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A Risk Classification Model to Predict Mortality Among Laboratory-Confirmed Avian Influenza A H7N9 Patients: A Population-Based Observational Cohort Study

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Background. Avian influenza A H7N9 (A/H7N9) is characterized by rapid progressive pneumonia and respiratory failure. Mortality among laboratory-confirmed cases is above 30%; however, the clinical course of disease is variable and patients at high risk for death are not well characterized.

Methods. We obtained demographic, clinical, and laboratory information on all A/H7N9 patients in Zhejiang province from China Centers for Disease Control and Prevention electronic databases. Risk factors for death were identified using logistic regression and a risk score was created using regression coefficients from multivariable models. We externally validated this score in an independent cohort from Jiangsu province.

Results. Among 305 A/H7N9 patients, 115 (37.7%) died. Four independent predictors of death were identified: older age, diabetes, bilateral lung infection, and neutrophil percentage. We constructed a score with 0–13 points. Mortality rates in low- (0–3), medium- (4–6), and high-risk (7–13) groups were 4.6%, 32.1%, and 62.7% ($P_{trend} < .0001$). In a validation cohort of 111 A/H7N9 patients, 61 (55%) died. Mortality rates in low-, medium-, and high-risk groups were 35.5%, 55.8, and 67.4% ($P_{trend} = .0063$).

Conclusions. We developed and validated a simple-to-use, predictive risk score for clinical use, identifying patients at high mortality risk.

Keywords. H7N9 infection; risk score; mortality; influenza.

Avian influenza A H7N9 (A/H7N9) virus first emerged in humans in early 2013 and over 1500 people have since acquired the infection from 5 epidemic waves [1–3]. The clinical course of the disease is characterized by rapidly progressive pneumonia and respiratory failure leading to mortality rates above 30% [4]. Although human-to-human transmission is rare [5, 6], the pandemic potential of A/H7N9 is concerning. In 2017, the Centers for Disease Control and Prevention (CDC) identified A/H7N9 virus as the greatest potential risk for sustained human-to-human transmission and danger to global public health of all influenza A viruses [7, 8].

Despite the high observed mortality seen among A/H7N9 patients, few studies have attempted to classify patients at elevated risk of death. Most reports investigating risk factors for mortality have had small sample sizes or included few patient characteristics or predictors [9–14]. How well predictors of mortality are applicable to the broader epidemic is unknown. In addition, previous studies have not included independent validation cohorts to confirm their results, an important step before any clinical prediction rule can be adopted in clinical practice.

We report on a large cohort of laboratory-confirmed A/H7N9 patients in Zhejiang province in eastern China with detailed epidemiological and clinical characteristics. We aimed to investigate risk factors for death in these patients and develop a clinical prediction risk classification model that may be clinically useful to identify and prioritize patients at greatest probability of death. We then tested the performance of this model to predict mortality in an independent cohort of laboratory-confirmed A/H7N9 patients from Jiangsu province.

METHODS

Study Participants and Data Collection

In April 2013, during the first wave of cases of the A/H7N9 epidemic, enhanced surveillance of A/H7N9 was put into effect as part of the Chinese sentinel surveillance system. Hospitalized patients with pneumonia and/or influenza-like symptoms and

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reported poultry exposure were classified as suspected A/H7N9 cases. Respiratory specimens were collected from all suspected A/H7N9 patients and demographic and clinical questionnaires were administered to all patients and accompanying family members using standardized forms. Epidemiologic data were collected through interviews and field observations by local, provincial, and national CDC field teams within 1 day of patients being classified as suspected A/H7N9 cases. Virological A/H7N9 confirmation of suspected patients was not required prior to field and patient data collection. All information was reported to the China CDC. HIV/AIDS screening was routine clinical practice for the hospitalized patients included in our study. None of the laboratory-confirmed H7N9 patients was infected with HIV.

Derivation Cohort—A/H7N9 Patients From Zhejiang Province

The derivation cohort included all laboratory-confirmed cases of A/H7N9 infection reported to the China Information System for Disease Control and Prevention in Zhejiang province [15]. The location of participants with laboratory-confirmed A/H7N9 was geospatially mapped and displayed based on their subsequent mortality. A standardized questionnaire was used to collect information on demographics, exposure history, clinical symptoms, and relevant dates in the disease process. For exposure history, we interviewed cases regarding activities such as visiting live poultry markets, intrahousehold poultry raising, occupational exposure, and direct contact with diseased or deceased poultry within 2 weeks of clinical onset. Patients were also asked about prior diagnoses of noncommunicable diseases such as chronic pulmonary disease (bronchiectasis, chronic obstructive pulmonary disease, and asthma), cardiovascular disease (hyperlipemia, coronary heart disease, hemorrhagic stroke, and ischemic stroke), and other conditions including hypertension, diabetes, gout, cancer/tumor, rheumatoid arthritis, and tuberculosis. These patient responses were validated with electronic medical records and interviewing clinicians who provided medical care for H7N9 patients. Chronic drug use was also recorded, that is long term drug use for a medical condition not illicit drug addiction. A timeline of disease and health care related processes for each patient was constructed. For all patients, we collected dates of onset of the illness, first visit to a medical care facility, hospitalization, antivirus treatment initiation, and confirmatory laboratory test results.

Clinical characteristics were recorded from physical examinations at initial clinical presentation by a pulmonary physician. In addition, whether the patient was infected in unilateral or bilateral lungs was recorded. Patients first presented with A/H7N9 at various levels of medical units. We defined the primary medical unit level as patients that presented to village, community, or private clinics; secondary medical level as those presenting to county or prefecture medical hospitals; and tertiary level as those presenting to provincial hospitals.

Validation Cohort—A/H7N9 Patients From Jiangsu Province

External validation was performed in an independent cohort of laboratory-confirmed A/H7N9 patients from Jiangsu province. This cohort has been described previously [9]. Briefly, similar to data collection for the derivation cohort, we collected patient information from the China Information System for Disease Control and Prevention. We limited our data collection on this cohort to geospatial data, disease-specific mortality, and variables included in the derived risk score.

Laboratory Diagnostic Procedures

RNA was extracted from throat specimens with the QIAamp Viral RNA Mini Kit (Qiagen, Valencia, CA). These specimens were examined using a specific real-time reverse transcription polymerase chain reaction (RT-PCR) with primers and probes specific to H7N9. RT-PCR tests were performed in biosafety level 3 facilities at provincial and national CDC laboratories. Suspected A/H7N9 patients testing negative for 3 consecutive days were considered disease free and were no longer examined.

Other laboratory examinations included measurement of white blood count, neutrophil percentage, lymphocyte percentage, body temperature, and levels of C-reactive protein. Neutrophil and lymphocyte percentages represent the proportion of white blood cells that are neutrophils or lymphocytes in each patient. These measurements were taken at several points throughout the disease process starting when patients were first suspected of A/H7N9. Because we aimed to predict mortality, we used laboratory measurements taken during the first clinical visit (ie, timing furthest from death).

Statistical Analysis

We summarized continuous variables as medians with interquartile ranges (IQR) and categorical variables using proportions. Mortality rates were estimated using standard contingency tables and then stratified by demographic, clinical, and laboratory-specific characteristics. Variables were initially analyzed as both continuous and categorical variables, but categorization was kept in multivariable analyses to optimize the score's use in a clinical setting. Neutrophil percentages were categorized into quartiles of the study population. We evaluated correlations among variables using polychoric correlation coefficients. Statistical significance was determined by confidence intervals (CI) and 2-sided P values less than .05. Proportions were compared with Pearson χ^2 statistics, Fisher exact test, or an unpaired Z test as appropriate.

Due to the acute nature of A/H7N9 infection, a binary logistic regression model was used to evaluate risk factors and calculate odds ratios (ORs) in univariable analyses. Variables suggestive of an association with patient mortality ($P < .2$) were considered candidate variables in multivariable model building. These variables were included in multivariable analyses in a forward selection process; variable selection was informed by the Akaike information criterion.

We followed previously published recommendations for developing predictive risk scores [16, 17]. Briefly, we computed how far each subcategory of a risk factor was from the base category for each predictor variable in the multivariable analysis and derived a constant for the points system relating to the number of regression units corresponding to 1 point. We then assigned a point score based on a transformation of corresponding β regression coefficients. The subsequent score was rounded to the nearest integer for clinical and programmatic practicality. We then calculated a risk score for each patient. The study population was categorized into 3 groups based on their subsequent mortality risk (low, medium, and high risk).

We tested the score's performance in the derivation cohort in 3 distinct techniques. First, we tested the score's performance using participants with complete data on all variables included in the score. Second, we used simulation-based methods to impute missing data. We assumed the data were missing at random and used a chained equations approach containing 5 imputed datasets [18]. We used all other relevant covariates as predictors to impute missing values. Results from all imputed datasets were merged using guidelines outlined by Rubin [19, 20]. Lastly, using all participants, we assumed all missing values equated to the absence of the risk factor. This is a conservative approach that would underestimate performance by biasing the association between mortality and risk factors towards the null.

To externally validate the model, we used a cohort of A/H7N9 patients from Jiangsu province with complete data from variables in the derived risk score. We added point totals to each patient and classified low-, medium-, and high-risk groups as described above. To test the score's performance, we compared mortality among patients in low-, medium-, and high-risk groups and calculated C-statistics and the Hosmer-Lemeshow statistic for each model [21]. We also compared the proportional difference in predicted mortality from high- and low-risk groups [16]. Cochran-Armitage tests were used to test for trends in mortality from increasing number of points and classification categories.

We conducted several sensitivity analyses including using genetic algorithm approaches for variable selection and fast-and-frugal decision trees to test the robustness of our results. Further information on methods and results of this analysis can be found in the Supplementary material.

Ethical Considerations

The National Health and Family Planning Commission determined that the collection of data from A/H7N9 case patients was part of a continuing public health investigation of an outbreak and was exempt from institutional review.

RESULTS

Patient Demographic and Clinical Characteristics

The study included 305 laboratory-confirmed influenza A/H7N9 patients from Zhejiang province (Figure 1). Patients were diagnosed in 10 prefecture cities (Lishui, Taizhou, Jiaxing, Ningbo, Hangzhou, Wenzhou, Huzhou, Shaoxing, Quzhou, and Jinhua). Most patients were from wave 2 (N = 94, 31%) and wave 5 (N = 87, 29%). Median patient age was 59 years (IQR, 49–68), 64% were male, and 51% resided in urban areas. Eight in 10 patients were administered antiviral treatment (Table 1). The median neutrophil percentage was 78 (IQR, 71–85).

Underlying medical conditions were common; 63% had at least 1 while 30% had 2 or more. Over 90% of patients were treated in a primary- or secondary-level medical unit. Poultry exposure was ubiquitous; 93% had some poultry exposure while 69% recently visited a live poultry market. Only 18 (6%) patients were poultry workers.

Mortality Analysis and Development of Predictive Risk Score

Overall, 115 (37.7%) A/H7N9 patients died (Table 2). In univariable analysis, older age was an important risk factor (OR, 1.06; 95% CI, 1.04–1.08 per additional year); 73.2% of patients aged ≥75 died (OR, 17.39; 95% CI, 6.29–48.04). Clinical risk factors for death included diabetes (OR, 1.84; 95% CI, 1.01–3.35) and having any comorbidity (OR, 1.73; 95% CI, 1.03–2.91). Patients with bilateral lung infections, fever, and chronic drug use were also more likely to die. Neutrophil and lymphocyte percentage were both associated with death. Antiviral treatment initiation or the timing of treatment was not associated with mortality (Table 2).

In multivariable analyses, 4 variables (older age, diabetes, bilateral lung infection, and neutrophil percentage) continued to predict death (Table 3). Compared to those <45 years old, patients between ≥55 and <65 years (adjusted OR [aOR], 6.21; 95% CI, 1.59–24.23), ≥65 and <75 years (aOR, 5.80; 95% CI, 1.44–23.26), and ≥75 years (aOR, 24.76; 95% CI, 5.53–10.82) were all at increased mortality risk. Mortality was also associated with diabetes (aOR, 2.81; 95% CI, 1.19–6.61), bilateral lung infection (aOR, 3.85; 95% CI, 1.34–11.06), and neutrophil percentage (compared to a <70% reference group, aOR, 3.15; 95% CI, 1.09–9.12 in those between 79% and 86%; aOR, 4.99; 95% CI, 1.71–14.60 in those above 86%).

When assigning a point score, patient age between ≥45 and <65 years old was assigned 3 points while those ≥75 years old were assigned 6 points. Diabetes, bilateral lung infection, and a neutrophil percentage between ≥79.0 and <86.0 were given 2 points. Patients with a neutrophil percentage ≥86.0 were assigned 3 points. The score ranged from 0 to 13 and mortality rates increased with higher score (P_{trend} < .0001). After grouping patients into low- (0–3 points), medium- (4–6 points), and high-risk (7–13 points) classification groups (Figure 2), most deaths (60/115) occurred in the high-risk group. Mortality rates were 4.6%, 32.1%, and 62.7% in low-, medium-, and high-risk groups, respectively (P_{trend} < .0001). This trend persisted when using multiple imputation (12.5%, 34.3%, and 56.9%; P_{trend} < .0001) or a conservative analytical

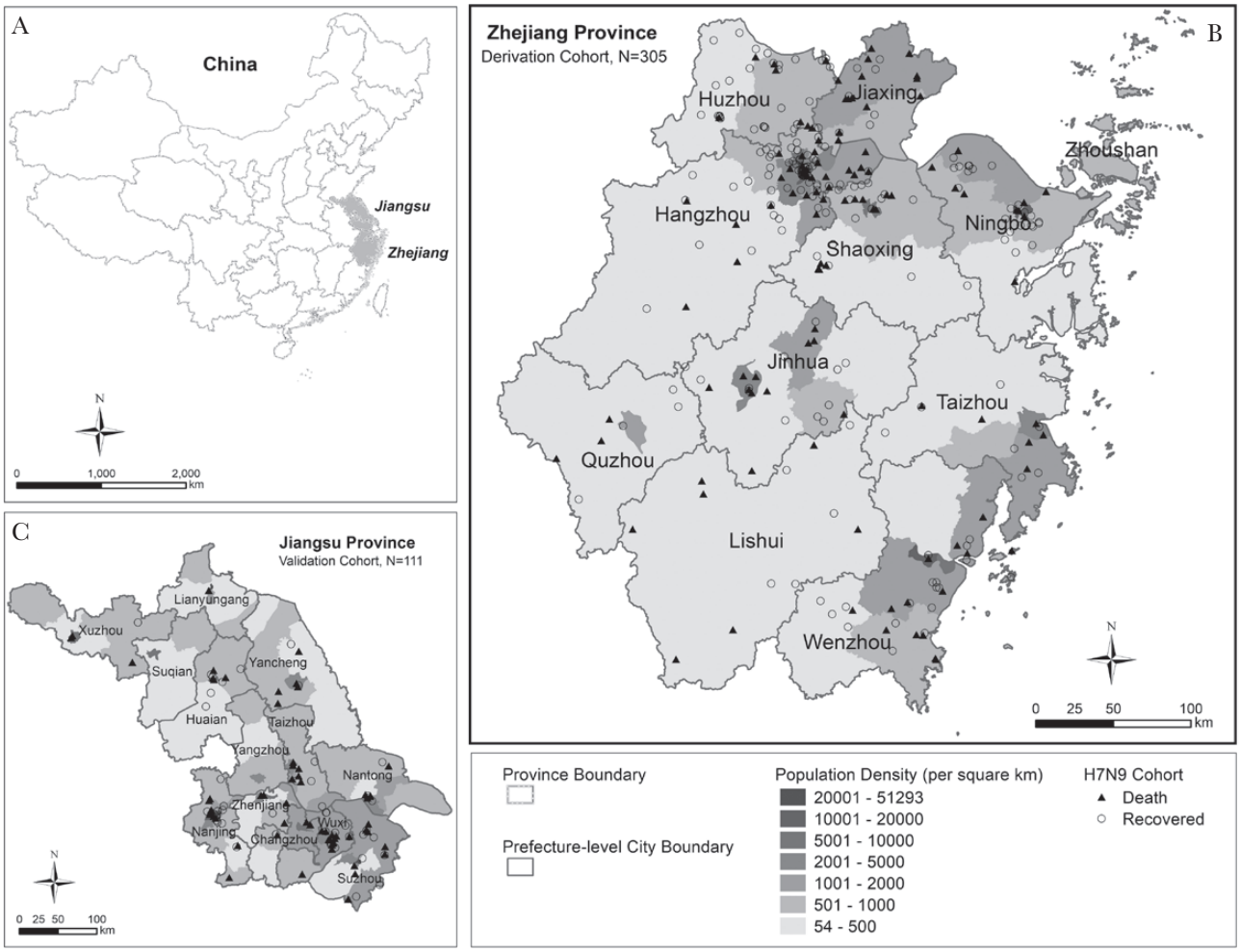

Figure 1. Geospatial coordinates of patients with laboratory-confirmed diagnoses of influenza A/H7N9 infection from 2 cohorts from Zhejiang and Jiangsu Province, eastern China (*A*), shown in grey. *B*, Geographical distribution of participants from the derivation cohort in Zhejiang province. *C*, Geographical distribution of participants from the validation cohort in Jiangsu province. Blue (recovered) and red (death) dots indicate final health status.

approach (20.5%, 33.3%, and 61.9%; $P_{trend} < .0001$), although the trend was less pronounced with an increased proportion of deaths in the low-risk group. The absolute difference in probability of death between high- and low-risk groups was 0.58 in the cohort with complete data, 0.44 using multiple imputation, and 0.41 using a conservative approach. The C-statistic was 0.79 (95% CI, 0.72–0.85), 0.73 (95% CI, 0.68–0.79), and 0.73 (95% CI, 0.67–0.78) when using complete data, multiple imputation, and a conservative approach, respectively (Figure 2). The Hosmer-Lemeshow X^2 statistic of the full model was 8.45 ($P = .5848$).

Independent Validation Cohort

In Jiangsu province, 111 laboratory-confirmed A/H7N9 patients were identified with complete information (Figure 1). Of these, 61 (55%) patients died. When the derived risk score was applied, mortality rates increased with increasing score ($P_{trend} = .0022$) and were 35.5%, 55.8, and 67.4% in low-, medium-, and high-risk groups, respectively ($P_{trend} = .0063$) (Figure 2). The C-statistic was 0.67 (95% CI, 0.57–0.77) and the differential probability of death between high- and low-risk groups was 0.32. Patients with complete and missing data were similar in regard to age ($P = .569$), sex ($P = .920$), disease severity ($P = .325$), and mortality ($P = .315$).

DISCUSSION

Avian influenza A/H7N9 is amongst the deadliest novel diseases, with mortality rates above 30% [4]. Despite this, few studies have systematically classified patients at high probability for death in large samples and a diverse set of variables. In a cohort of 305 laboratory-confirmed A/H7N9 patients from Zhejiang province, we derived a risk score to predict subsequent death by combining risk factors for mortality including diabetes, increasing age, neutrophil percentage, and bilateral lung infection. When partitioning out this score into low-, medium-, and high-risk groups, we found corresponding mortality rates

Table 1. Demographic, Clinical, and Laboratory Characteristics of 305 Laboratory-Confirmed A/H7N9 Patients

Variable	Value
Demographic characteristics	
N	305 (100)
Age, y, median (IQR)	59 (49–68)
Age group, y	
<45	59 (19.3)
≥45 and <55	55 (18.0)
≥55 and <65	86 (28.2)
≥65 and <75	64 (21.0)
≥75	41 (13.4)
Male	194 (63.6)
Smoker	
Yes	34 (11.2)
No	83 (27.2)
Missing	188 (61.6)
Type of residence	
Urban	156 (51.1)
Rural	149 (48.9)
First medical unit	
Primary level (village, community, private)	135 (44.3)
Secondary level (county, prefecture)	140 (45.9)
Tertiary level (provincial)	30 (9.8)
Epidemic wave	
1	45 (14.8)
2	94 (30.8)
3	45 (14.8)
4	34 (11.2)
5	87 (28.5)
City[a]	
Lishui	12 (3.9)
Taizhou	13 (4.3)
Jiaxing	22 (7.2)
Ningbo	35 (11.5)
Hangzhou	95 (31.2)
Wenzhou	32 (10.5)
Huzhou	39 (12.8)
Shaoxing	27 (8.9)
Quzhou	7 (2.3)
Jinhua	23 (7.5)
Clinical characteristics	
Diabetes	
Yes	54 (17.7)
No	230 (75.4)
Missing	21 (6.9)
Hypertension	
Yes	125 (41.0)
No	165 (54.1)
Missing	15 (4.9)
Cardiovascular disease[b]	
Yes	48 (15.7)
No	102 (33.4)
Missing	155 (50.8)
Pulmonary disease[c]	
Yes	9 (3.0)
No	141 (46.2)
Missing	155 (50.8)
Underlying medical conditions	
Yes	193 (63.3)
No	97 (31.8)
Missing	15 (4.9)
Number of underlying medical conditions[d]	
0	97 (33.7)
1	104 (36.1)
2	60 (20.8)
3	19 (6.6)
4	2.4 (2.4)
5	0.4 (0.4)
Antiviral treatment	248 (81.3)
Exposure-related characteristics	
Poultry worker	18 (5.9)
Visit live poultry markets	209 (68.5)
Intrahousehold poultry raising	115 (37.7)
Bought live or freshly slaughtered poultry	107 (35.1)
Contact with killed, live, or freshly slaughtered poultry	90 (29.5)
Direct contact with poultry or swine	178 (58.4)
Exposure to poultry or related environment	283 (92.8)
Health care and patient-related delay, d, median (IQR)	
Illness onset to first medical care	1 (1–3)
First medical visit to hospitalization	4 (3–6)
First medical care to laboratory result	5 (4–7)
Illness onset to treatment initiation	5 (4–7)
Illness onset to laboratory result	7 (5–9)
Illness onset to death	20 (11–30)
Laboratory variables	
Lymphocyte count, %, median (IQR)	16 (11–23)
Abnormal lymphocyte count, %	
Low, <0.20	106 (34.8)
Normal, 0.20 to 0.39	48 (15.7)
High, >0.40	8 (2.6)
Missing	143 (46.9)
Neutrophil %, median (IQR)	78 (71–85)
Neutrophil % quartiles	
<70.0	66 (25.1)
≥70.0 and <79.0	66 (25.1)
≥79.0 and <86.0	67 (25.5)
≥86.0	66 (25.1)
White blood count, 10^9/L, median (IQR)	5 (4–7)
Abnormal white blood count, 10^9/L	
<3.5	63 (20.7)
3.5 to 10.5	202 (66.2)
>10.5	19 (6.2)
Missing	21 (6.9)
Temperature, °C, median (IQR)	39 (39–40)
Fever (37.8 °C or above)	272 (89.2)
Chronic drug use[e]	79 (25.9)
Unilateral lung infection[f]	
Yes	255 (83.6)
No	2 (0.7)
Missing	48 (15.7)
Bilateral lung infection[g]	
Yes	177 (58.0)
No	43 (14.1)
Missing	85 (27.9)
Pneumonia[h]	232 (76.1)

Data are no. (%) of participants, unless otherwise indicated. Percentages refer to within-characteristic column totals among participants within each clinic and in entire study. Percentages may not total 100% because within-column percentages were rounded. Column totals vary across different characteristics due to missing values for some participants.

Abbreviations: CT, computed tomography; IQR, interquartile range.

[a]City where the participant was reported and hospitalized.

[b]Any patient with hyperlipemia, coronary heart disease, hemorrhagic stroke, or ischemic stroke.

[c]Any patient with bronchiectasis, chronic obstructive pulmonary disease, or asthma.

[d]Any patient with the presence of 1 of the following: hypertension, diabetes, cardiovascular disease, pulmonary disease, gout, cancer/tumor, or tuberculosis.

[e]Chronic drug use refers to medical addiction and not drug addiction. This occurs for some common chronic disease such as hypertension, diabetes, rheumatoid arthritis, and gout, which commonly require drugs.

[f]Any patient with a chest radiograph or CT imaging of pulmonary infections manifested single lung shadowing.

[g]Any patient with a chest radiograph or CT imaging of pulmonary infections manifested double lung shadowing.

[h]An acute illness with cough and at least 1 of new focal chest signs, fever >4 days, or dyspnea/tachypnoea supported by chest radiograph findings of lung shadowing that is likely to be new and without other obvious cause.

Table 2. Risk Factors for Mortality in 305 Laboratory-Confirmed A/H7N9 Patients Stratified by Demographic, Clinical, Exposure-Specific, and Laboratory Characteristics

Variable	No. of Deaths (%)	No. of Participants	Odds Ratio (95% CI), *P* value
All participants	115 (37.7)	305	…
Demographic characteristics			
Age, y	…	…	1.06 (1.04–1.08), <.0001
Age group, y			
<45	8 (13.6)	59	1 (Referent)
≥45 and <55	15 (27.3)	55	2.39 (.92–6.20), .073
≥55 and <65	33 (38.4)	86	3.97 (1.68–9.41), .002
≥65 and <75	29 (45.3)	64	5.28 (2.16–12.90), <.0001
≥75	30 (73.2)	41	17.39 (6.29–48.04), <.0001
Sex			
Female	41 (36.9)	111	1 (Referent)
Male	74 (38.1)	194	1.05 (.65–1.71), .834
Smoker			
No	33 (39.8)	83	1 (Referent)
Yes	14 (41.2)	34	1.06 (.47–2.39), .887
Area			
Urban	55 (36.9)	149	1 (Referent)
Rural	60 (38.5)	156	1.07 (.67–1.70), .780
First medical unit			
Primary level (village, community, private)	55 (40.7)	135	1 (Referent)
Secondary level (county, prefecture)	52 (37.1)	140	0.86 (.53–1.40), .541
Tertiary level (provincial)	8 (26.7)	30	0.53 (.22–1.27), .156
Clinical characteristics			
Diabetes			
No	81 (35.2)	230	1 (Referent)
Yes	27 (50.0)	54	1.84 (1.01–3.35), .046
Hypertension			
No	61 (37.0)	165	1 (Referent)
Yes	50 (40.0)	125	1.14 (.71–1.83), .599
Cardiovascular disease[a]			
No	42 (41.2)	102	1 (Referent)
Yes	18 (37.5)	48	0.86 (.42–1.73), .668
Pulmonary disease[b]			
No	55 (39.0)	141	1 (Referent)
Yes	5 (55.6)	9	1.95 (.50–7.60), .333
Underlying medical conditions			
No	29 (29.9)	97	1 (Referent)
Yes	82 (42.5)	193	1.73 (1.03–2.91), .038
Number of underlying medical conditions[c]			
0	30 (30.9)	97	1 (Referent)
1	45 (43.3)	104	1.70 (.95–3.04), .072
2	27 (45.0)	60	1.83 (.94–3.56), .076
3	6 (31.6)	19	1.03 (.36–2.97), .955
4	4 (57.1)	7	2.98 (.63–14.14), .170
5	0 (0)	1	NA
Exposure-related characteristics			
Antivirus D treatment			
No	23 (40.4)	57	1 (Referent)
Yes	92 (37.1)	248	0.87 (.48–1.57), .648
Poultry market worker			
No	109 (38.1)	286	1 (Referent)
Yes	6 (31.6)	18	0.75 (.28–2.03), .571
Recently visited live poultry market			
No	32 (33.3)	96	1 (Referent)
Yes	83 (39.7)	209	0.87 (.54–1.40), .565
Intrahousehold poultry raising[d]			
No	74 (39.0)	190	1 (Referent)
Yes	41 (35.7)	115	0.87 (.54–1.40), .565
Poultry purchase[e]			
No	75 (37.9)	198	1 (Referent)
Yes	40 (37.4)	107	0.98 (.60–1.59), .932

Table 2. Continued

Variable	No. of Deaths (%)	No. of Participants	Odds Ratio (95% CI), *P* value
Killed poultry[f]			
No	78 (36.3)	215	1 (Referent)
Yes	37 (41.1)	90	1.23 (.74–2.03), .427
Direct contact with poultry or swine[g]			
No	48 (37.8)	127	1 (Referent)
Yes	67 (37.6)	178	0.99 (.62–1.59), .978
Exposure to poultry-related environment			
No	8 (36.4)	22	1 (Referent)
Yes	107 (37.8)	283	1.06 (.43–2.62), .983
Area of exposure			
Rural	60 (38.5)	156	1 (Referent)
Urban	55 (36.9)	149	1.07 (.67–1.70), .780
Time from symptom onset and treatment initiation	…	…	1.02 (.94–1.10), .682
Time from hospital admission and treatment initiation	…	…	1.08 (.96–1.22), .181
Time from first medical visit and treatment initiation	…	…	1.02 (.94–1.11), .672
Laboratory characteristics			
Neutrophil %			65.53 (5.00–858.21), .01
Neutrophil % quartiles			
<70.0	13 (19.7)	66	1 (Referent)
≥70.0 and <79.0	23 (34.9)	66	2.18 (.99–4.81), .053
≥79.0 and <86.0	28 (41.8)	67	2.93 (1.35–6.37), .007
≥86.0	32 (50.0)	66	4.08 (1.87–8.89), <.0001
White blood count (continuous), 10^9/L	…	…	1.08 (1.00–1.17), .044
Abnormal white blood count, 10^9/L			
Low, <3.5	21 (33.3)	63	0.88 (.49–1.61), .685
Normal, 3.5 to 10.5	73 (36.1)	202	1 (Referent)
High, >10.5	11 (57.9)	19	2.43 (.94–6.32), .068
Lymphocyte count, %	…	…	0.03 (.00–1.03), .052
Abnormal lymphocyte count, %			
Low, <0.20	2 (33.3)	6	3.98 (1.70–9.32), .001
Normal, 0.20 to 0.39	15 (19.7)	76	1 (Referent)
High, >0.40	74 (45.4)	163	3.00 (.59–15.16), .184
Temperature, °C	…	…	1.21 (.87–1.69), .250
Fever (37.8 °C or above)			
No	3 (15.8)	19	1 (Referent)
Yes	107 (39.3)	272	3.46 (.98–12.16), .053
Chronic drug use[h]			
No	25 (31.7)	79	1 (Referent)
Yes	40 (50.6)	79	2.22 (1.16–4.23), .016
Unilateral lung infection[i]			
No	0 (0)	2	…
Yes	95 (37.3)	160	…
Bilateral lung infection[j]			
No	8 (18.6)	43	1 (Referent)
Yes	79 (44.6)	177	3.53 (1.55–8.03), .003
Pneumonia[k]			
No	1 (11.1)	9	1 (Referent)
Yes	96 (41.4)	232	5.65 (.69–45.89), .105

Abbreviations: CI, confidence interval; CT, computed tomography.

[a]Any patient with hyperlipemia, coronary heart disease, hemorrhagic stroke, or ischemic stroke.

[b]Any patient with bronchiectasis, chronic obstructive pulmonary disease, or asthma.

[c]Any patient with 1 of the following: hypertension, diabetes, cardiovascular disease, pulmonary disease, gout, cancer/tumor, or tuberculosis.

[d]Raising poultry within or around the household.

[e]Bought live or freshly slaughtered poultry.

[f]Poultry exposure or poultry-related environment.

[g]Live or freshly slaughtered.

[h]Chronic drug use refers to medical addiction and not drug addiction. This occurs for some common chronic disease such as hypertension, diabetes, rheumatoid arthritis, and gout which commonly require drugs.

[i]Any patient with a chest radiograph or CT imaging of pulmonary infections manifested single lung shadowing.

[j]Any patient with a chest radiograph or CT imaging of pulmonary infections manifested double lung shadowing.

[k]An acute illness with cough and at least 1 of new focal chest signs, fever >4 days, or dyspnea/tachypnoea supported by chest radiograph findings of lung shadowing that is likely to be new and without other obvious cause.

Table 3. Multivariable Logistic Regression Analysis of the Development Cohort and Derivation of the Risk Score Classification

Risk Factor	Regression Coefficient	*P* value	Odds Ratio	95% CI	Points
Intercept	−5.966	<.0001	…	…	…
Age, y					
<45			1	Referent	…
≥45 and <55	0.98	.192	2.67	.61–11.68	0
≥55 and <65	1.83	.009	6.21	1.59–24.23	3
≥65 and <75	1.76	.013	5.80	1.44–23.26	3
≥75	3.21	<.0001	24.76	5.53–110.82	6
Diabetes[a]	1.03	.018	2.81	1.19–6.61	2
Bilateral lung infection[b]	1.35	.012	3.85	1.34–11.06	2
Neutrophil % quartile[c]					
<70.0		…	1	Referent	…
≥70.0 and <79.0	0.82	.159	2.26	.72–7.02	0
≥79.0 and <86.0	1.15	.034	3.15	1.09–9.12	2
≥86.0	1.61	.003	4.99	1.71–14.60	3

Abbreviations: CI, confidence interval; CT, computed tomography.

[a]Patients were asked about prior diagnoses of noncommunicable diseases such as hypertension, chronic pulmonary disease, diabetes, and cardiovascular disease. These patient responses were validated with electronic medical records and interviewing clinicians who provided medical care for H7N9 patients.

[b]Whether infection occurred in bilateral lungs was recorded from physical examinations by a pulmonary physician. Bilateral lung infection was defined as any patient with a chest radiograph or CT, imaging of pulmonary infections manifested double lung shadowing.

[c]Neutrophil percentage measurements were taken at several points throughout the disease process starting when patients were first suspected of A/H7N9. We only used laboratory measurements taken during the first clinical visit (timing furthest from death).

of 4.6%, 32.1%, and 62.7%. In a validation cohort from a neighboring province, mortality rates in these groups were 35.5%, 55.8, and 67.4%. Combined, these 2 cohorts represent approximately one-fourth of all diagnosed A/H7N9 patients globally and results suggest that laboratory-confirmed A/H7N9 patients with elevated mortality risk may be identifiable when patients present to health care clinics and are suspected of A/H7N9.

Findings from this study may be useful for physicians to predict individual survival probabilities when an A/H7N9 patient is diagnosed and subsequently directing presumptive therapy and intensive clinical monitoring towards those at highest risk. In addition, grouping H7N9 patients by risk profile may be useful for randomizing severity and mortality risk of clinical trials assessing treatment efficacy. We found that several characteristics

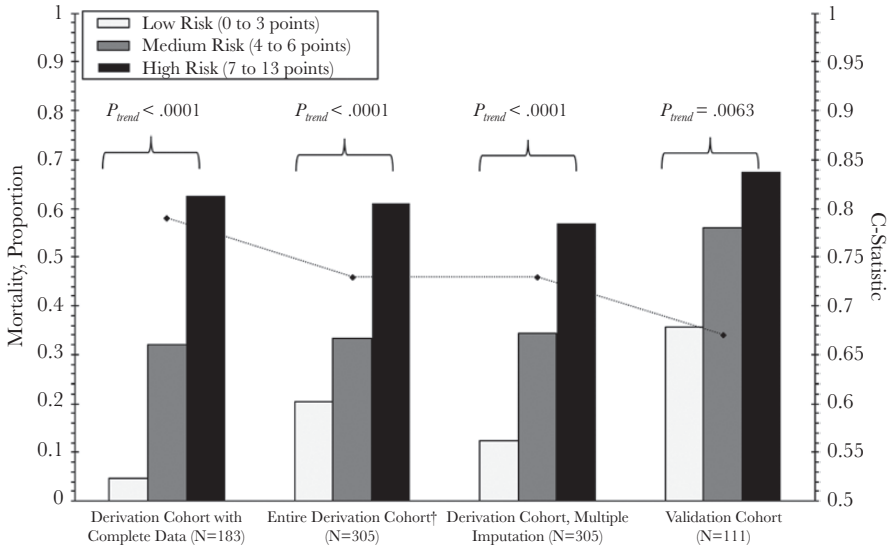

Figure 2. Patient mortality and C-statistics from laboratory-confirmed A/H7N9 influenza patients in low-, medium-, and high-risk classification groups. Data was segregated in 4 ways: (1) the derivation cohort with complete data on all covariates in the final risk score (N = 183); (2) the complete derivation cohort (N = 305) where missing data from 1 of the variables included in the score were analyzed as if the participant did not have the risk factor in question (conservative approach); (3) the derivation cohort using multiple imputation (N = 305) on all missing values; and (4) the validation cohort (N = 111). Patient mortality in the 3 risk classification groups (left y-axis, bar graph), along with C-statistics (right y-axis, line graph), among participants. C-statistics for the overall score are reported. †Includes all 305 A/H7N9 influenza patients from the derivation cohort. Patients with missing data from 1 of the variables included in the score (age, diabetes, bilateral lung infection, or neutrophil percentage) were analyzed conservatively (ie, as if they did not have the risk factor in question.

related to immune regulation were statistically related to elevated mortality risk. Elderly A/H7N9 patients and those with high neutrophil percentages were especially at risk of death. A/H7N9 infection can cause systemic inflammatory responses leading to immunological overload [14, 22]. The baseline immunological profile of patients that contract A/H7N9 may be especially important for projecting subsequent mortality.

Importantly, antiviral treatment did not protect against death in our derivation cohort. Although the majority of patients in our study received treatment, administration was often delayed. Efficacy of antiviral drugs for influenza, including H7N9, have been heavily debated in recent years [23]. Influenza virus replication plateaus 3 days after illness onset and therefore administration of neuraminidase inhibitors is widely promoted early in the disease process. Several studies have reported improved survival among H1N1 influenza patients receiving early treatment [23–25]. Whether this is also true for A/H7N9 remains unclear. In 2 recent studies, A/H7N9 patients receiving neuraminidase inhibitors <3 days after symptom onset had lower mortality [13] and lower rates of viral shedding [26] compared to those receiving delayed treatment.

We included only laboratory-confirmed A/H7N9 cases in this sample and therefore our results are unlikely applicable to asymptomatic, mild A/H7N9 cases. Asymptomatic patients have been identified previously and have lower risk of mortality compared to those seen in our study [6, 27]. We believe our results may be applicable to other severe cases that have been microbiologically confirmed. All laboratory-confirmed A/H7N9 patients in Zhejiang province were included in the derivation cohort. Unlike past studies investigating A/H7N9 mortality [9, 11, 13, 15, 22], we also externally validated our risk score in patients from Jiangsu province. These results suggest classifying future laboratory-confirmed A/H7N9 patients into medium- and high-risk groups, as done here, may be predictive of high mortality from A/H7N9 elsewhere in China. However, we did not test this score in patients with the recently emerged highly pathogenic A/H7N9 strain [28, 29] due to the low number of these cases currently reported—whether this score is valid among this select patient population should be determined in future epidemic waves.

There are several limitations to this study. First, clinical diagnoses such as diabetes, hypertension, and cardiovascular disease were self-reported and may be subject to social desirability and reporting biases. Diabetes may be underestimated because of underdiagnosis [30, 31]. If present, this bias would modify the association seen between diabetes and mortality towards the null and lead our predictive score to conservatively predict mortality. Second, the derived score performed worse in the validation cohort displaying modest discrimination. This was likely due to the higher mortality in the validation cohort (55%) compared to the derivation cohort (39%). Third, other risk factors for death may not have been collected by health care workers but may affect disease resolution and clinical outcomes. Refining this score with further risk factors may be useful to provide further optimization and separate mortality rates among low- and high-risk groups further. For example, we did not include higher neutralizing antibody responses, which may have predictive value to H7N9 patient mortality. Further field evaluation may be needed. Last, not all participants had full data on included risk factors. We used several techniques, including multiple imputation and a conservative approach assuming all missing values were a lack of the risk factor, to test the durability of our results and found that mortality remained substantially greater among participants with high point totals.

In conclusion, in 305 laboratory-confirmed A/H7N9 patients from eastern China, we derived an easy-to-use predictive risk score to identify patients at highest mortality risk after clinical presentation. The score disaggregated mortality into low-, medium-, and high-risk groups. In an independent cohort of 111 laboratory-confirmed A/H7N9 patients from a neighboring province, those classified as high risk had almost 70% mortality; however, the overall score displayed modest discrimination. These findings may be important for clinical management and prioritization of suspected A/H7N9 patients at high probability for death.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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