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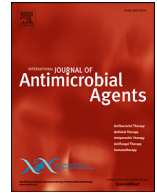
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Effectiveness of oseltamivir in reduction of complications and 30-day mortality in severe seasonal influenza infection

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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. As the burden of influenza disease is substantial and oseltamivir treatment is biologically plausible, this study assessed the clinical benefit of oseltamivir treatment in adult patients admitted with severe seasonal influenza virus infection in daily practice.

Patients and methods: A multi-centre, retrospective cohort study was conducted to compare the effectiveness of treatment with and without oseltamivir <48 h 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 clinically relevant outcome variables.

Results: In total, 390 patients were included in this study, of whom 80% had comorbidities. Thirty-day mortality, as well as the composite endpoint of 30-day mortality or intensive care unit admission >48 h 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 3 days.

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

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1. 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 USA, 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 influenza

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%, respectively [2,3]. In 2013, the annual costs for patients hospitalized with influenza virus infection in Germany were estimated to be €90 million [4].

Neuraminidase inhibitors are the primary treatment option for patients with severe influenza infection. However, evidence regarding the clinical effectiveness of neuraminidase inhibitors is 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 use of the neuraminidase inhibitor

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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 h of the onset of symptoms [14,15]. In clinical practice, the majority of patients who present to a hospital have had symptoms for >48 h [14]. In these cases, the benefit of later initiation of treatment (>48 h after symptom onset) is not yet known.

Moreover, the majority of clinical studies have enrolled young, H1N1pdm09-infected patients with limited comorbidities [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 with treatment guidelines may be poor due to uncertainty about the diagnosis at initial hospital presentation. Once influenza has been confirmed in a laboratory, 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 uncertainty of the potential benefit of oseltamivir [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 have been present for >48 h at hospital presentation. Therefore, this study 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 >48 h of illness. An observational cohort study using propensity score methods was performed to assess the clinical effectiveness of oseltamivir.

2. Patients and methods

2.1. Design and study population

A multi-centre, 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 Centre (585 beds) and University Medical Centre 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 1 October 2013 and 1 April 2016 were screened for eligibility. Lists of adult patients (≥ 18 years) with positive polymerase chain reaction test results for influenza A or B virus in respiratory samples (sputum, nasopharyngeal or throat swab; endotracheal aspirates or bronchoalveolar lavage) were obtained. Children were excluded from this study as they have different influenza immunological response and disease dynamics. Patients with influenza A or B virus positive samples who were hospitalized within 7 days before or after virologic confirmation were included. Patients with hospital-acquired influenza infection (i.e. if symptoms had started ≥ 72 h after hospital admission) were excluded.

2.2. Data collection and study definitions

Data on demographic characteristics, start of symptoms, dates of hospital admission and discharge, influenza type (A or B), comorbidities, CURB-65 score (most consistent marker of severity at presentation) [23], presence of pneumonia (consolidation on chest X-ray) at admission, start and stop of oseltamivir treatment, start

of antibacterial treatment at hospital admission, and ICU admission within 48 h of admission were obtained from electronic medical records. ICU admission <48 h 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, haematological malignancy, haematopoietic stem cell transplantation, chronic use of immunosuppressive medication or chemotherapy in the past 6 months, or human immunodeficiency virus with CD4+ T-lymphocyte count ≤ 200 cells/ μ L.

In this study, the commencement of oseltamivir treatment within 48 h of hospital admission was considered as adequate treatment [14]. This group of patients was compared with a group who had not been treated with oseltamivir within 48 h of admission. During the study period, oseltamivir was the only neuraminidase inhibitor used in the three hospitals. The 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.

The 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 h after hospital admission. ICU admission >48 h after hospital admission is regarded as a complication of influenza virus infection (i.e. severe morbidity). This composite endpoint was used to assess the clinical benefit of oseltamivir for individual decision-making in patient care – both outcome parameters are clinically relevant.

For subgroup analysis, chest X-rays were assessed for the presence or absence of a consolidation by independent radiologists. A consolidation is regarded as a 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.

2.3. Statistical analyses

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

Propensity score matching (PSM) and inverse probability weighting (IPW) were used to compare the outcome parameters 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 Version 14 (StataCorp, College Station, TX, USA).

2.4. Propensity score methods

Propensity score methods can be used to analyse observational data concerning a specific treatment outcome by defining which individuals have the same probability of receiving the intervention (adequate oseltamivir treatment in this case), and by 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, the aim is to attain the results that reflect those of a randomized study [24].

In this study, propensity scores were generated using a multi-variable logistic regression model based on confounding variables

Table 1
Baseline characteristics before and after propensity score matching

	Cohort before matching				<i>P</i> ^a	Cohort after matching				<i>P</i> ^a
	<i>n</i> ^b	%	<i>n</i> ^b	%		<i>n</i>	%	<i>n</i>	%	
Total	138		252			88		88		
Gender										
Male	80	58.0	146	57.9	>0.99	51	58.0	51	58.0	>0.99
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 (years)	58.4		65.1		<0.01	62.3		62.5		0.93
Elderly (>65 years)					<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 ≤48 h 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	

ICU, intensive care unit.

^a Fisher's exact test, or Chi-squared test if more than two rows.^b Numbers do not always add up to 390 as there are some missing data. In particular, CURB-65 scores are missing in 67 patients.

as identified by the univariate analyses. Variables that were associated ($P<0.20$) with the allocation of treatment and the primary endpoint of 30-day mortality, and were plausible confounders, were selected for input into a logistic regression model to calculate the propensity scores. The matching algorithm used a nearest neighbour method in a 1:1 ratio without replacement and a caliper (maximum probability distance) of 0.20. The available variables were used to optimize the model. To balance baseline variables between groups of patients treated adequately 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 with Student's *t*-test, Fisher's exact test 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).

2.5. Reporting and ethics

This 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]. Re-

search data were pseudonymized and stored securely in accordance with the General Data Protection Regulation.

3. Results

3.1. 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. Therefore, 390 patients admitted to the hospitals with laboratory-confirmed, community-acquired influenza virus infection were included in the final analysis. Their median age was 65 years (IQR 51–77) and 42% were female. Comorbidities were present in 80% of patients; of these, 60% had cardiovascular comorbidities, 42% had pulmonary comorbidities and 46% were immunocompromised. Forty-seven solid organ transplant recipients (12%) and 21 (5%) stem cell transplant recipients were included in the cohort.

One hundred and 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 h after admission and 203 (81%) were not treated with os-

Table 2
CURB-65 score and 30-day mortality

	30-day mortality
CURB-65 score	
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; U, urea >7 mmol/L; R, respiratory rate $\geq$ 30/min;

B, blood pressure (systolic <90 mmHg or diastolic $\leq$ 60 mmHg); 65, age $\geq$ 65 years.

eltamivir. Overall, the median length of hospital stay was 5.0 days (IQR 2.9–10.0). Seventy (18%) patients needed to be admitted to the ICU, 23 (34%) required non-invasive ventilator support, 37 (54%) required invasive mechanical ventilation, and three (4%) needed extracorporeal membrane oxygenation support. Of the ICU patients, 62 were admitted within 48 h of hospital admission. In-hospital mortality was 21/390 (5.4%) and 30-day mortality was 30/390 (7.7%).

Baseline characteristics differed between the patients who received adequate treatment ($n=138$) and the patients who did not ($n=252$). Younger patients, patients with comorbidities or with concomitant antibiotics, and patients admitted to the ICU within 48 h of 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).

3.2. Propensity score matching

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

3.3. 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 h of 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, the median duration of symptoms before start of treatment was 3.0 days (IQR 2.0–4.1).

3.4. Outcome with inverse 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 showed a trend towards reduction (Table 4).

3.5. Survival analysis

Survival analyses are presented in Fig. A1 and A2 (see online supplementary material). Thirty-day mortality and the composite

endpoint were better in the group who received adequate treatment. The first death occurred 3 days after hospital admission.

3.6. Subgroup analysis in patients with consolidation on chest X-ray

Sixty (34%) patients in the matched cohort had a consolidation on 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 compared with two (7%) patients who received adequate treatment ($P=0.07$). In-hospital mortality was 17% (5/30) in patients who did not receive adequate treatment compared with 3% (1/30) in patients who received adequate treatment ($P=0.09$).

4. Discussion

During three consecutive influenza seasons, the burden of patients admitted with community-acquired influenza virus infection in the three hospitals was substantial: the median length of stay was 5 days, and 70 of 390 patients needed ICU admission. In the PSM cohort (mean age of 62 years and substantial comorbidities), oseltamivir treatment within 48 h of hospital admission reduced 30-day mortality as well as the composite endpoint of 30-day mortality and/or ICU admission >48 h after hospital admission. The median duration between symptom onset and initiation of oseltamivir was 3.0 days.

This 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 patients infected with influenza A (H1N1)pdm09 virus who were treated with oseltamivir (odds ratio 0.81) [14]. The odds ratio for 30-day mortality in the present cohort was 0.30.

There are important differences between the Muthuri cohort and the present cohort that need consideration. Firstly, in the Muthuri cohort, only 5% of patients were aged $\geq$ 65 years 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]. The present cohort reflects this type of patient: 193 of 390 (49%) patients were >65 years of age and 143 of 389 (37%) patients were immunocompromised.

Secondly, the healthcare systems in the countries contributing to the meta-analysis of Muthuri et al. differ 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 means that patients present at hospital later, and potentially start oseltamivir longer after the onset of symptoms. However, in the study by Muthuri et al., the median time from symptom onset to start of antiviral treatment was 3 days, similar to the time for the complete cohort in the present study (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 h) seems less relevant. In addition, self-reported duration of symptoms is often unreliable.

In the study cohort, of the 87 of 125 (70%; 13 missing) treated patients who had symptoms for more than 2 days, treatment with

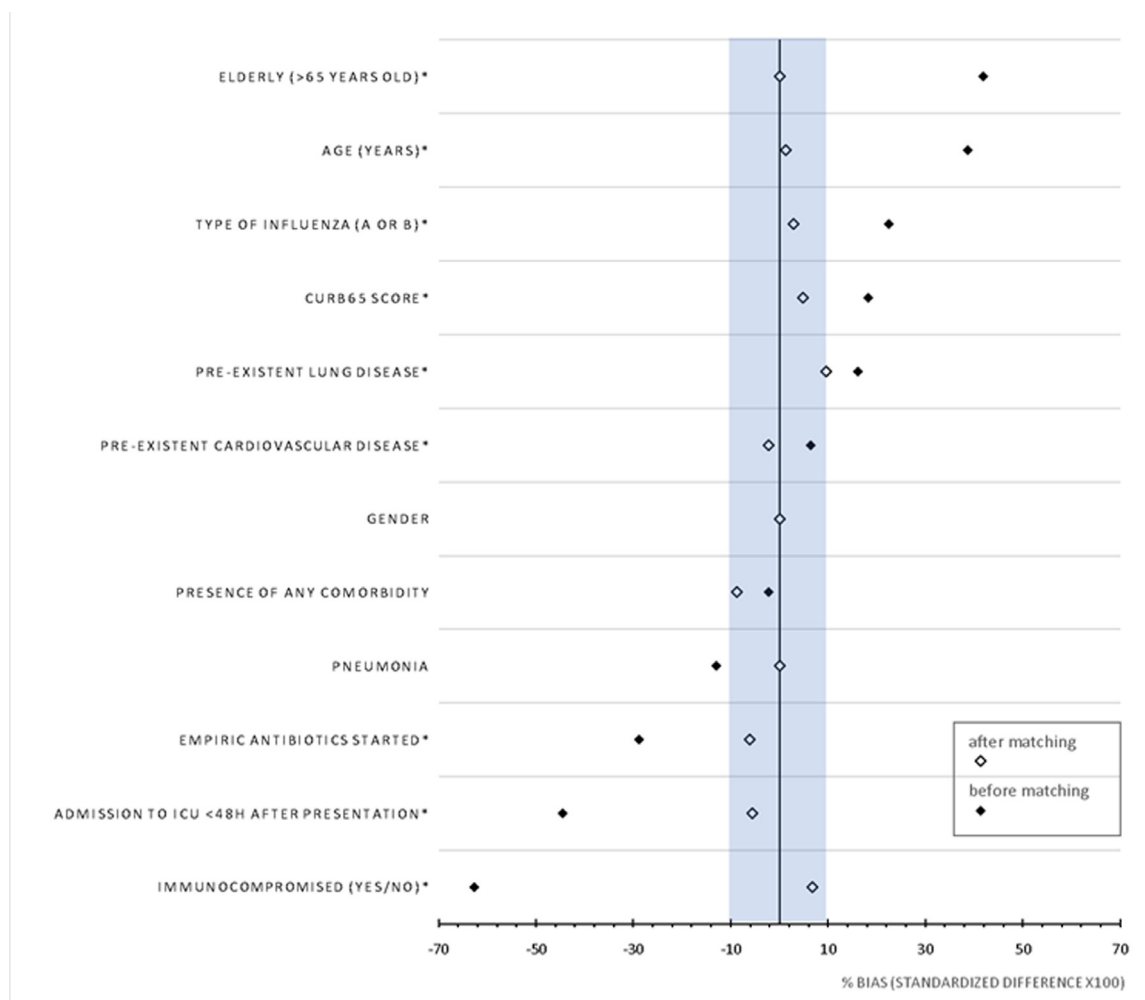


Figure 1. Standardized differences before and after propensity matching. Variables marked with an asterisk have been used in the propensity score model. ICU, intensive care unit.

Table 3

Outcome using propensity score matching in the group of influenza patients treated with oseltamivir within 48 h of hospital admission compared with the group of patients without this treatment

Outcome variable	Untreated (%)	Treated (%)	Difference (%)	OR	95% CI	P
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 (IQR) length of hospital stay (days)	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 >48 h after hospital admission.

Table 4

Outcome using inverse probability weighting in the group of influenza patients treated with oseltamivir within 48 h of hospital admission compared with 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 (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 >48 h after hospital admission.

oseltamivir within 48 h of hospital admission reduced 30-day mortality and the composite endpoint. This illustrates the biological plausibility of the treatment effect of oseltamivir over a larger time window in patients with prolonged viral replication (i.e. patients who are hospitalized). This becomes clearer in 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 a consolidation. These results provide pragmatic guidance in the decision to start oseltamivir treatment in patients hospitalized with influenza virus infection.

A strength of this study is the multi-centre 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. Patients who present to a hospital generally have severe disease or 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 PSM and IPW are consistent, and use of these statistical methods enabled the authors to reduce the impact of selection bias as much as possible. A similar study in 506 patients with influenza in South Korea found completely different results [31], but did not use a propensity score model.

Hospital mortality as an outcome parameter, used in the meta-analysis by Muthuri et al. [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]. The use of 30-day mortality in the present study is, therefore, a more appropriate outcome parameter. Other concerns regarding the meta-analysis by Muthuri et al. concerned the potential time-dependent bias [8]. In the present study, this bias was reduced by the limited window (48 h) of adequate treatment and by the time-to-event in the survival analysis of at least 3 days [8]. Morbidity and complications are important outcome parameters in influenza virus infection, particularly in hospitalized patients. Although the authors are aware of the impediments of the use of composite endpoints, the composite endpoint used in this study reflects both morbidity and mortality in the study cohort.

Only 176 patients from the complete cohort ($n=390$) were included in the matched cohort. This is partly due to missing data for the CURB-65 score ($n=67$). This score has not been recorded routinely in 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 was the selection of patients who had been sampled to test for influenza virus infection. In a recent report, test frequency for influenza virus infection is inhomogeneous in various countries. In the Dutch patients in this study, test frequency was, however, high at 72% (33/46). It has been assumed that missing tests were most substantial among the least ill patients [32].

Furthermore, the unmeasured confounders were not considered and the presence of these cannot be ruled out.

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 the study cohort of hospitalized patients with seasonal influenza, and that CURB-65 was incorporated correctly in the propensity score model. In this study, with 323 laboratory-confirmed hospitalized patients with influenza virus infection for whom CURB-65 scores were 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, the CURB-65 score

predicted 30-day mortality inconsistently [34], or showed higher mortality in each risk class [35].

5. Conclusion

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

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijantimicag.2020.106155](https://doi.org/10.1016/j.ijantimicag.2020.106155).

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