International Journal of Infectious Diseases 103 (2021) 573–578

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Effectiveness of neuraminidase inhibitors to prevent mortality in patients with laboratory-confirmed avian influenza A H7N9

Wei Cheng[a], Anqi Pan[b], Stephen L. Rathbun[b], Yang Ge[b], Qian Xiao[c], Leonardo Martinez[d], Feng Ling[a], Shelan Liu[a], Xiaoxiao Wang[a], Zhao Yu[a], Mark H. Ebell[b], Changwei Li[b,e], Andreas Handel[b,f,g], Enfu Chen[a], Ye Shen[b,*]

[a] Zhejiang Provincial Centre for Disease Control and Prevention, Hangzhou, China
[b] University of Georgia, College of Public Health, Department of Epidemiology and Biostatistics, Athens, GA, USA
[c] University of Georgia, Department of Statistics, Athens, GA, USA
[d] Stanford University, School of Medicine, Division of Infectious Diseases and Geographic Medicine, Stanford, CA, USA
[e] Tulane University School of Public Health and Tropical Medicine, Department of Epidemiology, New Orleans, LA, USA
[f] University of Georgia, College of Public Health, Health Informatics Institute, Athens, GA, USA
[g] University of Georgia, Center for the Ecology of Infectious Diseases, Athens, GA, USA

ARTICLE INFO

Article history:
Received 7 October 2020
Received in revised form 9 December 2020
Accepted 10 December 2020

Keywords:
H7N9 infection
Influenza
Mortality
Neuraminidase inhibitors
Effectiveness

ABSTRACT

Objectives: Avian influenza virus A(H7N9) remains a threat to humans and has great potential to cause a pandemic in the foreseeable future. Antiviral treatment with neuraminidase inhibitors has been recommended to treat patients with H7N9 infection as early as possible, although evidence-based research on their effectiveness for H7N9 infection is lacking.
Methods: Data from all laboratory-confirmed cases of H7N9 infection in Zhejiang Province between 2013 and 2017 were retrieved, and time-dependent survival models were used to evaluate the effectiveness of treatment with neuraminidase inhibitors to reduce the risk of mortality.
Results: The final optimal model found no significant association (odds ratio 1.29, 95% confidence interval 0.78–2.15) between time to treatment with neuraminidase inhibitors and survival after controlling for age and white blood cell count. Sensitivity analyses with multiple imputation for missing data concurred with the primary analysis.
Conclusions: No association was found between treatment with neuraminidase inhibitors and survival in patients with H7N9 infection using various adjusted models and sensitivity analyses of missing data imputations.

Background

Human infection with avian influenza virus A(H7N9) was first reported in mainland China in March 2013. H7N9 virus frequently causes severe human illness, characterized by pneumonia that rapidly develops into acute respiratory distress syndrome (ARDS), multiple organ dysfunction and shock (Gao et al., 2013a, b). To date, 1568 laboratory-confirmed cases of human H7N9 infection have been reported to the World Health Organization (WHO), with a case fatality rate of 40% (World Health Organization, 2020). The most recent report of a human H7N9 infection was on 31st March 2019 from Gansu Province, China (Yu et al., 2019). Although the reported number of cases of H7N9 infection has dropped remarkably since September 2017, and there is currently no evidence of sustained person-to-person spread, H7N9 virus still poses a threat to global health and safety because of its continued detection in both human and avian species. H7N9 is also considered to have great potential to cause a pandemic, and would potentially pose a great risk to public health if it were to achieve sustained human-to-human transmission (Iuliano et al., 2017). Previous studies found that ARDS, heart failure, septic shock, increased duration of disease, increased white blood cell count, fever, older age, secondary bacterial infections and the presence of comorbidities were predictive of death (Wang et al., 2016; Ma et al., 2017; Yang et al., 2019; Zheng et al., 2019).

Antiviral treatment, mainly with neuraminidase inhibitors (NAIs), is commonly used to treat patients with H7N9 infection. WHO and the National Health and Family Planning Commission of

* Corresponding author at: University of Georgia, College of Public Health, Department of Epidemiology and Biostatistics, 105 Spear Rd, Athens, GA 30602, USA.
E-mail address: yeshen@uga.edu (Y. Shen).

https://doi.org/10.1016/j.ijid.2020.12.028

China have recommended that antiviral treatment should be administrated as early as possible, preferably within 48 h of disease onset. However, in the case of H7N9 treatment, the nationwide case fatality rate has remained at a high level despite the recommended antiviral treatment, with reported fatality rates of 34%, 43%, 47%, 41% and 38% across the five epidemic waves (Wang et al., 2017). Evidence from Zhejiang Province, China has shown a similar pattern. Located in south-east China, Zhejiang Province has the highest number of H7N9 cases among all Chinese provinces, with a total of 305 cases as of July 2020. In recent years, NAIs have been advocated for use as early as possible in patients with H7N9 infection in Zhejiang Province, in accordance with national guidelines. However, the case fatality rate of patients with H7N9 infection in Zhejiang Province remained high in various epidemic waves between 2013 and 2017, ranging from 22% to 56% (Cheng et al., 2018). The recommendation for early use of NAIs for the treatment of H7N9 infection is primarily based on findings from seasonal influenza studies (Dobson et al., 2015; Nicholson et al., 2000; Treanor et al., 2000), but their efficacy has been questioned (Ebell et al., 2013). In addition, several observational studies have reached inconsistent conclusions on the effect of antiviral drugs on the outcomes of patients with H7N9 infection (Wang et al., 2017; Zheng et al., 2018; Yang et al., 2019). More evidence-based research is warranted to understand whether NAIs reduce mortality in patients with H7N9 infection, and guide better clinical practices considering the persistently high case fatality rate.

This study aimed to assess the effectiveness of NAI treatment as an intervention to reduce the risk of death among patients with H7N9 infection in Zhejiang Province between 2013 and 2017. Additional factors that may have influenced the effect of NAI treatment were also considered in the analyses. Previous studies have explored the association between the risk of death and antiviral treatment (Wang et al., 2017; Zheng et al., 2018; Yang et al., 2019). However, previous multi-variable analyses (adjusted for confounders) studying the impact of NAI treatment on H7N9 mortality have typically relied on logistic regression without considering the lifetime to death information for each subject (Zheng et al., 2018; Yang et al., 2019), and the timing of the initiation of NAI treatment was often categorized but not fully adjusted throughout the study period (Wang et al., 2017). Study findings have been inconsistent, and thus far, no time-dependent survival models have been applied to fully utilize the time information from death and initiation of NAI treatment. Moreover, most existing studies conducted complete case analyses, in which observations with missing information on key variables were removed from the analyses; this could have introduced significant bias (Rubin, 1987). The present study used time-dependent survival models and multiple imputation to improve statistical power.

Methods

Study participants

Patients with confirmed infection were defined as those with clinical symptoms consistent with acute influenza (fever, coughing, coryza, difficulty in breathing), or an epidemiologically linked exposure history of contact with poultry, a poultry-related environment, a confirmed or suspected case, and a positive laboratory result for H7N9 virus based on real-time reverse transcription polymerase chain reaction. All laboratory-confirmed cases of H7N9 infection in Zhejiang Province were reported to the China Information System for Disease Control and Prevention. In Zhejiang Province, the last confirmed case of H7N9 infection was reported in June 2017. Consistent with previous studies (Cheng et al., 2018; Martinez et al., 2019), the present authors divided the study period into five epidemic waves. All laboratory-confirmed cases of H7N9 infection reported from Zhejiang Province (n = 305) were included in this study.

Data collection

According to national guidelines for the control and prevention of H7N9 infection, a field investigation by staff from the local centre for disease control and prevention (CDC) was required for each suspected case of H7N9 infection. A standardized questionnaire was used to collect information on demographics, exposure history, underlying diseases, medical visit process, clinical signs and examinations. Patients with H7N9 infection were asked about underlying comorbidities, including non-communicable diseases such as chronic pulmonary disease (bronchiectasis, chronic obstructive pulmonary disease and asthma), cardiovascular disease (hyperlipidaemia, coronary heart disease, haemorrhagic stroke and ischaemic stroke), hypertension, diabetes, gout, cancer/tumour, rheumatoid arthritis and tuberculosis. Chronic drug use was defined as long-term use of drug(s) for a medical condition (not illicit drug addiction). In addition, it was recorded whether lung infection was unilateral or bilateral.

A range of data were collected on medical visits (generally the first medical visit alone). Information was also collected on the level of the medical institution (i.e. community level, county level, prefecture level, private clinic, provincial level or village level). Dates of onset of illness and NAI treatment initiation were collected for all patients. The NAI dose was standardized based on the national H7N9 treatment guidelines. Date of death was collected for deceased patients. White blood cell count, neutrophil percentage, lymphocyte percentage and body temperature were measured, and these examinations were completed several times for patients during medical diagnosis and treatment. Laboratory measurements taken during the first clinical visit (i.e. the visit furthest from death, loss to follow-up or study completion) were used to adjust for the potential impact of NAI treatment on death. A timeline of disease and healthcare-related processes was constructed for each patient.

In this study, the primary outcome variable was the interval between disease onset (as reported by study participants) and death. The primary predictor of interest was NAI treatment, measured by the interval between disease onset and initiation of NAI treatment.

Statistical analysis

Descriptive analysis

Descriptive statistics were used to summarize patients' characteristics. All descriptive analyses were performed on the total sample and stratified by health outcomes. Counts and percentages have been reported for categorical variables, and means and standard deviations have been reported for continuous variables.

Survival analysis

To assess the association between risk of death and treatment with time information included, a time-dependent indicator variable was created, with a value of 0 prior to the initiation of NAI treatment, and a value of 1 following the initiation of NAI treatment. Both univariate and multi-variate analyses were performed using the Cox proportional hazards model for the risk of death:

$$\boldsymbol{h}(\boldsymbol{t}) = \boldsymbol{h}_0(\boldsymbol{t})\boldsymbol{exp}\left\{\boldsymbol{\beta}^{\boldsymbol{T}}\boldsymbol{x}(\boldsymbol{t})\right\}$$

In the model defined above, t is the interval of time from disease onset measured in days, and $h_0(t)$ is the baseline hazard. β is a vector of coefficients, and $x(t)$ includes both time-dependent and time-invariant predictors. The only time-dependent predictor in this model is whether or not NAI treatment was being used at time t, as determined by the time of disease onset and the time of initiation of NAI treatment. Other variables related to patients' demographic and clinical characteristics are time-invariant as they are constant over time. Each coefficient in the Cox regression model represents change in the expected log risk ratio relative to a one-unit change in the corresponding covariate, holding all other predictors constant. Only variables with fewer than 10% missing values were included in the primary analysis.

As the primary interest of this study was to model the impact of NAI treatment on survival of patients with H7N9 infection, univariate analyses were used initially to identify variables associated with patient survival. Next, a multi-variate analysis was performed to identify which covariates should be included in the model. Backward stepwise regression was used to identify the final optimal model. Subsequently, time to initiation of NAI treatment was added to both the univariate and multi-variate models to determine if this explained a significant amount of variation. Statistical analyses were undertaken using R Version 3.3.4 and SAS (University Version).

Missing data imputation

A significant proportion of information was missing from the dataset. Smoking status had the highest number of missing values, with only 120 complete observations. Chronic drug use also had a significant proportion of missing values, with only 158 complete observations. Bilateral lung infection had approximately 30% missing values, with 220 complete observations, and pneumonia had approximately 20% missing values, with 241 complete observations. Smoking status was assumed to be a risk factor of death as this can result in pneumonia. Bilateral lung infection is known to be strongly associated with death as it relates directly to the function of this major organ. Failure to account for missing values in these mortality risk factors may result in biased estimates of the impact of covariates on survival. In addition, ignoring the missing data and performing the analysis solely on cases with complete data may cause bias as these cases may not be representative of the population. Also, larger standard errors of estimates may result from the smaller sample size when using cases with complete data. As such, multiple imputation analysis was undertaken on the data in this study as a sensitivity check for the primary analysis. Missing data for the 13 variables were imputed. Of these, four were continuous variables (highest temperature, white blood cell count, neutrophil cell count percentage and lymphocyte cell count percentage) and nine were binary variables (underlying disease, hypertension, diabetes,

Table 1
Descriptive statistics of participants' characteristics[a].

Variable	Total (n = 305)	Died (n = 115)	Survived (n = 190)
Use of antiviral drug	248 (81.3%)	92 (37.1%)	156 (62.9%)
Underlying disease (n = 290)	193 (66.6%)	82 (42.5%)	111 (57.5%)
Hypertension (n = 290)	125 (43.1%)	50 (40%)	75 (60%)
Diabetes (n = 284)	54 (21.8%)	27 (50%)	27 (50%)
Pulmonary disease (n = 270)	18 (6.7%)	11 (61.1%)	7 (38.9%)
Pneumonia (n = 241)	232 (96.3%)	96 (41.4%)	136 (58.6%)
Cardiovascular disease (n = 270)	57 (21.1%)	23 (40.4%)	34 (59.6%)
Smoking (n = 120)	35 (29.2%)	14 (40%)	21 (60%)
Chronic drug use (n = 158)	79 (50%)	40 (50.6%)	39 (49.4%)
Bilateral lung infection (n = 220)	177 (80.5%)	79 (44.6%)	98 (55.4%)
Epidemic wave			
Wave 1	45 (14.8%)	10 (22.2%)	35 (77.8%)
Wave 2	94 (30.8%)	39 (41.5%)	55 (58.5%)
Wave 3	45 (14.8%)	24 (53.3%)	21 (46.7%)
Wave 4	34 (11.2%)	13 (38.2%)	21 (61.8%)
Wave 5	87 (28.5%)	29 (33.3%)	58 (66.7%)
Residential area			
Urban	163 (53.4%)	63 (38.7%)	100 (61.3%)
Rural	142 (46.6%)	52 (36.6%)	90 (63.4%)
Sex			
Male	194 (63.6%)	74 (38.1%)	120 (61.9%)
Female	111 (36.4%)	41 (36.9%)	70 (63.1%)
First medical unit attended			
Community level	38 (12.5%)	15 (39.5%)	23 (60.5%)
County level	103 (33.8%)	37 (35.9%)	66 (64.1%)
Prefecture level	37 (12.1%)	15 (40.5%)	22 (59.5%)
Private clinics	24 (7.9%)	12 (50%)	12 (50%)
Provincial level	30 (9.8%)	8 (26.7%)	22 (73.3%)
Village level	73 (23.9%)	28 (38.4%)	45 (61.6%)
Age	57.56 ± 15.20	64.3 ± 13.16	53.47 ± 14.92
White blood cell count $\times 10^3$ (n = 290)	5.78 ± 5.25	6.71 ± 7.71	5.22 ± 2.82
Neutrophil cell count percentage (n = 263)	0.77 ± 0.13	0.79 ± 0.15	0.75 ± 0.12
Lymphocyte cell count percentage (n = 190)	0.18 ± 0.13	0.15 ± 0.15	0.2 ± 0.11
Highest temperature (n = 291)	39.25 ± 0.74	39.32 ± 0.64	39.21 ± 0.79
Antiviral onset[b] (n = 248)	5.83 ± 3.39	5.95 ± 3.59	5.76 ± 3.28

[a] Data are mean ± standard deviation or frequency (percentage).
[b] Interval between disease onset and initiation of antiviral drug treatment.

pulmonary disease, cardiovascular disease, pneumonia, bilateral lung infection, chronic drug use and smoking). The Fully Conditional Specification method was employed for imputing missing data. Missing data for continuous variables were imputed via linear regression, and those for dummy variables were imputed via logistic regression. Details of imputation can be found in the online supplementary material.

Results

Table 1 shows the results of descriptive analyses. In total, 305 laboratory-confirmed cases of H7N9 infection were reported, with 45 cases from the first epidemic wave, 94 cases from the second epidemic wave, 45 cases from the third epidemic wave, 34 cases from the fourth epidemic wave and 87 cases from the fifth epidemic wave. Overall, 190 (62%) patients survived and 115 (38%) patients died. The case fatality rates were 22.2%, 41.5%, 53.3%, 38.2% and 33.3% for Waves 1–5, respectively. The median age was 59 years, and 64% of the patients were male. Of the 305 reported cases, 248 (81%) patients received antiviral drugs; of these, 92 (37%) patients died. One hundred and ninety-three (67%) patients had at least one underlying disease. Hypertension, chronic drug use, pneumonia and bilateral lung infection were common among all cases. Approximately half of the patients were from urban areas and the other half were from rural areas. The majority of patients initially went to a county level medical unit (34%) or a village level medical unit (24%). Among the enrolled subjects, the mean time to NAI treatment was approximately 6 days, and this was similar in patients who died and patients who survived. Both mean white blood cell count and neutrophil cell count percentage were higher among patients who died compared with those who survived, while mean lymphocyte cell count percentage was lower in patients who died compared with those who survived. The mean age of patients who died was 11 years older compared with patients who survived (64 vs. 53 years).

Results of the univariate analyses (Table 2) indicate that NAI treatment was not associated with risk of death. Age, white blood cell count, diabetes and underlying disease were significantly negatively associated with survival at a significance level of 0.05. The estimated hazard ratio relative to a 1-year increase in age was 1.050 and the estimated hazard ratio relative to a one-unit increase in white blood cell count was 1.033. The risk of death in patients with diabetes was 1.605 times higher compared with patients without diabetes. The risk of death in patients with at least one underlying disease was 1.570 times higher compared with patients without any underlying diseases.

Results of the multi-variate analysis (Table 3) show the final optimal model selected by stepwise model selection, which includes age and white blood cell count alone. None of the adjusted models revealed an association between NAI treatment and survival. Both age and white blood cell count remained significantly and positively associated with risk of death, with similar hazard ratios as the univariate analyses. Figure 1 presents the estimates of the survival curve for the final optimal model including antiviral treatment, age and white blood cell count. Few deaths occurred in the first 5 days after disease onset, and then the survival curve shows a rapid drop between day 5 and day 20 after disease onset, suggesting that the risk of death is highest during this interval.

Bivariate analyses (Table 4) were undertaken to determine if time to NAI treatment was significantly associated with survival after controlling for each of the other predictors. Although no significant association was found between time to NAI treatment and survival, after accounting for time to NAI treatment, similar significantly negative associations were found between older age and survival, and between white blood cell count and survival as in the univariate analyses. The risk of death was also higher in patients with diabetes and other underlying diseases. Multivariate analysis was performed to determine if time to NAI treatment was significantly associated with survival after controlling for both age and white blood cell count, which were found to be significantly associated with survival in the univariate analyses (Table 5). The results of the final optimal model show no significant association between time to NAI treatment and survival after controlling for age and white blood cell count. The significant hazard ratios found between older age and survival and between white blood cell count and survival were similar to those found in the univariate analyses. An additional analysis was conducted regarding the association of survival with/without NAI treatment in patients, replacing the time-dependent predictor of the initiation of NAI treatment with the predictor of whether or not an antiviral drug was used. No association was found between the initiation of NAI treatment and survival in patients with H7N9 infection (hazard ratio 0.89, 95% confidence interval 0.54–1.47), consistent with the findings shown in Table 5.

Sensitivity analyses on multiply imputed data were performed to check if the results still held after addressing the problem of missing data. For outcome variables missing in $\geq$10% of subjects from the entire cohort, analyses initially conducted for complete cases were later repeated with missing data imputed using multiple imputation procedures. Results obtained from the multiply imputed datasets are shown in Tables S1–S4 in Section S2 of the online supplementary material These results were compared with those generated from the original dataset, and the overall message remained the same, with time to initiation of NAI treatment not significantly associated with survival, and age and white blood cell count being predictive of death. The final optimal model from the imputed datasets shows that, in addition to age and white blood cell count, neutrophil cell count percentage was also significantly and positively associated with risk of death.

Table 2
Univariate Cox regression for baseline covariate.

Variable	Hazard ratio	95% CI	*p*-value
Age	1.050	1.034–1.066	<0.0001
Sex	0.942	0.644–1.381	0.762
White blood cell count	1.033	1.011–1.055	0.003
Diabetes	1.605	1.038–2.482	0.033
Hypertension	1.076	0.741–1.566	0.700
Underlying disease	1.570	1.028–2.398	0.037
Use of antiviral drug	0.910	0.576–1.437	0.685
Highest temperature	1.152	0.890–1.491	0.284
First medical unit attended			0.781
Community level	1.069	0.571–2.001	
County level	0.906	0.554–1.480	
Prefecture level	1.120	0.598–2.100	
Private clinic	1.210	0.615–2.379	
Provincial level	0.653	0.298–1.433	

CI, confidence interval.

Discussion

H7N9 remains an important public health threat with the potential to cause a pandemic in the foreseeable future. Previous studies have suggested that predictors of death among infected patients include ARDS, heart failure, septic shock, increased white blood cell count, longer duration of disease, older age and diabetes (Wang et al., 2016; Ma et al., 2017; Zheng et al., 2019; Yang et al., 2019). Consistent with the findings from these studies, the present analysis evaluated the major factors associated with survival, and found that mortality is an increasing function of age and white blood cell count. Treatment with an NAI was not found to be significantly associated with lower risk of mortality.

Table 3
Multi-variate Cox regression for baseline covariate.

Final optimal model including age and white blood cell count	Hazard ratio	95% CI	*p*-value
Age	1.047	1.031–1.064	<0.0001
White blood cell count	1.033	1.010–1.057	0.005

CI, confidence interval.

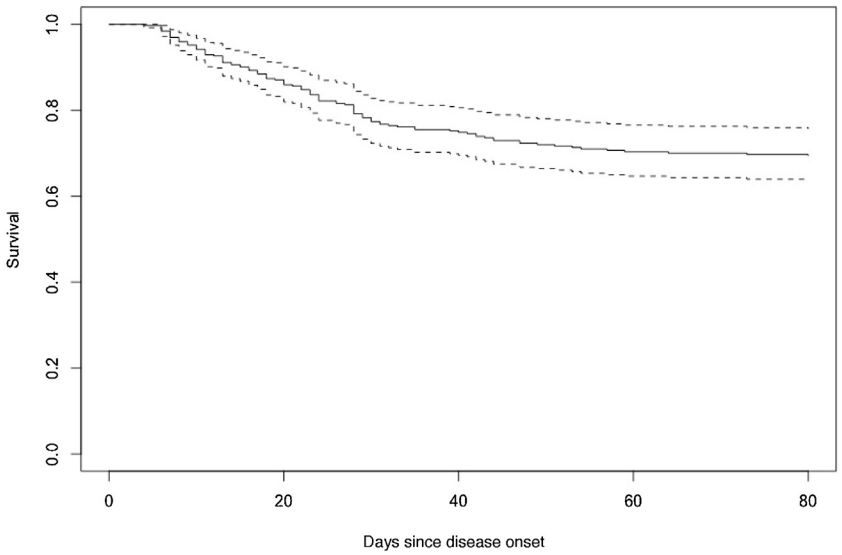

Figure 1. Survivor function estimates (with 95% confidence limits) for the final optimal model including antiviral treatment, age and white blood cell count.

Table 4
Bivariate Cox regression models for the impact of antiviral treatment controlling for individual demographic and clinical covariates.

Model	Variable	Hazard ratio	95% CI	*p*-value
1	Antiviral treatment	1.212	0.760–1.932	0.420
	NA			
2	Antiviral treatment	1.092	0.685–1.742	0.712
	Age	1.049	1.034–1.066	<0.0001
3	Antiviral treatment	1.211	0.759–1.930	0.422
	Sex	0.944	0.644–1.382	0.767
4	Antiviral treatment	1.439	0.866–2.390	0.160
	White blood cell count	1.033	1.012–1.055	0.002
5	Antiviral treatment	1.271	0.780–2.071	0.335
	Diabetes	1.638	1.058–2.537	0.027
6	Antiviral treatment	1.248	0.767–2.031	0.373
	Hypertension	1.060	0.728–1.542	0.762
7	Antiviral treatment	1.237	0.761–2.009	0.391
	Underlying disease	1.560	1.021–2.384	0.040
8	Antiviral treatment	1.294	0.796–2.105	0.299
	Highest temperature	1.143	0.881–1.481	0.314
9	Antiviral treatment	1.160	0.724–1.857	0.538
	First medical unit attended			0.818
	Community level	1.064	0.568–1.992	
	County level	0.913	0.559–1.494	
	Prefecture level	1.116	0.596–2.090	
	Private clinic	1.213	0.617–2.386	
	Provincial level	0.670	0.304–1.476	

CI, confidence interval.

The effect of antiviral drugs on the outcomes of patients with H7N9 infection has been inconsistent between observational studies and is worth further exploration. Zheng et al. found that the interval from disease onset to initiation of antiviral therapy was an independent risk factor for death, and that administration of NAI therapy within 2 days of symptom onset was associated with a clinically and significantly decreased risk of death (Zheng et al., 2018). Another study conducted in Guangdong Province found that a shorter interval between disease onset and initiation of oseltamivir treatment was protective against death in patients with H7N9 infection (Yang et al., 2019). However, a national study found that patients with H7N9 infection who received antiviral treatment within 2 days of symptom onset were not significantly less likely to die compared with patients who started antiviral treatment $\geq$3 days after system onset across the five epidemic waves (Wang et al., 2017). Consistent with the results from the national study, the present study found that NAI treatment had no significant effect when included alone in a model, or when controlling for the significant effects of age and white blood cell count, with time-dependent survival models applied to the multiply imputed dataset to minimize the impact of missing data for better statistical power.

The unobserved efficacy of NAI treatment for patients with H7N9 infection was not surprising. On one hand, the definitive pathogenic mechanism of H7N9 virus in humans is still unclear, and the recommendation for early use of antiviral drugs for these patients was based on experience with seasonal influenza (Nicholson et al., 2000; Treanor et al., 2000; Dobson et al., 2015). In particular, initiation of oseltamivir treatment within 48 h of symptom onset has a modest benefit in terms of symptom reduction, but independent systematic reviews (not funded by the manufacturer) have failed to find an effect of oseltamivir or zanamivir on influenza mortality (Ebell et al., 2013; Jefferson et al., 2014; Dobson et al., 2015; Muthuri et al., 2016). However, most patients included in this analysis initiated treatment with an NAI outside of the 48-h window. As such, future well-designed randomized clinical trials may be needed to further evaluate the efficacy of NAI therapy for patients with H7N9 infection. On the other hand, the consistently high fatality rate in each epidemic wave reflected the absence of effective antiviral drugs for H7N9 despite the tremendous efforts made to advocate for early diagnosis and antiviral treatment.

Table 5
Multi-variate Cox regression models for the impact of antiviral treatment controlling for age and white blood cell count.

Variable	Hazard ratio	95% CI	*p*-value
Antiviral treatment	1.292	0.777–2.149	0.323
Age	1.047	1.030–1.063	<0.0001
White blood cell count	1.034	1.010–1.057	0.004

CI, confidence interval.

Findings from this study raise the important issue of drug resistance. Several studies have found that NA-R292K, NA-E119V, NA-I222K, NA-I222R and other site mutations of the H7N9 virus are directly associated with NAI resistance (Marjuki et al., 2015a, b; Yang et al., 2018). Widespread use of NAIs may increase the likelihood of drug resistance (Handel et al., 2007). If the effectiveness of NAI treatment is limited and only guaranteed in certain circumstances, such as early use within 48 h of symptom onset, these antiviral drugs should be administered with caution and only during this window.

This study has several limitations. Underlying medical conditions such as diabetes, hypertension and cardiovascular disease were self-reported and may be subject to social desirability and reporting biases. The date of disease onset is the self-reported day on which symptoms first appeared, rather than the date that patients were infected. The interval between infection and initiation of antiviral drug therapy may be a better predictor of survival. However, the date of infection is not available, as patients can be asymptomatic following initial infection. Meanwhile, self-reported days of infection may also be subject to recall bias, resulting in biased estimates of hazard ratios and low statistical power. Missing data imputation was reliant on an ignorable missing data mechanism that might be difficult to verify and is somewhat subjective. As such, results from variables with close to or over half of the observations missing, such as smoking status and chronic drug use, should be interpreted with caution. Additionally, this study only evaluated the effectiveness of NAI treatment without specific classification, so there was no comparison between the effects of oseltamivir monotherapy and oseltamivir–peramivir combination therapy. However, Zhang et al. suggested that oseltamivir–peramivir combination therapy was not superior to oseltamivir monotherapy (Zhang et al., 2016).

In conclusion, this study did not find an association between NAI treatment and survival in patients with H7N9 infection. The high fatality rate of patients with H7N9 infection demands a prospective, randomized controlled study to further assess the effectiveness of antiviral therapy. Moreover, new drugs with different mechanisms of action should be developed to combat the high fatality rate in patients with H7N9 infection and the emergence of drug resistance in NAIs.

Conflict of interest

None declared.

Funding

None.

Ethical approval

The National Health and Family Planning Commission ruled that the collection of data for laboratory-confirmed cases of avian influenza A(H7N9) virus infection was part of a continuing public health investigation of an emerging outbreak. The study was therefore exempt from institutional review board assessment.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.12.028.

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