mycobacterium tuberculosis* meningitis.

Baseline Features and Laboratory Findings

Baseline sociodemographic characteristics, comorbidities, clinical and laboratory findings, and follow-up data are shown in Table 1. The derivation and validation cohorts were similar with respect to age, sex, race, comorbidities, immunocompetence, season of presentation, fever, and stiff neck, but they had several important statistically significant differences. The derivation cohort had higher rates of sicker patients with more reduced levels of consciousness ($P<.001$) and seizures ($P=.01$), more patients who underwent MRI ($P=.05$), and more ACOs ($P<.001$). The validation cohort had a higher proportion of patients with headache ($P=.01$), photophobia ($P<.001$), and empirical antibiotic therapy ($P=.03$).

The total cohort consisted primarily of young adults (median age, 36 years); 312 patients (55%) were female, and 265 (47%) were white. Most patients presented during the summer and fall months, but 235 patients (41%) presented from December to May. Comorbidity, defined as a Charlson score of more than 1, was present in 70 patients (12%), and 44 patients (8%) had human immuno-

deficiency virus; 13 (2%) had a history of intravenous drug use. Most patients presented with headache (510 [90%]), fever (363 [64%]), photophobia (280 [49%]), and stiff neck (246 [44%]); 57 patients (10%) had a focal neurologic examination, and 25 patients (4%) had a seizure within 1 week before arrival at the ED. A minority of patients demonstrated reduced level of consciousness (106 [19%]), a positive Kernig or Brudzinski sign (28 [5%]), or a vesicular or petechial rash (10 [2%]). The median CSF leukocyte count was greater than 0.5×10^6 cells/L with a range of 6 to 44,040 cells/ μ L; the median CSF protein level was 78 mg/dL (to convert to mg/dL, multiply by 10) (range, 18-706 mg/dL); and the median CSF glucose level was 57 mg/dL, 3.1635 mmol/L (to convert to mmol/L, multiply by 0.05551) (range, 1-421 mg/dL, 0.0555-23.3655 mmol/L).

Management, Clinical Outcome, and Etiology

Most patients (546 [96%]) were admitted to the hospital for a median duration of 3 days (range, 0-47 days), and 413 (73%) received empirical antibiotic therapy while physicians awaited culture results (median duration of antibiotic therapy was 2 days);

155 patients (27%) also received empirical intravenous antiviral therapy with acyclovir (Table 1). Head computed tomography was performed in 512 patients (90%) as part of their initial evaluation in the ED, only 36 (7%) of whom had abnormal findings. Additionally, 228 patients (40%) also underwent MRI of the brain, 77 (34%) of whom had abnormal findings. Follow-up information at discharge was available for all patients. Although most of the patients (507 [89%]) had no residual neurologic morbidity, 60 patients (11%) had an ACO (persistent moderate or severe disability in 53 patients and death in 7). Causes of death were encephalitis of unknown etiology (2 patients), methicillin-sensitive *Staphylococcus aureus* bacteremia and meningitis (1), CMV encephalitis (1), VZV encephalitis (1), central nervous system lymphoma (1), and *Mycobacterium tuberculosis* meningitis (1).

The cause of the meningitis was identified in 159 (28%) of the 567 patients in the total cohort. An urgent treatable cause was identified in 74 patients (13%), including bacterial meningitis, *Cryptococcus neoformans* meningitis, VZV, herpes simplex virus, or CMV encephalitis, toxoplasmosis, tuberculosis, brain tumors, neurocysticercosis, and other miscellaneous conditions. Untreatable conditions (enterovirus, Epstein-Barr virus, West Nile virus, or St Louis encephalitis virus) were identified in 44 patients (8%). Forty-one patients (7%) had a nonurgent treatable etiology, which included Mollaret meningitis, neurosyphilis, multiple sclerosis, human immunodeficiency virus seroconversion, and influenza virus type A. No cause was identified in 407 patients (72%) (Table 2.)

Development and Validation of Risk Classification for an ACO

The following variables were associated with an ACO in bivariate analyses in the derivation cohort: a CSF protein level greater than 100 mg/dL, fever, serum leukocyte count greater than 12,000 cells/ μ L (to convert to $\times 10^9$ /L, multiply by 0.001), abnormal neurologic examination findings (altered mental status, focal neurologic examination, or seizures), a CSF glucose level less than 45 mg/dL, comorbidity, and age greater than 60 years (Table 3). All variables with a bivariate association ($P < .05$) with the outcome were entered into the logistic regression. As shown in Table 4, age greater than 60 years, a CSF glucose level less than 45 mg/dL, and abnormal neurologic examination findings were all independently associated with an ACO ($P < .05$).

Using these 3 variables (age > 60 years, a CSF glucose level < 45 mg/dL, and abnormal neurologic examination findings), we developed a predictive model that classified patients into 2 levels of risk for an ACO: low (0 variables) and high (≥ 1 variables).

TABLE 2. Etiologies and Outcomes in 567 Patients With Meningitis and a Negative Cerebrospinal Fluid Gram Stain^a

Etiology	No. (%) of patients	No. (%) of adverse clinical outcomes ^b
Unknown	408 (72)	19 (5)
Urgent treatable	74 (13)	27 (36)
Bacterial meningitis ^c	22	
<i>Cryptococcus neoformans</i>	14	
Herpes simplex virus encephalitis	13	
Varicella zoster virus	5	
<i>Mycobacterium tuberculosis</i>	5	
CNS lymphoma/carcinomatosis	3	
CNS vasculitis	3	
<i>Escherichia coli</i> urosepsis	1	
<i>Toxoplasma gondii</i>	1	
Brain abscess	1	
Cytomegalovirus encephalitis	1	
Rubella encephalitis	1	
Histoplasmosis	1	
Subarachnoid bleed	1	
Epidural abscess	1	
Infective endocarditis	1	
Untreatable	44 (8)	14 (32)
West Nile virus	29	
Enterovirus	11	
St Louis encephalitis virus	3	
Epstein-Barr virus	1	
Nonurgent treatable	41 (7)	0 (0)
Mollaret meningitis	34	
Acute HIV	3	
Neurosyphilis	1	
Multiple sclerosis	1	
Influenza virus type A	1	
Infectious mononucleosis due to cytomegalovirus	1	

^aCNS = central nervous system; CSF = cerebrospinal fluid; HIV = human immunodeficiency virus.

^bGlasgow Outcome Scale score from 1-4.⁹

^cFourteen organisms were identified by positive CSF cultures: *Streptococcus pneumoniae* (6), methicillin-susceptible *Staphylococcus aureus* (1), *Streptococcus agalactiae* (2), *Haemophilus influenzae* (2), *Enterococcus* (2), and *Listeria monocytogenes* (1). Thirteen organisms were identified by positive blood cultures: *S pneumoniae* (6), methicillin-susceptible *S aureus* (1), methicillin-resistant *S aureus* (1), *S agalactiae* (2), α -hemolytic streptococcus (1), *Streptococcus pyogenes* (1), and *L monocytogenes* (1). Some patients had positive results on both CSF and blood cultures.

As shown for the derivation cohort in Table 5, 1 patient (0.6%) in the low-risk and 42 (32.8%) in the high-risk subgroup had an ACO. In the validation cohort, 1 patient (0.5%) in the low-risk and 16 (21.1%) in the high-risk subgroup had an ACO. Calculation of model discrimination with use of the

TABLE 3. Baseline Variables Associated With an Adverse Clinical Outcome^a in 292 Adults With Meningitis and a Negative Gram Stain (Derivation Cohort)^{b,c}

Variable	No. of patients	No. of ACOs	Odds ratio (95% CI)	P value ^d
CSF protein >100 mg/dL	114	27	1.75 (1.17-2.61)	<.001
CSF ANC >500 cells/ μ L ^e	136	20	1.00 (0.52-1.92)	.99
Fever ^f	92	25	3.93 (2.0-7.73)	<.001
Serum leukocyte count >12,000/ μ L	81	20	2.68 (1.38-5.21)	.003
Abnormal neurologic examination ^g	93	38	6.70 (2.93-15.31)	<.001
CSF glucose <45 mg/dL	44	15	4.06 (1.95-8.49)	<.001
Comorbidity ^h	41	16	1.43 (1.13-1.81)	<.001
Age >60 y	34	17	8.92 (4.07-19.56)	<.001

^aGlasgow Outcome Scale score of 1-4^g (1, 5 patients; 3, 20 patients; 4, 18 patients).

^bACO = adverse clinical outcome; ANC = absolute neutrophil count; CSF = cerebrospinal fluid.

^cSI conversion factors: To convert CSF protein to mg/L, multiply by 10; to convert CSF ANC to 10⁹/L, multiply by 0.001; to convert serum leukocyte count to 10⁹/L, multiply by 0.001; to convert CSF glucose to mmol/L, multiply by 0.05551.

^dP<.05 was considered statistically significant.

^eCSF ANC was calculated as the multiplication of the CSF leukocyte count by the neutrophilic percentage of the CSF differential.

^fTemperature >38.4°C or <35°C.

^gDisorientation or Glasgow Coma Scale score <15, focal neurologic deficits, or seizures.

^hCharlson Comorbidity Index score >1.

concordance index was 0.91 for the derivation cohort and 0.93 for the validation cohort. The χ^2 test for linear trend comparing the observed proportion of patients with an ACO between risk groups for both the derivation and validation groups was significant ($P<.001$).

DISCUSSION

Meningitis most commonly presents with a negative Gram stain (654 of the 747 patients screened for this study [88%]), and although it is often considered an enteroviral meningitis with a benign clinical outcome, it presents a diagnostic challenge to physicians because of its broad differential diagnosis that includes some etiologies requiring urgent therapy for cure and survival. Furthermore, up to 11% of cases have serious associated neurologic morbidity

or mortality. Accurate prediction of the likelihood of an ACO in patients with this syndrome could aid ED physicians in identifying those at high risk who need urgent empirical antimicrobial therapy. To our knowledge, this is the first study to evaluate risk factors for an ACO in adults with meningitis and a negative Gram stain. Other large studies that have included patients with meningitis and a negative Gram stain have focused on describing the clinical epidemiology or developing and validating models to differentiate viral vs bacterial meningitis but have not evaluated patient outcomes.^{2,3,5,12-16} In our study, 3 clinically cogent and easily obtainable baseline variables (age >60 years, a CSF glucose level <45 mg/dL, and abnormal neurologic examination findings) were used to derive and validate a model that classifies patients into low and high risk for an ACO. Our low-

TABLE 4. Variables Independently Associated With an Adverse Clinical Outcome^a in 292 Adult Patients With Meningitis and a Negative Gram Stain (Derivation Sample)

Variable	Adjusted odds ratio	95% CI	P value ^b
Abnormal neurologic examination ^c	17.66	5.76-54.10	<.001
Cerebrospinal fluid glucose <45 mg/dL ^d	6.80	2.36-19.56	<.001
Age >60 y	7.56	1.46-10.66	<.001

^aGlasgow Outcome Scale score of 1-4^g.

^bP<.05 was considered statistically significant.

^cDisorientation or Glasgow Coma Scale score <15, focal neurologic deficits, or seizures.

^dTo convert to mmol/L, multiply by 0.05551.

risk group had a 0.5% risk of an ACO and represented the majority of our cohort (64%).

Many features of our cohort were similar to those in previous studies of meningitis and a negative Gram stain: the predominance of young adults, clinical features, CSF findings, and the high proportion of hospitalization, cranial imaging, and empirical antibiotic use.^{2-5,12-16} However, there were several noteworthy observations in our study. First, the differential diagnosis of the meningitis causes was broad, and because a large proportion of the patients were immunosuppressed, one of the most commonly recognized urgent treatable causes was *C neoformans*. Second, most patients were hospitalized (96%) and received empirical intravenous antibiotic therapy (73%), even though only a minority of patients (4%) had bacterial meningitis. Third, the majority underwent cranial imaging (90%) and had normal results, despite the fact that only a minority of patients met imaging criteria.^{1,17} Fourth, despite extensive diagnostic testing with current techniques, most of the patients (72%) had an unknown etiology.

In developing a predictive model for an ACO in adults with meningitis and a negative Gram stain, our study provided several advantages. Data for all variables were collected at a specified “zero time” (on initial presentation to the ED). Our predictive model is practical because it was derived from variables easily available to the clinician in the ED. Our outcome definition was based on a well-characterized outcome scale that has been used previously in studies of bacterial meningitis.⁴ To reduce the hazards of multiple statistical contrasts, bivariate analysis emphasized only clinically plausible variables, and the inclusion of a limited number of variables allowed us to avoid hazards of overfitting in multivariate analysis.^{10,11} Finally, we tested the prediction accuracy of the model in a large independent validation cohort comprising a different patient population from community hospitals in the Houston area.

Despite its methodological advantages, our study has some limitations. Although CSF bacterial culture was obtained in most of the 544 patients (96%), only 262 patients (46%) had polymerase chain reaction tests on the CSF for herpes viruses and 104 (18%) for enteroviruses. Furthermore, because this study was retrospective in design, diagnostic testing was at the discretion of the treating physician, and missing data were inevitable. Although we included most patients who received oral antibiotics within 2 weeks of presentation, we excluded a total of 32 patients who received oral antibiotics before lumbar puncture, were treated with intravenous antibiotics for more than 48 hours, and had no identifiable etiology. This was done to avoid

TABLE 5. Risk Classification for an Adverse Clinical Outcome in Adults With Meningitis and a Negative Gram Stain ($P < .001^a$)

Risk group	No. of variables ^b	No. of patients	No. (%) of adverse clinical outcomes ^c
Derivation sample (N=292)			
Low	0	164	1 (0.6)
High	≥ 1	128	42 (32.8)
Validation sample (N=275)			
Low	0	199	1 (0.5)
High	≥ 1	76	16 (21.1)

^a χ^2 test for linear trend comparing observed proportion of patients with an adverse clinical outcome between risk groups for both derivation and validation groups. C-index = 0.91 for derivation cohort and 0.93 for validation cohort.

^b Variables: age >60 y, abnormal neurologic examination (altered mental status, focal neurologic examination, or seizures), and cerebrospinal fluid glucose level <45 mg/dL (to convert to mmol/L, multiply by 0.05551).

^c Glasgow Outcome Scale score of 1-4.⁹

misclassification bias because such patients could have had bacterial meningitis that was partially treated with oral antibiotics and cured with more than 48 hours of intravenous antibiotic therapy and yet been misclassified as not having an urgent treatable cause. Our clinical model was derived and validated in the Houston area only, and our results should be confirmed in other populations before the model can be generalized to other geographic areas. A few cases that presented as meningitis were discovered after the ED evaluation to not be meningitis (eg, vasculitis, lymphoma, bleed, abscess). This is part of the challenging aspect of this disorder because it can mimic other conditions that require urgent recognition and treatment. Lastly, most of the patients (408 [72%]) had unknown causes of their meningitis. This is the frustrating reality of this syndrome, and we hope that novel molecular tools and standardized diagnostic algorithms can improve our current understanding.

CONCLUSION

Meningitis with a negative CSF Gram stain has a wide differential diagnosis, with some etiologies associated with ACOs. Accurate prediction of patients at higher risk for an ACO could aid physicians in the ED with management decisions. The findings in our study suggest that adults with meningitis and a negative CSF Gram stain can be accurately stratified for the risk of an ACO using clinical variables available at presentation. Further studies should focus on assessing newer diagnostic techniques to increase diagnostic yield, validating this model in other geographic areas, and evaluating the impact of evidence-based guidelines

on reducing the cost of this common clinical dilemma.

ACKNOWLEDGMENTS

All the authors contributed equally to this work: Drs Wootton and Hasbun developed the study, obtained funding, and wrote the manuscript; Drs Khoury and Salazar enrolled the patients in the study; and Dr Hossain performed the statistical analyses.

Abbreviations and Acronyms: ACO = adverse clinical outcome; CMV = cytomegalovirus; CSF = cerebrospinal fluid; ED = emergency department; MRI = magnetic resonance imaging; VZV = varicella zoster virus

Grant Support: This work was supported by grant NIH-1 K23 RR018929-01A2 from the National Center for Research Resources (R.H.); a grant from Grant-A-Starr Foundation (S.H.W.); and by the Center for Clinical and Translational Sciences at The University of Texas Health Science Center at Houston (UL1 RR024148).

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