Severe acute respiratory infections, the missing link in the surveillance pyramid

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CHAPTER 6

Effectiveness of oseltamivir in reduction of complications and 30-day mortality in severe seasonal influenza

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ABSTRACT

OBJECTIVES

The benefit of oseltamivir treatment in patients admitted with influenza virus infection and the design of studies addressing this issue, have been questioned extensively. Since the influenza disease burden is substantial and oseltamivir treatment is biologically plausible, we assessed the clinical benefit of oseltamivir treatment in adult patients admitted with severe seasonal influenza virus infection in daily practice.

METHODS

A multicenter, retrospective cohort study was conducted to compare the effectiveness of treatment with and without oseltamivir <48 hours after admission in patients admitted with laboratory-confirmed influenza virus infection in three large hospitals in the Netherlands. Propensity score matching was used to compare clinical relevant outcome variables.

RESULTS

We included 390 patients, of whom 80% had comorbidity. Thirty-day mortality, as well as the composite endpoint of 30-day mortality or intensive care unit admission >48 hours after admission, were reduced by 9% ($p = 0.04$) and 11% ($p = 0.02$) respectively. Length of hospital stay and in-hospital mortality rates all showed a trend towards reduction. The median duration between symptom onset and initiation of treatment was three days.

CONCLUSIONS

This study supports that, in daily practice, patients admitted with influenza virus infection should be treated with oseltamivir within 48 hours of admission, even if they have had complaints for more than 48 hours.

INTRODUCTION

Patients with seasonal influenza virus infection can develop severe disease which requires hospitalization. In these patients, optimal treatment may reduce morbidity, mortality and associated costs substantially. In the United States, the cumulative influenza incidence of laboratory-confirmed influenza hospitalizations was 10.3 per 10,000 and 6.4 per 10,000 in the 2017/2018 and 2018/2019 flu seasons respectively.[1] Unfortunately, these data are not available for Europe. In hospitalized patients, intensive care unit (ICU) admission rates and mortality rates are 15-34% and 4-12%.[2,3] In 2013, the annual costs for patients hospitalized with influenza virus infection in Germany were estimated to be 90 million euros.[4]

Neuraminidase inhibitors are the primary treatment option for patients with severe influenza infection. Evidence regarding clinical effectiveness of neuraminidase inhibitors is however inconsistent. No benefit was demonstrated in several studies[5,6], and the statistical methods of studies showing benefit have been questioned extensively.[7-10] In hospitalized patients, most treatment guidelines recommend the use of the neuraminidase inhibitor oseltamivir despite the lack of solid evidence.[11,12] Hence, compliance with these guidelines is poor.[13] This may be due to the lack of evidence for the prevention of complications by oseltamivir treatment in hospitalized patients and the finding that a reduction in mortality is most evident in patients who start treatment within 48 hours after the onset of symptoms.[14,15] In clinical practice, the majority of patients who present to a hospital has had symptoms for more than 48 hours.[14] In these cases, the benefit of later initiation of treatment (>48 hours after symptom onset) is yet unknown.

6

Moreover, in the majority of clinical studies, young, influenza A(H1N1)pdm09 infected patients with limited comorbidity were enrolled.[14] These patients do not represent the older, comorbid patients who currently form the predominant population admitted with seasonal influenza in real-life clinical practice.

Compliance to treatment guidelines may be poor due to the uncertainty about the diagnosis at initial hospital presentation. Once influenza is laboratory-confirmed, physicians are more inclined to prescribe oseltamivir.[13] All these factors interfere with physicians' confidence in the benefits of oseltamivir treatment.[16,17] In addition, negative reporting about oseltamivir has further increased the uncertainty of oseltamivir´s potential benefit.[18,19]

Prolonged viral replication is present in the majority of patients who need hospital admission for influenza virus infection.[20] Consequently, oseltamivir treatment would be biologically plausible[21], even when symptoms are present for more than 48 hours at hospital presentation. Therefore, we investigated the effect of oseltamivir treatment in adult patients hospitalized for influenza virus infection in a healthcare system where the majority of patients come to hospital after more than 48 hours of illness. To assess clinical effectiveness of oseltamivir, an observational cohort study using propensity score methods was performed.

PATIENTS AND METHODS

DESIGN AND STUDY POPULATION

A multicenter, retrospective cohort study was conducted to estimate the effectiveness of oseltamivir in patients admitted with laboratory-confirmed influenza virus infection.[22] Two university medical hospitals (Leiden University Medical Center, 585 beds, and University Medical Center Utrecht, 1100 beds) and one teaching hospital (Jeroen Bosch hospital, 575 beds) participated in the study.

All patients with laboratory-confirmed influenza from two or three consecutive influenza seasons between October 1st, 2013 and April 1st, 2016 were screened for eligibility. Lists with adult patients (≥18 years) with positive PCR test results for influenza A or B virus in respiratory samples (sputum, nasopharyngeal or throat swab, endo-tracheal aspirates or bronchoalveolar lavage (BAL)) were obtained. We excluded children since they have different influenza immunological response and disease dynamics. Patients with influenza A or B virus-positive samples who were hospitalized within seven days before or after virologic confirmation were included. Patients with hospital-acquired influenza infection, i.e., if symptoms had started ≥72 hours after hospital admission, were excluded.

DATA COLLECTION AND STUDY DEFINITIONS

Data about demographic characteristics, start of symptoms, dates of hospital admission and discharge, influenza type (A or B), comorbidity, CURB-65 score as the most consistent marker of severity at presentation[23], presence of pneumonia (consolidation on chest X-ray) at admission, start and stop of oseltamivir treatment, and start of antibacterial treatment at hospital admission and intensive care unit (ICU) admission within 48 hours after admission were obtained from the electronic medical records. ICU admission <48 hours after hospital admission was used as a second marker of severity. Comorbidity was categorized into cardiovascular disease, chronic pulmonary disease, and immunodeficiency. Immunodeficiency was defined as either the presence of solid organ transplantation (SOT), hematological malignancy, or hematopoietic stem cell transplantation (HSCT), chronic use of immunosuppressive medication or chemotherapy in the past six months, or HIV with CD4+-T-lymphocyte counts ≤200 cells/µl.

We defined oseltamivir treatment started within 48 hours after hospital admission as adequate treatment.[14] We compared this group of patients with the group who had not been treated with oseltamivir within 48 hours after admission. During the study period, oseltamivir was the only neuraminidase inhibitor used in the three hospitals. Guideline based dosing regimen was 75 mg bid and 75 mg qd in patients with impaired renal function (creatinine clearance between 10 and 30 ml/min). Dutch national guidelines did not recommend the use of oseltamivir for outpatients. Therefore, it was assumed that the patients did not receive oseltamivir before hospital admission.

Primary outcome parameters were: 30-day mortality, in-hospital mortality, length of hospital stay, and the composite endpoint of 30-day mortality and/or ICU admission >48 hours after hospital admission. ICU admission >48 hours after hospital admission is regarded as a complication of influenza virus infection (i.e. severe morbidity). We used this composite endpoint to assess the clinical benefit of oseltamivir as for individual decision making in patient care, both outcome parameters are clinically relevant.

For subgroup analysis, chest X-rays have been assessed for the presence or absence of a consolidation by independent radiologists. Consolidation is regarded as marker for ongoing viral replication and inflammatory response in the lower respiratory tract. In a secondary analysis, outcome parameters were assessed in the subgroup of patients with a consolidation on chest X-ray.

STATISTICAL ANALYSES

Continuous variables were reported depending on distribution as means with standard deviations or as medians with interquartile ranges (IQR), categorical variables were reported as numbers with percentages. Univariate analyses were performed to compare baseline variables between groups, using Fisher's Exact tests, Chi-squared tests, and Wilcoxon rank tests as appropriate.

By using the Propensity Score Matching (PSM) and Inversed Probability Weighting (IPW) the outcome parameters were compared between the group who received adequate treatment and the group who did not receive adequate treatment (see below).

Survival analysis was performed to assess the time to event in both groups. The log-rank test was used to compare the survival distributions. All statistical analyses were performed using STATA software version 14 (StataCorp, College Station, TX, USA).

Propensity score methods

Propensity score methods can be used to analyze observational data concerning a specific treatment outcome by defining which individuals have the same probability of receiving the intervention (here: adequate oseltamivir treatment) and by also accounting for the probability of a defined outcome. By assessing the outcome in relation to the intervention for patients with similar (i.e. matched) propensity scores, it is aimed to attain the results that reflect those of a randomized study.[24]

In this study, propensity scores were generated using a multivariable logistic regression model based on confounding variables as identified by the univariate analyses. Variables that were associated ($p<0.20$) with the allocation of treatment and with the primary endpoint of 30-day mortality, and were plausible confounders, were selected for input in a logistic regression model to calculate the propensity scores. The matching algorithm used a nearest neighbor method in a 1:1 ratio without replacement and a caliper (maximum probability distance) of 0.20. We used the available variables to optimize the model. To balance baseline variables between groups of patients adequately treated with oseltamivir and those who were not, the model was calibrated to allow a maximum standardized difference of 0.1 (10%).

In the matched cohort, comparison of endpoints between groups was performed by assessment of the average treatment effect in the treated population (ATT) with Student's-t-test, Fishers' exact, or Wilcoxon signed rank test, as appropriate.

IPW was used as a sensitivity analysis, i.e. to assess the robustness of the results obtained by PSM.

REPORTING AND ETHICS

The study was approved by each hospital's ethical review board and performed and reported according to the STROBE statement for observational studies and a checklist of proposed guidelines for the reporting of propensity score methods [25,26]. Research data were pseudonymized and securely stored, according to the General Data Protection Regulation (GDPR).

RESULTS

CHARACTERISTICS OF THE COMPLETE COHORT

Of 408 screened patients, 18 were excluded because they had hospital-acquired infection, missing data of onset of symptoms, or viral testing could not rule out hospital acquisition. In the final analysis, 390 patients admitted to the hospitals with laboratory-confirmed, community-acquired influenza virus infection, were included. Median age was 65 years (IQR 51-77), 42% was female. Comorbidity was present in 80% of patients, of these 60% had cardiovascular comorbidity, 42% had pulmonary comorbidity, and 46% was immunocompromised. A considerable number of 47 solid organ transplant recipients (12%) and 21 (5%) stem cell transplant recipients were included in the cohort. One-hundred-thirty-eight (35%) patients received adequate treatment. The median duration between symptom onset and initiation of oseltamivir was 3.0 days (IQR 2.0-4.6; missing data in 13 patients).

Of the remaining 252 patients, 49 (19%) received oseltamivir > 48 hours after admission and 203 (81%) were not treated with oseltamivir. Overall, median length of hospital stay was 5.0 days (IQR 2.9-10.0). Seventy patients (18%) needed to be admitted to the ICU, 23 (34%) required non-invasive ventilator support, 37 (54%) required invasive mechanical ventilation and three of them (4%) needed ECMO support. Of the ICU patients, 62 were admitted within 48 hours after hospital admission. In-hospital mortality was 21/390 (5.4%), 30-day mortality was 30/390 (7.7%).

Baseline characteristics differed between the patients who received adequate treatment (n=138) versus patients who did not (n=252). Younger patients, patients with comorbidity, or with concomitant antibiotics, and patients admitted to the ICU within 48 hours after admission were more likely to be treated with oseltamivir (Table 1).

Thirty-day mortality in influenza patients increased with higher CURB-65 scores at admission (Table 2).

PROPENSITY SCORE MATCHING

The propensity score model was built with nine variables from the multivariable logistic regression model (age, age>65, type of influenza, CURB-65 score, pre-existing lung disease, pre-existing cardiovascular disease, immunocompromised, empiric antibiotics, and ICU admission within 48 hours after hospital admission). The hospital of admission was not a confounder. After successful propensity score matching, 88 patients remained in both groups (Table 1 and Figure 1).

OUTCOME WITH PROPENSITY SCORE MATCHING

Thirty-day mortality and the composite endpoint in the adequate treatment group were, respectively, 9.1% and 11.4% lower than in the group who did not receive oseltamivir within 48 hours after admission. The number needed to treat to prevent one ICU admission or death within 30 days is approximately nine. Both in-hospital mortality and length of hospital stay were reduced in patients who received adequate treatment (Table 3). In these patients, median duration of symptoms before start of treatment was 3.0 days (IQR 2.0-4.1 days).

Table 1. Baseline characteristics before and after propensity score matching

	Cohort before matching					Cohort after matching				
	oseltamivir ≤48h		no oseltamivir ≤48h			oseltamivir ≤48h		no oseltamivir ≤48h		
	n#	%	n#	%	p*	n	%	n	%	p -value*
Total	**138**		**252**			**88**		**88**		
Gender					>0.99					>0.99
Male	80	58.0	146	57.9		51	58.0	51	58.0	
female	58	42.0	106	42.1		37	42.0	37	42.0	
Type of influenza					0.05					>0.99
A	115	84.6	186	75.6		71	80.7	70	79.5	
B	21	15.4	60	24.4		17	19.3	18	20.5	
Presence of any comorbidity					0.04					0.7
No	23	16.7	53	21.0		15	17.0	18	20.5	
Yes	115	83.3	198	78.6		73	83.0	70	79.5	
Pre-existing cardiovascular disease					0.59					>0.99
No	74	53.6	127	50.4		43	48.9	44	50.0	
Yes	64	46.4	125	49.6		45	51.1	44	50.0	
Pre-existing lung disease					0.15					0.63
No	98	71.0	160	63.5		60	68.2	56	63.6	
Yes	40	29.0	92	36.5		28	31.8	32	36.4	
Immunocompromised					<0.01					0.76
No	61	44.2	185	73.7		50	56.8	47	53.4	
Yes	77	55.8	66	26.3		38	43.2	41	46.6	
Mean age in years	58.4		65.1		<0.01	62.3		62.5		0.93
Elderly (>65 years old)					<0.01					>0.99
No	88	63.8	109	43.4		45	51.1	45	51.1	
Yes	50	36.2	143	56.7		43	48.9	43	48.9	
CURB-65 score					0.27					0.38
0	18	15.9	27	12.9		14	15.9	15	17.0	
1	35	31.0	56	26.7		25	28.4	23	26.1	
2	36	31.9	60	28.6		29	33.0	22	25.0	
3	18	15.9	54	25.7		15	17.0	24	27.3	
4	4	3.5	12	5.7		3	3.4	4	4.5	
5	2	1.8	1	0.5		2	2.3	0	0	
Pneumonia present at admission					0.09					>0.99
No	68	49.3	145	58.5		58	65.9	58	65.9	
Yes	70	50.7	103	41.5		30	34.1	30	34.1	
Admission to ICU ≤48h after presentation					<0.01					0.21
No	101	73.2	227	90.1		69	78.4	71	80.7	
Yes	37	26.8	25	9.9		19	21.6	17	19.3	
Empiric antibiotics					0.01					0.85
No	20	14.6	65	25.9		13	14.8	11	12.5	
yes	117	85.4	185	74.1		75	85.2	77	87.5	

* Fisher´s exact test, or Chi-squared test if >2 rows.

Numbers do not always add up to 390 since there are some missing data. In particular, CURB-65 scores are missing in 67 patients.

Table 2. CURB-65 score and 30-day mortality

CURB-65 score	30-day mortality
0	0/45 (0)
1	2/91 (2.2)
2	8/96 (8.3)
3	12/72 (16.7)
4	4/16 (25.0)
5	1/3 (33.3)

CURB-65 severity score: C= new onset confusion, urea >7mmol/l, R= respiratory rate ≥30/minute, B= Blood pressure (systolic <90 mm Hg or diastolic ≤60 mm Hg), 65= Age ≥65.

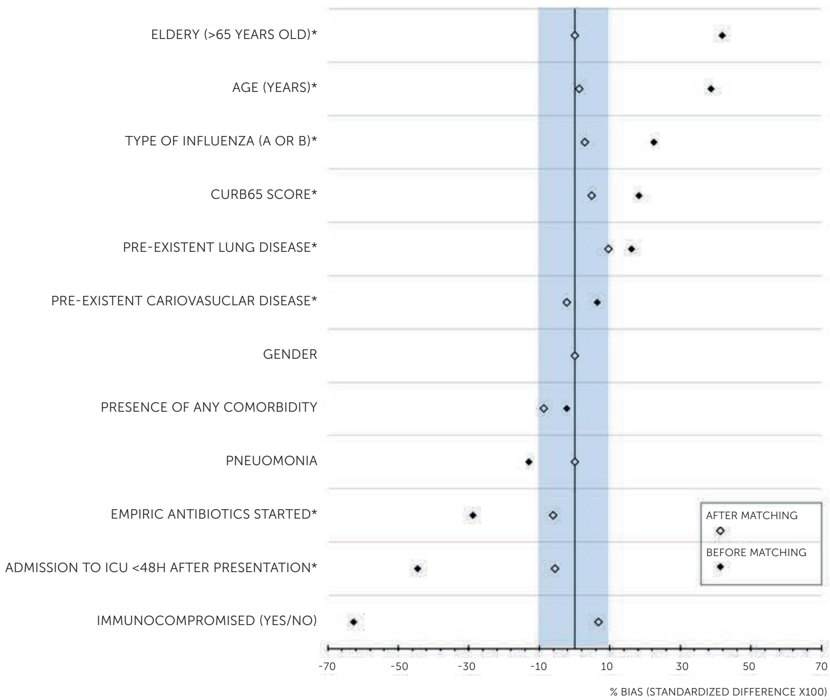

Figure 1. Standardized differences before and after propensity matching
Variables marked with an * have been used in the propensity score model. ICU: intensive care unit.

Table 3. Outcome using propensity score matching in the group of influenza patients treated with oseltamivir within 48 hours after hospital admission versus the group without this treatment

Outcome variable	Untreated (%)	Treated (%)	Difference (%)	OR	95%CI	p-value
30-day mortality	12/88 (13.6)	4/88 (4.6)	-8/88 (9.1)	0.30	0.07-1.07	0.04
In-hospital mortality	9/88 (10.2)	3/88 (3.4)	-6/88 (6.8)	0.31	0.05-1.31	0.13
Composite endpoint	14/88 (15.9)	4/88 (4.6)	-10/88 (11.4)	0.25	0.06-0.86	0.02
Median length of hospital stay in days (IQR)	6 (2.8-11.0)	4 (2.6-8.0)	-	-	-	0.14

OR: odds ratio, CI: confidence interval, ICU: intensive care unit, IQR, interquartile range.
Composite endpoint = 30-day mortality and/or ICU admission >48h after hospital admission.

6

OUTCOME WITH INVERSED PROBABILITY WEIGHTING

The composite endpoint showed a reduction of 8% (p=0.05). This leads to a number needed to treat to prevent one ICU admission or death within 30 days of approximately 13. Thirty-day mortality, in-hospital mortality and median length of stay all showed a trend towards reduction (Table 4).

Table 4. Outcome with IPW in the group of influenza patients treated with oseltamivir within 48 hours after hospital admission versus the group without this treatment

Outcome variable	Coefficient	SE	95% CI	p-value
30-day mortality	-0.07	0.38	-0.14 - 0.00	0.06
In-hospital mortality	-0.04	0.03	-0.11 - 0.03	0.22
Composite endpoint	-0.08	0.04	-0.15 - 0.00	0.05
Median length of hospital stay in days	-1.38	-1.05	-3.44 - 0.67	0.19

SE: standard error, CI: confidence interval, ICU: intensive care unit.
Composite endpoint = 30-day mortality and/or ICU admission >48h after hospital admission.

SURVIVAL ANALYSIS

Survival analyses are presented in Figure A.1 and A.2 in the appendix. Thirty-day mortality and the composite endpoint were better in the group who received adequate treatment. The first death occurred three days after hospital admission.

SUBGROUP ANALYSIS IN PATIENTS WITH CONSOLIDATION ON CHEST X-ray

Sixty patients (34%) in the matched cohort had a consolidation on the chest X-ray on the day of hospital admission. Half of the patients (n=30) received adequate treatment. Seven patients who did not receive this treatment (23%) died within 30 days or reached the composite endpoint versus two (7%) who did receive adequate treatment (p=0.07). In-hospital mortality was 17% (5/30) in patients who did not receive adequate treatment versus 3% (1/30) in the ones who did (p=0.09).

DISCUSSION

During three consecutive influenza seasons, the burden of patients admitted with community-acquired influenza virus infection in three hospitals was substantial: the median length of stay was five days, and 70 of 390 patients needed ICU admission. In the propensity score matched cohort (mean age of 62 years and substantial comorbidity), oseltamivir treatment within 48 hours after hospital admission reduced 30-day mortality as well as the composite endpoint of 30-day mortality and/or ICU admission >48h after hospital admission. The median duration between symptom onset and initiation of oseltamivir was 3.0 days.

Our study confirms the 30-day mortality benefit of adequate treatment which has been observed previously.[27] Similarly, the meta-analysis by Muthuri et al. using PSM, showed a reduction of in-hospital mortality in influenza A (H1N1)pdm09 virus infected patients that were treated with oseltamivir, odds ratio 0.81.[14] The odds ratio for 30-day mortality in our cohort is 0.30.

There are important differences between the Muthuri cohort and our cohort that need consideration. Firstly, in the Muthuri cohort only 5% of patients were aged 65 or older and only 6% were immunocompromised.[14] This does not reflect the type of patients with seasonal influenza virus infection that presented to the hospital in more recent influenza seasons [28]. Nowadays, mostly elderly patients are affected and become hospitalized by an influenza virus infection and/or secondary bacterial infection. In addition, increasing numbers of hospitalized patients are immunocompromised.[1] Our cohort reflects this type of patients with 193/390 (49%) are over 65 years of age, and 143/389 (37%) are immunocompromised. Secondly, the healthcare systems in the countries contributing to the meta-analysis of Muthuri are different from the Dutch healthcare system. In the Netherlands and other European countries, patients are usually referred to hospitals after consulting their general practitioner. This gatekeeper function of the general practitioner leads patients to come to the hospital later and potentially to start oseltamivir longer after onset of symptoms. However, in the study by Muthuri, the median time from start of symptoms to start of antiviral treatment was three days, similar to that time in our complete cohort (3.0 days, IQR 2.0-4.6).

In contrast to patients with uncomplicated influenza virus infection, hospitalized patients have prolonged influenza viral shedding.[29,30] With ongoing viral replication in patients admitted with influenza virus infection, antiviral treatment may improve disease outcomes. Therefore, the time window to start treatment after symptom onset (within 48 hours), seems less relevant. In addition, self-reported duration of symptoms is often unreliable.

In our cohort, with 87/125 (70%; 13 missing) of the treated had symptoms for more than two days, treatment with oseltamivir within 48 hours after hospital admission reduced 30-day mortality and the composite endpoint. This illustrates the biological plausibility of oseltamivir treatment effect during a larger time window in patients with prolonged viral replication, i.e., the ones that are hospitalized. This becomes more clear in the patients with chest X-ray-confirmed pneumonia. Although not significant due to the small size of the subgroup, the differences in 30-day mortality and composite endpoint between the treated and untreated groups are more striking than in the overall matched cohort. However, this also indicates that the difference in the matched cohort is not caused by an effect limited to the patients with consolidation. These results provide pragmatic guidance in the decision to start oseltamivir treatment in patients hospitalized with influenza virus infection. The strength of our study is the multicenter design in a community with a well-developed primary care network. In the Netherlands, most patients with seasonal influenza are treated by their general practitioner. The selection of patients who present to a hospital consists of patients with severe disease and patients who are vulnerable, especially through immunocompromised status. In daily practice, this is the most relevant patient group in which to assess the clinical effect of oseltamivir.

The analyses with both the PSM and IPW are consistent and with these statistical methods we maximally reduced the impact of selection bias. A similar study in 506 influenza patients in South Korea found completely different results[31], but did not use a propensity score model.

Hospital mortality as outcome parameter, used in the meta-analysis from Muthuri[14], has been questioned extensively because of the bias that discharged patients are more likely to be in a better condition than those who could not be discharged (competing risk for death).[10] Our 30-day mortality is, therefore, a more appropriate outcome parameter. Other concerns regarding the Muthuri meta-analysis concerned the potential time-dependent bias.[8] In our study, this bias has been reduced by the limited window (48 hours) of adequate treatment and by the time-to-event in the survival analysis of at least three days.[8] Morbidity and complications are important outcome parameters in influenza virus infection, particularly in the hospitalized subgroup of patients. Although we are aware of the impediments of the use of composite endpoints, the composite endpoint used in this study reflects both morbidity and mortality in our cohort of patients.

Only 176 patients from the complete cohort (n=390) were included in the matched cohort. This is partly due to missing data regarding the CURB-65 score (n=67). This score has not been recorded routinely in the patients´ medical records. Without the availability of this score, patients could not be matched and consequently were not included in the matched cohort. A potential additional weakness is the selection of patients who have been sampled to test for influenza virus infection. In a recent report, test frequency for influenza virus infection is inhomogenous in various countries. In the Dutch patients in this study, test frequency was, however, high at 72% (33/46). We assume that missing tests were most substantial among the least ill patients.[32]

Furthermore, the unmeasured confounders were not considered and we could not rule out the presence of these.

Interestingly, the data show a steady increase in 30-day mortality as the CURB-65 score increases. This demonstrates that the CURB-65 score is a plausible confounder in our cohort of hospitalized patients with seasonal influenza and that CURB-65 was correctly incorporated in the propensity score model. In this study, with 323 laboratory-confirmed hospitalized patients with influenza virus infection for which CURB-65 scores are available, the 30-day mortality rate in the various CURB-65 risk classes corresponds to the risk profile of community-acquired pneumonia.[33] In other cohorts of patients with influenza, CURB-65 score predicted 30-day mortality inconsistently[34], or showed higher mortality in each risk class.[35]

CONCLUSION

Patients with prolonged symptoms, admitted with seasonal influenza virus infection and treated with oseltamivir within 48 hours after hospital admission, had a significantly reduced 30-day mortality and a significantly reduced composite endpoint of 30-day mortality and/or ICU admission >48h after hospital admission. A new cohort of these, mostly older and comorbid patients could confirm the benefit of oseltamivir treatment within 48 hours after hospital admission and could assess the trend in improvement in length of hospital stay and in-hospital mortality.

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REFERENCES

1. FluView: Influenza Hospitalization Surveillance Network, Centers for Disease Control and Prevention. 2019 Available at: https://gis.cdc.gov/GRASP/Fluview/FluHospRates.html.
2. Oliva J, Delgado-Sanz C, Larrauri A. Estimating the burden of seasonal influenza in Spain from surveillance of mild and severe influenza disease, 2010-2016. Influenza Other Respir Viruses. 2018;12(1):161-70.
3. Loubet P, Samih-Lenzi N, Galtier F, et al. Factors associated with poor outcomes among adults hospitalized for influenza in France: A three-year prospective multicenter study. J Clin Virol. 2016;79:68-73.
4. Haas J, Braun S, Wutzler P. Burden of influenza in Germany: a retrospective claims database analysis for the influenza season 2012/2013. Eur J Health Econ. 2016;17(6):669-79.
5. Zhang G, Xia Z, Liu Y, et al. Epidemiological and clinical features of 308 hospitalized patients with novel 2009 influenza A (H1N1) virus infection in China during the first pandemic wave. Intervirology. 2011;54(3):164-70.
6. Cao B, Li XW, Mao Y, et al. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. N Engl J Med. 2009;361(26):2507-17.
7. Kmietowicz Z. Study claiming Tamiflu saved lives was based on “flawed” analysis. BMJ. 2014;348:g2228.
8. Jones M, Del Mar C, Hama R. Statistical and methodological concerns about the beneficial effect of neuraminidase inhibitors on mortality. Lancet Respir Med. 2014;2(7):e9-e10.
9. Antes G, Meerpohl JJ. Statistical and methodological concerns about the beneficial effect of neuraminidase inhibitors on mortality. Lancet Respir Med. 2014;2(7):e10.
10. Wolkewitz M, Schumacher M. Statistical and methodological concerns about the beneficial effect of neuraminidase inhibitors on mortality. Lancet Respir Med. 2014;2(7):e8-9.
11. van Dissel JT, Vossen A, Boucher CAB, et al. Richtlijn klinische behandeling met antivirale therapie van opgenomen patiënten met influenza. Seizoen 2012-2013 Available at: https://lci.rivm.nl/sites/default/files/2017-06/BehandelrichtlijnGriepv2.4.f.pdf
12. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza. Clin Infect Dis. 2019 Mar 5;68(6):e1-e47.
13. Dugas AF, Monteforte B, Puri A, Awad M, Hsieh YH, Rothman R. ED compliance with influenza antiviral recommendations. Am J Emerg Med. 2014;32(12):1550-2.
14. Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med. 2014;2(5):395-404.
15. Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. J Antimicrob Chemother. 2003;51(1):123-9.
16. Rothberg MB, Bonner AB, Rajab MH, Kim HS, Stechenberg BW, Rose DN. Effects of local variation, specialty, and beliefs on antiviral prescribing for influenza. Clin Infect Dis. 2006;42(1):95-9.
17. Groves T. What does oseltamivir do, and how will we know? BMJ. 2013;347:f4687.
18. Kmietowicz Z. WHO downgrades oseltamivir on drugs list after reviewing evidence. BMJ. 2017;357:j2841.
19. Kmietowicz Z. Choice of oseltamivir in 2009 flu pandemic was “worrying,” says MP. BMJ. 2013;346:f3371.
20. Lee N, Chan PK, Hui DS, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. J Infect Dis. 2009;200(4):492-500.
21. Baccam P, Beauchemin C, Macken CA, Hayden FG, Perelson AS. Kinetics of influenza A virus infection in humans. J Virol. 2006;80(15):7590-9.
22. Haynes B. Can it work? Does it work? Is it worth it? The testing of healthcare interventions is evolving. BMJ. 1999;319(7211):652-3.
23. Capelastegui A, Espana PP, Quintana JM, et al. Validation of a predictive rule for the management of community-acquired pneumonia. Eur Respir J. 2006;27(1):151-7.
24. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46(3):399-424.
25. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-9.
26. Yao XI, Wang X, Speicher PJ, et al. Reporting and Guidelines in Propensity Score Analysis: A Systematic

Review of Cancer and Cancer Surgical Studies. J Natl Cancer Inst. 2017;109(8).
27. Lee N, Leo YS, Cao B, et al. Neuraminidase inhibitors, superinfection and corticosteroids affect survival of influenza patients. Eur Respir J. 2015;45(6):1642-52.
28. Centre for Infectious Disease Control, National Institute for Public Health and the Environment. Annual report Surveillance of influenza and other respiratory infections in the Netherlands: winter 2017/2018 2018 Available at: https://www.rivm.nl/bibliotheek/rapporten/2018-0049.pdf.
29. Giannella M, Alonso M, Garcia de Viedma D, et al. Prolonged viral shedding in pandemic influenza A(H1N1): clinical significance and viral load analysis in hospitalized patients. Clin Microbiol Infect. 2011;17(8):1160-5.
30. Fielding JE, Kelly HA, Mercer GN, Glass K. Systematic review of influenza A(H1N1)pdm09 virus shedding: duration is affected by severity, but not age. Influenza Other Respir Viruses. 2014;8(2):142-50.
31. Choi SH, Kim T, Park KH, Kwak YG, Chung JW, Lee MS. Early administration of neuraminidase inhibitors in adult patients hospitalized for influenza does not benefit survival: a retrospective cohort study. Eur J Clin Microbiol Infect. 2017;36(9):1673-7.
32. Radovanovic D, Sotgiu G, Jankovic M, et al. An international perspective on hospitalized patients with viral community-acquired pneumonia. Eur J Intern Med. 2019;60:54-70.
33. Aujesky D, Auble TE, Yealy DM, et al. Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. Am J Med. 2005;118(4):384-92.
34. Myles PR, Nguyen-Van-Tam JS, Lim WS, et al. Comparison of CATs, CURB-65 and PMEWS as triage tools in pandemic influenza admissions to UK hospitals: case control analysis using retrospective data. PloS one. 2012;7(4):e34428.
35. Shi SJ, Li H, Liu M, et al. Mortality prediction to hospitalized patients with influenza pneumonia: PO2 /FiO2 combined lymphocyte count is the answer. Clin Respir J. 2017;11(3):352-60.