ORIGINAL ARTICLE
RESPIRATORY INFECTIONS

Early oseltamivir treatment improves survival in critically ill patients with influenza pneumonia

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ABSTRACT

Background: The relationship between early oseltamivir treatment (within 48 h of symptom onset) and mortality in patients admitted to intensive care units (ICUs) with severe influenza is disputed. This study aimed to investigate the association between early oseltamivir treatment and ICU mortality in critically ill patients with influenza pneumonia.

Methods: This was an observational study of patients with influenza pneumonia admitted to 184 ICUs in Spain during 2009–2018. The primary outcome was to evaluate the association between early oseltamivir treatment and ICU mortality compared with later treatment. Secondary outcomes were to compare the duration of mechanical ventilation and ICU length of stay between the early and later oseltamivir treatment groups. To reduce biases related to observational studies, propensity score matching and a competing risk analysis were performed.

Results: During the study period, 2124 patients met the inclusion criteria. All patients had influenza pneumonia and received oseltamivir before ICU admission. Of these, 529 (24.9%) received early oseltamivir treatment. In the multivariate analysis, early treatment was associated with reduced ICU mortality (OR 0.69, 95% CI 0.51–0.95). After propensity score matching, early oseltamivir treatment was associated with improved survival rates in the Cox regression (hazard ratio 0.77, 95% CI 0.61–0.99) and competing risk (subdistribution hazard ratio 0.67, 95% CI 0.53–0.85) analyses. The ICU length of stay and duration of mechanical ventilation were shorter in patients receiving early treatment.

Conclusions: Early oseltamivir treatment is associated with improved survival rates in critically ill patients with influenza pneumonia, and may decrease ICU length of stay and mechanical ventilation duration.

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Controversy persists regarding the effectiveness of NAIs in the treatment of severe influenza due to a lack of data from RCTs. This propensity score-matched observational study reaffirms that early oseltamivir treatment is associated with better outcomes. https://bit.ly/2KdW5AJ

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Introduction

Influenza is one of the leading causes of mortality from infectious diseases worldwide, resulting in an estimated 300 000–645 000 deaths in adults each year [1]. Up to a third of adults hospitalised with influenza require admission to an intensive care unit (ICU), of whom >60% require mechanical ventilation, frequently due to viral pneumonia and acute respiratory distress syndrome (ARDS) [2], with a resulting mortality rate of up to 30% [3]. Beyond supportive therapy, neuraminidase inhibitors (NAIs) are the first-line option for severe influenza [4–6]. Both the US Centers for Disease Control and Prevention and the World Health Organization recommend oseltamivir for patients hospitalised with severe, progressive, complicated influenza or for those at risk of developing complications. However, the timing of antiviral treatment may be critical in improving outcomes, as reports indicate that starting antivirals within 48 h of symptom onset can reduce mortality [7]. Thus, the mainstay of therapy for patients with severe influenza is the initiation of antiviral treatment as soon as possible after the onset of illness [8].

In the absence of strong evidence from randomised controlled trials (RCTs) involving critically ill patients, clinical knowledge relies on extrapolation from observational studies, which currently suggest that the effectiveness of NAIs is greatest when they are started within 48 h of symptom onset [3, 9–11]. A large meta-analysis, which included 5103 critically ill adults with influenza A(H1N1)pdm09, found a reduction in mortality of 38% in those receiving early NAI compared with those receiving treatment later [12]. However, this study has been widely criticised due to the high risk of biases [13, 14].

There has been a long-standing debate regarding the role and benefit of NAIs in the treatment of influenza. Current evidence suggests that the effect of NAIs on mortality depends on the population being treated and the clinical setting [15]. However, ethical constraints limit the ability to randomise severely ill patients and obtain the highest level of evidence from RCTs in intensive care settings. Therefore, to strengthen the evidence base, new observational studies need to focus on reducing biases and improving the quality of observational data.

In this study, we evaluated the association between early oseltamivir treatment and ICU mortality compared with later treatment in critically ill patients with influenza pneumonia. Our approach aimed to account for the biases present in previous observational studies.

Materials and methods

Study design

This was a retrospective analysis of prospectively collected data from subjects admitted to 184 ICUs in Spain (>50% of the country's ICUs) between June 2009 and April 2018. Data were obtained from a nationwide registry created by the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC). The information was recorded either by the attending physician or obtained by reviewing clinical case notes, laboratory data and radiological records. All consecutive cases admitted to an ICU who met the entry criteria were enrolled. The study was approved by the Ethics Committee of Joan XXIII University Hospital (Tarragona, Spain) (approval 11809). All data were anonymised, allowing the requirement for informed consent to be waived. The ICU admission criteria and treatment decisions were not standardised between the centres, and were left to the discretion of the attending physicians in accordance with the recommendations of the SEMICYUC [16].

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Subjects

The inclusion criteria were: patients admitted to an ICU with a severe acute respiratory infection [17], acute respiratory failure, radiological findings consistent with pneumonia and microbiological confirmation of influenza A or B by reverse transcription (RT)-PCR at ICU admission, and receipt of oseltamivir prior to ICU admission. Nasopharyngeal swab specimens were collected at admission and lower respiratory tract secretions were also obtained in intubated patients. The exclusion criteria were: children <15 years old, patients with missing data (about antiviral therapy or the start of antiviral therapy, time from symptom onset to hospital and ICU admission, or incomplete follow-up), patients without pneumonia and those with an ICU length of stay <48 h.

Data collection

The following information was collected at and during ICU admission (supplementary table S1): demographic data, comorbidities, time from illness onset to hospital admission, time to first dose of antiviral delivery and dosage of oseltamivir, time from hospital admission to ICU admission, complications during the ICU stay, and microbiological, laboratory and chest radiological findings. Illness severity was determined with the Acute Physiology and Chronic Health Evaluation (APACHE) II score, which was calculated for all patients within the first 24 h of ICU admission. Organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) score.

Study definitions

Two treatment groups were defined: 1) the early oseltamivir group (who received oseltamivir within 2 days of symptom onset) and 2) the later oseltamivir group (who received oseltamivir after 2 days since symptom onset).

Primary viral pneumonia was defined as acute respiratory failure and the presence of pulmonary infiltrates on chest radiography in combination with a positive RT-PCR test result for influenza and negative respiratory and blood bacterial cultures during the acute phase of infection [18]. Community-acquired respiratory co-infection (CARC) or bacterial co-infection was defined as any infection diagnosed within the first 2 days of hospitalisation by isolation of respiratory or blood cultures positive for bacteria/fungi during ICU admission [19]. All remaining definitions are summarised in the supplementary material.

Outcomes

The primary outcome was to investigate the association between early oseltamivir treatment and ICU mortality compared with later treatment. Secondary outcomes were to analyse: 1) factors associated with later oseltamivir administration, 2) ICU length of stay in the two treatment groups and 3) duration of mechanical ventilation in survivors in the two treatment groups.

Statistical analysis

Discrete variables are expressed as count (percentage), while continuous variables are presented as median (interquartile range (IQR)). For the demographic and clinical characteristics, differences between the groups were assessed with the Chi-squared test and Fisher's exact test for categorical variables or the t-test or Mann–Whitney U-test for continuous variables. Time zero of follow-up was ICU admission. To avoid immortal time bias, we controlled for internal left-truncation in the data from patients who initiated oseltamivir treatment after this time-point. Thus, all patients have initiated oseltamivir at time zero of the follow-up. Data from patients with ICU length of stay <48 h were also left-truncated to ensure that the effect of treatment exposure was guaranteed. A binary logistic regression was used to analyse the factors associated with later oseltamivir initiation. In the unmatched cohort, a multiple logistic regression analysis was performed to evaluate the association between early oseltamivir treatment and ICU mortality. The results of these analyses are presented as the odds ratio with 95% confidence interval. Model integrity was tested using standard diagnostic statistics, and plots and the goodness of fit for each model were assessed for all outcomes with the Hosmer–Lemeshow test.

Propensity score matching was used to address confounding by indication when investigating treatment effects [20, 21]. A 2:1 matched analysis without replacement and with a caliper of 0.2 was performed using an optimal matching algorithm between patients in the early and later oseltamivir treatment groups using estimated propensity scores. To predict the likelihood of treatment, we performed a multivariate logistic regression analysis regularised by the lasso method that included all the covariates. For the matched set, we used two types of survival models: a Cox proportional hazards model applied to a cause-specific hazard (CSH) function and a competing risk analysis using a Fine–Gray model [22–24]. Models were constructed for a 60-day follow-up. The CSH model considered ICU discharge as a censoring event, allowing the interpretation of aetiological relationships between early oseltamivir use and patient outcomes. The results are presented as the hazard ratio (HR) with 95% confidence interval. The competing

risk analysis was performed by treating ICU mortality and discharge as competing events [13, 25]. The Fine–Gray model calculates the probability of any event (death or discharge) at time *t* based on the assumption that no other event has occurred and, therefore, it can be used to predict events. This procedure was performed using a subdistribution hazard function (subdistribution HR (sHR)). Cumulative incidences were plotted for early *versus* later oseltamivir treatment and for both competing events. We checked the proportional hazards assumption model and the proportionality of the subdistribution from the Fine–Gray model. No violations were found.

Data analysis was performed with SPSS version 24 (IBM, Armonk, NY, USA), except for the survival models, for which R version 3.6 (cran.r-project.org) was used.

Results

During the study period, 4175 patients were admitted to an ICU for severe influenza. Among them, 2124 met the inclusion criteria of this study (figure 1).

Baseline characteristics

The median (IQR) age of the cohort was 54 (43–65) years and 1299 (61.2%) were male. The most frequent underlying chronic disease was obesity (n=675 (31.8%)), followed by chronic obstructive pulmonary disease (COPD) (n=393 (18.5%)). The median (IQR) APACHE II and SOFA scores were 16 (11–21) and 6 (4–8), respectively. Regarding the influenza strain, influenza A(H1N1)pdm09 was the most frequently isolated (n=1533 (72.2%)), followed by influenza A(H3N2) (n=336 (15.8%)) and influenza B (n=148 (7%)). The remaining strains (n=107 (5%)) were nontypeable influenza A. Only 308 (14.5%) patients in the full cohort had been vaccinated against influenza.

All patients were diagnosed with influenza-related pneumonia, of whom 1586 (74.7%) had primary viral pneumonia and 538 (25.3%) had CARC. The median (IQR) number of lobes showing pulmonary infiltrates on chest radiographs was 2 (2–4). The rate of invasive mechanical ventilation was 59.1%, with 618 (29.1%) patients receiving prone therapy. At ICU admission, septic shock was frequent (n=1157 (54.5%)) and 611 (28.7%) patients developed acute renal failure. All patients received oseltamivir before ICU admission (supplementary figure S1) and early oseltamivir treatment was administered in 529 (24.9%) patients.

Factors associated with later oseltamivir initiation

Before the propensity score matching, a multivariate logistic regression analysis was performed in the unmatched cohort to determine the factors associated with later antiviral therapy. The baseline

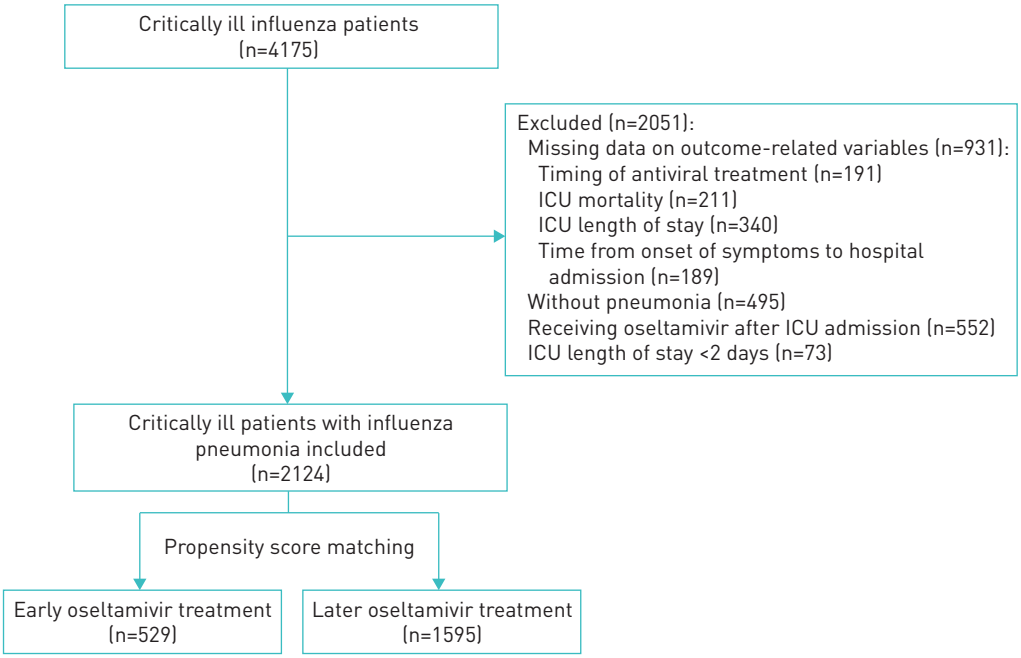

FIGURE 1 Study flowchart. ICU: intensive care unit. The early treatment group comprised patients who received oseltamivir within the first 2 days of illness onset. The later treatment group comprised patients who received oseltamivir after 2 days since illness onset.

demographic factors included in the model were age, immunosuppression, asthma, COPD, congestive heart failure and obesity. The only variable associated with later oseltamivir treatment was obesity (OR 1.49, 95% CI 1.18–1.87; p=0.01) (supplementary table S2).

Mortality analysis

The overall ICU mortality rate was 21.3%. Despite the absence of significant differences, there was a trend towards a lower mortality rate with early oseltamivir treatment compared with later treatment in the subgroups based of age and severity of illness (except for those extremely ill with an APACHE II score >30), as shown in supplementary figures S2 and S3. In the unmatched cohort, there were significant differences between survivors and nonsurvivors (supplementary table S3). The multivariate logistic regression analysis was adjusted for age, sex, APACHE II and SOFA scores, chronic kidney disease, immunosuppression, pregnancy, number of pulmonary infiltrates, mechanical ventilation, acute renal failure, septic shock, CARC, ventilator-associated pneumonia, oseltamivir treatment duration, and adjuvant corticosteroid treatment. It revealed a significant association between early oseltamivir treatment and lower ICU mortality compared with later treatment (OR 0.69, 95% CI 0.51–0.95; p=0.02) (figure 2).

Propensity score matching was performed by matching 529 patients in the early oseltamivir treatment group with 1058 patients in the later oseltamivir treatment group. Table 1 shows the baseline characteristics and complications at ICU admission of the unmatched and matched cohorts. The study groups were well balanced in terms of demographic characteristics, severity of illness, comorbidities and complications at ICU admission (table 1 and supplementary figure S4). The median time from hospital to ICU admission was 1 day in both groups. However, this median time showed a statistically significant difference between the groups, being longer in the early oseltamivir treatment group. The ICU mortality rate was significantly different between the early and later oseltamivir treatment groups in the propensity score-matched cohort (19.1% *versus* 24.6%; p=0.01). ICU length of stay and duration of mechanical ventilation were both significantly reduced by early oseltamivir treatment compared with later treatment (median (IQR) 8 (4–16) *versus* 10 (5–21) days and 5.7 (2.7–12) *versus* 8 (3–18) days, respectively).

The effect of early oseltamivir treatment on overall mortality was evaluated using the CSH model. There was a significant difference in the 60-day mortality rate between the groups. A forest plot showing the effects of different clinical variables included in the model (supplementary figure S5) demonstrated the

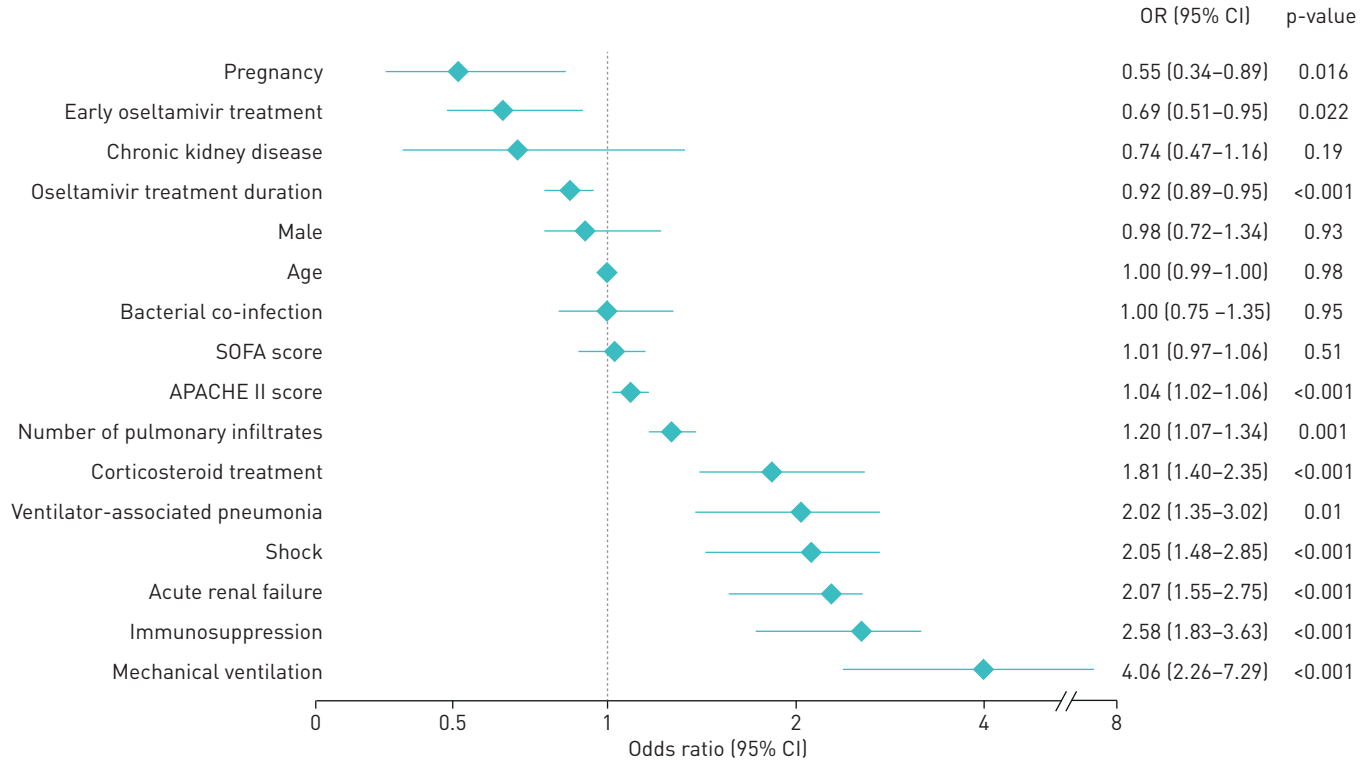

FIGURE 2 Multivariate logistic regression analysis for factors associated with intensive care unit mortality in the unmatched cohort. SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation.

TABLE 1 Baseline characteristics of the unmatched and propensity score-matched groups of patients[#]

	Unmatched cohort				Matched cohort			
	Early oseltamivir	Later oseltamivir	SMD	p-value	Early oseltamivir	Later oseltamivir	SMD	p-value
Demographic characteristics								
Age years	57 (46–68)	52 (42–63)	0.2309	<0.001	57 (46–68)	56 (46–67)	0.0159	0.49
Male	325 (61.4)	974 (61.1)		0.92	325 (61.4)	657 (61.7)		0.84
Disease severity								
APACHE II score	16 (12–23)	15 (11–21)	0.1941	<0.001	16 (12–23)	17 (12–22)	0.0011	0.52
SOFA score	6 (4–9)	6 (4–8)		0.38	6 (4–9)	6 (4–8)		0.56
Pulmonary infiltrates			−0.1931	<0.001			−0.0025	0.78
⩽2	328 (62.0)	780 (48.9)			328 (62.0)	647 (61.1)		
>2	201 (38.0)	815 (51.1)			201 (38.0)	411 (38.9)		
Disease timeframe								
Time from symptom onset to hospital admission days	2 (1–2)	5 (3–6)		<0.001	2 (1–2)	4 (3–6)		<0.001
Time from symptom onset to oseltamivir initiation days	2 (1–2)	5 (4–7)		<0.001	2 (1–2)	5 (4–7)		<0.001
Time from hospital admission to ICU admission days	1 (1–2)	1 (1–2)		0.002	1 (1–2)	1 (1–1)		0.04
Time from symptom onset to ICU admission days	3 (2–4)	6 (5–8)		<0.001	3 (2–4)	6 (4–8)		<0.001
Laboratory data								
White blood cell count $\times 10^9$ L^{-1}	9.1 (4.7–13.7)	6.9 (3.9–11.2)		<0.001	9.1 (4.7–13.7)	7.4 (4.0–12.3)		<0.001
Creatinine mg·mL^{-1}	1 (0.7–1.5)	0.9 (0.7–1.4)		0.05	1 (0.7–1.5)	1 (0.7–1.6)		0.36
Urea mg·mL^{-1}	45 (30–72)	41 (28–67)		0.33	45 (30–72)	48 (31–77)		0.13
Underlying conditions								
Any comorbidity	401 (75.8)	1099 (68.9)		0.003	401 (75.8)	738 (69.7)		0.01
Asthma	62 (11.7)	103 (6.4)	0.1634	<0.001	62 (11.7)	100 (9.4)	0.0704	0.18
COPD	116 (21.9)	277 (18.1)		0.02	116 (21.9)	204 (19.3)		0.24
Congestive heart failure	81 (15.3)	148 (17.4)	0.1673	<0.001	81 (15.3)	138 (13.0)	0.0629	0.24
Chronic kidney disease	44 (8.3)	128 (8.0)		0.90	44 (8.3)	107 (10.1)		0.28
Haematological disease	49 (9.3)	112 (7.0)		0.11	49 (9.3)	101 (9.5)		0.92
Immunosuppression	89 (16.8)	174 (10.9)	0.1579	<0.001	89 (16.8)	160 (15.1)	0.0454	0.42
Obesity	132 (24.9)	543 (34.0)	−0.2098	<0.001	132 (24.9)	261 (24.6)	0.0065	0.95
Pregnancy	54 (10.2)	182 (11.4)		0.49	54 (10.2)	131 (12.3)		0.23
HIV/AIDS	10 (1.9)	40 (2.5)		0.52	10 (1.9)	31 (2.9)		0.28
Neuromuscular disease	15 (2.8)	39 (2.5)		0.73	15 (2.8)	23 (2.1)		0.52
Autoimmune disease	17 (3.2)	65 (4.0)		0.44	17 (3.2)	51 (4.8)		0.17
Complications								
Acute renal failure	154 (29.1)	457 (28.6)		0.88	154 (29.1)	358 (33.8)		0.06
Mechanical ventilation[¶]	420 (79.4)	1289 (80.2)		0.51	420 (79.4)	869 (82.1)		0.21
Septic shock	294 (55.6)	863 (54.1)		0.59	294 (55.6)	608 (57.4)		0.50
Bacterial co-infection	144 (27.2)	394 (24.7)		0.27	144 (27.2)	308 (29.1)		0.46
Treatment								
Oseltamivir treatment duration days	7 (5–10)	8 (6–10)		<0.001	7 (5–10)	8 (5–10)		0.02
Adjuvant corticosteroids	209 (39.5)	598 (37.5)		0.43	209 (39.5)	407 (38.4)		0.72
Antibiotic combination	439 (82.9)	1398 (87.6)		0.008	439 (82.9)	919 (86.8)		0.05
Outcomes								
ICU length of stay days[+]	8 (4–16)	10 (5–21)		<0.001	8 (4–16)	10 (5–21)		<0.001
Duration of mechanical ventilation days[+]	5.7 (2.7–12)	7 (2.3–16)		<0.001	5.7 (2.7–12)	8 (3–18)		<0.001
ICU mortality	101 (19.1)	351 (22.0)		0.17	101 (19.1)	261 (24.6)		0.01

Data are presented as median (interquartile range) or n (%), unless otherwise stated. SMD: standardised mean difference; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit. [#]: unmatched cohort n=2124 (early oseltamivir n=529; later oseltamivir n=1595) and matched cohort n=1587 (early oseltamivir n=529; later oseltamivir n=1058); [¶]: noninvasive and invasive mechanical ventilation; [+]: only in survivors.

significant protective effect of early oseltamivir treatment (HR 0.77, 95% CI 0.61–0.99; p=0.03). A CSH model for ICU discharge also showed beneficial effects of early oseltamivir treatment (HR 1.21, 95% CI 1.07–1.36; p=0.002) (supplementary figure S6). Additionally, we performed a competing risk analysis to compare the probability of event with the probability of being discharged from hospital (figure 3 and

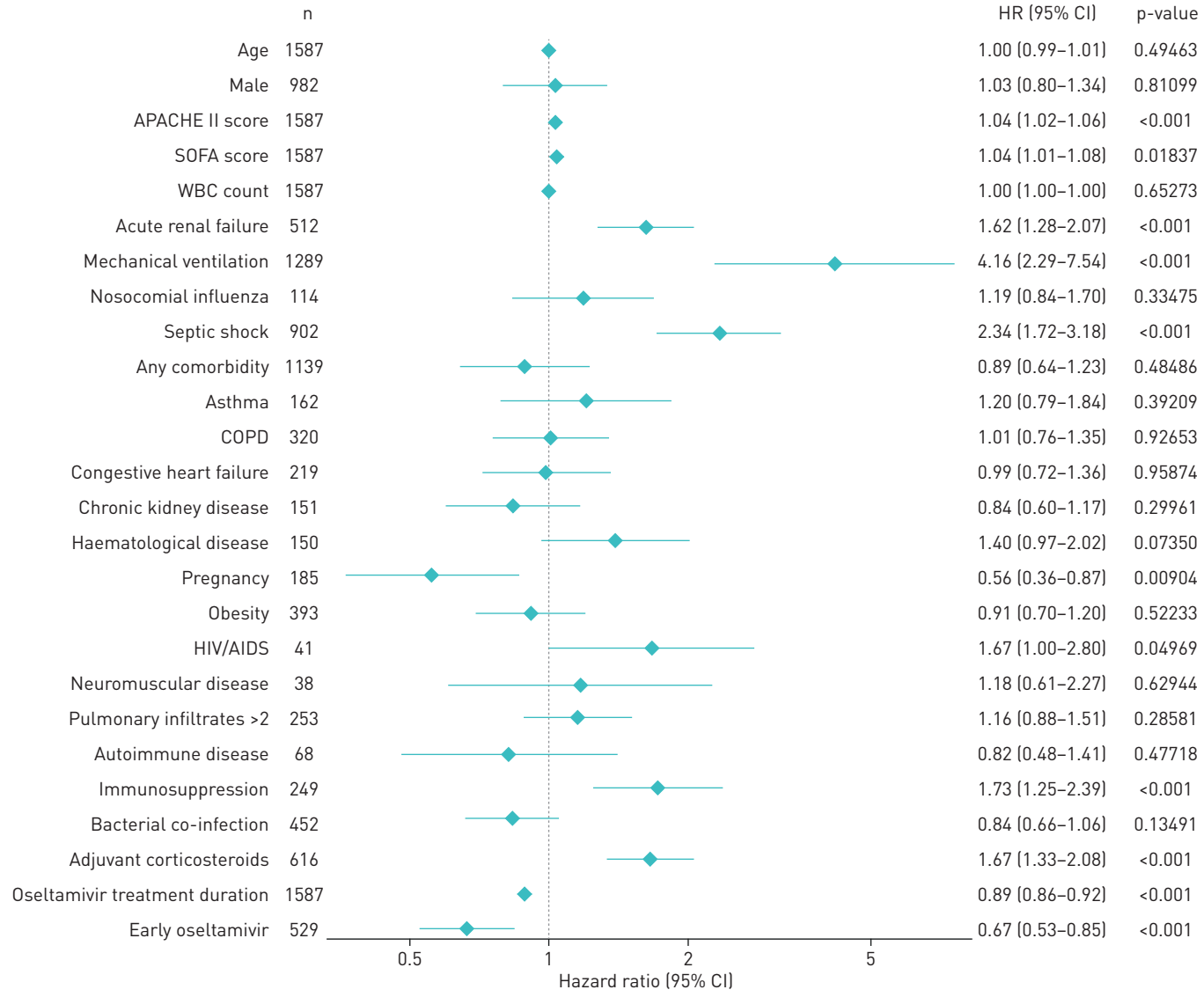

FIGURE 3 Forest plot of the competing risks analysis for the association of early oseltamivir treatment and 60-day intensive care unit mortality. APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; WBC: white blood cell; COPD: chronic obstructive pulmonary disease.

supplementary figure S7). Models were adjusted for age, sex, APACHE II and SOFA scores, white blood cell count, acute renal failure, mechanical ventilation, nosocomial influenza, septic shock, presence of any comorbidity, asthma, COPD, congestive heart failure, chronic kidney disease, haematological disease, pregnancy, obesity, HIV/AIDS, neuromuscular disease, pulmonary infiltrates (more than two lobes involved), autoimmune disease, immunosuppression, bacterial co-infection, adjuvant corticosteroids, and oseltamivir treatment duration. The predicted survival curves showed that early oseltamivir treatment was associated with a significantly lower probability of ICU mortality (sHR 0.67, 95% CI 0.53–0.85; p<0.001) and a higher probability of ICU discharge (sHR 1.28, 95% CI 1.13–1.44; p<0.001) compared with later treatment (figure 4).

Discussion

Early oseltamivir treatment in critically ill adults with influenza pneumonia was significantly associated with a reduction of 33% in ICU mortality compared with later treatment. This association was evident in a large, broadly representative sample of critically ill patients with pandemic and seasonal influenza after adjusting for disease severity and controlling for confounders and other time biases. Furthermore, the effect was consistently seen across a broad range of analytical approaches, adding substantial robustness to the overall findings.

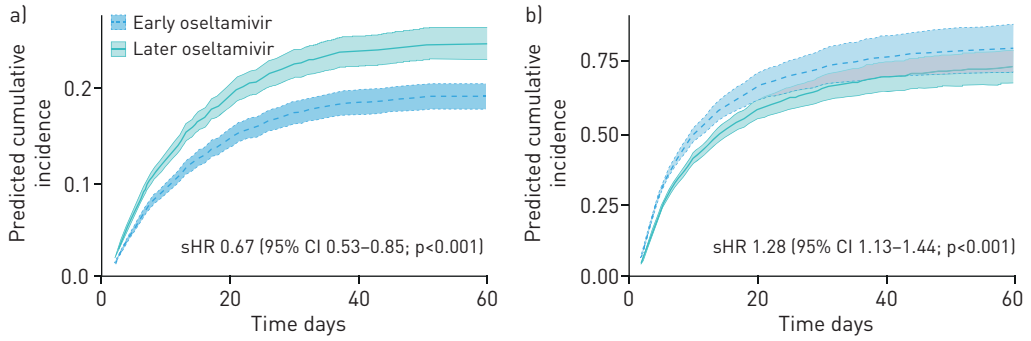

FIGURE 4 Survival plots of 60-day intensive care unit (ICU) mortality rates from the competing risk analysis between the early and later oseltamivir treatment groups: a) predicted cumulative incidence of ICU mortality for both treatment groups and b) predicted cumulative incidence of being discharged alive from the ICU. sHR: subdistribution hazard ratio. sHRs are adjusted for age, sex, Acute Physiology and Chronic Health Evaluation II scores, Sequential Organ Failure Assessment scores, white blood cell count, acute renal failure, mechanical ventilation, nosocomial influenza, septic shock, presence of any comorbidity, asthma, chronic obstructive pulmonary disease, congestive heart failure, chronic kidney disease, haematological disease, pregnancy, obesity, HIV/AIDS, neuromuscular disease, pulmonary infiltrates (more than two lobes involved), autoimmune disease, immunosuppression, bacterial co-infection, adjuvant corticosteroids, and oseltamivir treatment duration.

Our findings are consistent with those of several observational studies on the effectiveness of NAIs published since the influenza A(H1N1)pdm09 pandemic [3, 9, 26, 27]. Lee *et al.* [28] reported that NAI treatment (predominantly oseltamivir) was independently associated with survival in hospitalised patients (with a low proportion of critically ill patients), with the highest benefit observed when treatment was started within the first 2 days of illness onset (HR 0.20, 95% CI 0.12–0.32). However, there was also benefit with treatment within 3–5 days compared with no treatment. This observation was made after carefully controlling for confounding factors and immortal time bias. Muthuri *et al.* [12] performed a large meta-analysis of individual participant data which included 5103 adults with influenza A(H1N1) pdm09 admitted to an ICU. They found a reduction in mortality of 38% in those receiving early NAI compared with those receiving treatment later. Despite controlling for potential biases related to the timing of therapy and death, the study has been widely criticised due to the high risk of selection biases, possible confounding by indication, and possible immortal time bias [13, 14].

Most previous studies have focused only on influenza A(H1N1)pdm09. Recently, Lytras *et al.* [29] published data from 1330 adults in ICUs with severe influenza. They observed a 30% reduction in mortality with early oseltamivir treatment compared with later therapy among patients with influenza A (H3N2), although this benefit was not found in patients with influenza B or A(H1N1), suggesting that the effectiveness of oseltamivir may vary between influenza viral strains. However, the authors did not adjust for baseline severity (*e.g.* APACHE II or SOFA scores), which is important for predicting mortality. In addition to using mechanically ventilated patients as a marker of severity, it is very important to adjust for severity given that patients can develop pneumonia, ARDS, septic shock and multiorgan failure [30]. In our study, after accounting for this severity and other confounding factors with propensity score matching, we observed a clear association between early oseltamivir therapy and lower ICU mortality for the different virus strains, predominantly influenza A(H1N1)pdm09. It is noteworthy that the mortality rate in the study of Lytras *et al.* [29] was 46% compared with the ICU mortality rate of 21.3% in our study. Moreover, Lytras *et al.* [29] did not mention any possible complications during the ICU stay that could explain the high mortality rate. This might be the reason for the differences with our results regarding the usefulness of early oseltamivir treatment for the different types of influenza strains. Data from the FluSurv-NET indicated that influenza A and B resulted in similar morbidity and mortality rates among hospitalised patients; therefore, therapeutic intervention should not be influenced by the type of influenza virus [31].

Early oseltamivir treatment appeared to be beneficial in our study, based on multiple analytical approaches. This suggests that patients with severe influenza pneumonia should be treated immediately based on clinical suspicion during influenza epidemics, without waiting for a diagnostic confirmation. This is in line with current guidance and expert reviews that recommend starting treatment as soon as possible [4, 7, 8, 16]. Even in the cases of delayed hospital admission, oseltamivir should be initiated promptly because viral shedding may be prolonged in severe or potentially fatal cases [32–34]. This was observed by Muthuri *et al.* [12], who reported that mortality was reduced in ICU patients when treatment was commenced late (*versus* no treatment). Moreover, virological studies have found a strong correlation

between viral replication, clinical symptoms and disease severity [35]. Despite these recommendations, the rate of early antiviral treatment remains low, ranging from 17% to 33.7% in previous reports [9, 12, 29, 36, 37]. Indeed, when influenza is circulating in the community, it is suggested that early NAI treatment should be emphasised for outpatients who are at risk or present with severe disease, while hospitalised patients should be treated promptly without waiting for influenza test results [38, 39]. Some studies have suggested that the delayed initiation of antiviral therapy may contribute to increased illness severity and worse clinical outcomes [36, 40]. Early NAI therapy has been associated with a substantially decreased length of hospital stay [37, 41]. We also observed this in our study, as early oseltamivir treatment was associated with an increased probability of being discharged alive from the ICU and shorter durations of mechanical ventilation and ICU stays.

We noted that obesity was the only variable independently associated with the later initiation of oseltamivir treatment. Although critically ill obese patients might not have increased mortality, there may be an association between obesity and a higher consumption of ICU resources [42]. Thus, oseltamivir treatment should be immediately started based on a clinical suspicion of influenza in patients at risk of developing complications without waiting for virological confirmation, especially in obese patients who are at risk of receiving antiviral treatment later.

This is one of the largest observational studies of critically ill patients with both pandemic and seasonal influenza pneumonia. We evaluated the effectiveness of early oseltamivir treatment by carefully controlling for important confounders by propensity score matching, as well as for immortal time bias and competing risks. The study was also performed in multiple centres that provided data about influenza type and time from symptom onset to treatment. Therefore, this study improves on previous investigations by addressing the issues of those earlier studies.

However, we must acknowledge some limitations of our study. First, we did not review the duration of viral shedding or the appearance of drug-resistant viral strains in the groups. Fortunately, the incidence of oseltamivir resistance has remained low since the emergence of influenza A(H1N1)pdm09 [5]. Nevertheless, antiviral resistance should be an area for concern and must be considered in patients with immunosuppression or severe disease. Second, we did not collect data on oseltamivir side-effects or adjustment for patients with kidney failure and/or kidney replacement therapy. Oseltamivir is generally well tolerated, with the most common side-effects being gastrointestinal (*e.g.* nausea and vomiting). Evidence also suggests that drug clearance is significantly reduced in patients receiving kidney replacement therapy, necessitating dose adjustments. Third, the high number of excluded patients can result in attrition bias. However, there were no clinically relevant differences between the included and excluded patients in terms of age, illness severity and comorbidities. Fourth, despite effectively addressing several known potential biases, the nature of the observational study design meant that residual confounding and bias could have remained. However, the propensity score matching analysis should have balanced the population and observed confounders, and should have yielded the best evidence to date for physicians in the absence of firm data from RCTs.

In conclusion, among critically ill adults with influenza pneumonia, early oseltamivir therapy compared with later treatment was associated with improved survival rates and a considerable reduction in the use of healthcare resources, as evidenced by the reduced durations of both mechanical ventilation and ICU stay.

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