

## RESEARCH ARTICLE

# Outcomes of early oseltamivir treatment for hospitalized adult patients with community-acquired influenza pneumonia

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## Abstract

Early initiation of oseltamivir within 48 h to 5 days from illness onset has been associated with improved survival among patients with community-acquired influenza pneumonia. Delay of hospitalization limits early treatment and the survival of patients. To date, the effects of early oseltamivir initiation within 24 hours from admission on patient mortality has remained unknown. This retrospective study reviewed and analyzed the clinical and non-clinical outcomes of 143 patients, with community-acquired influenza pneumonia, who received oseltamivir within 24 h (group A) and after 24 h (group B) from admission. Among the patients, 82 (57.3%) received oseltamivir within 24 h while 61 (42.7%) received oseltamivir after 24 h. The median time from symptom onset to admission for group A and group B was not statistically significant ( $P < 0.001$ ). The 14-day mortality rate was 9% and 23% for group A and B, respectively ( $P = 0.03$ ), while the 30-day mortality were 15% and 30% for group A and B, respectively ( $P = 0.05$ ). Administration of oseltamivir within 24 h significantly affected 30-day mortality rates (adjust OR: 0.14, 95% CI: 0.47–0.04,  $P < 0.01$ ), particularly among patients with respiratory failure at admission (adjust OR: 0.08, 95% CI: 0+.30–0.06,  $P < 0.01$ ). Survival analysis of patient with influenza pneumonia and respiratory failure at admission demonstrated significant difference between those who received oseltamivir within and after 24 h ( $P = 0.002$ ). The results indicated that early oseltamivir initiation within 24 h improved the survival outcome mainly among those with respiratory failure at admission.

## Introduction

Influenza viral infection causes substantial morbidity and mortality as well as economic burden, particularly among patients with pneumonia [1]. The Center for Disease Control and Prevention estimated 9.4 million– 45 million cases of symptomatic illness due to influenza between 2010–2020, with annual hospitalization of 140,000–810,000 cases and 12,000–61,000

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cases of mortality [2]. Mortality due to influenza pneumonia was highest among the elderly (>65 years), accounting for 62% of all influenza-related deaths. However, 32% of death occurred in adults aged 18–64 years [2]. This indicated that influenza-related deaths affect a wide age range of patients with influenza related pneumonia. Several studies have shown that influenza virus was the most prevalent among community-acquired viral pneumonia [3–5]. Treatment with neuraminidase inhibitors demonstrated clinical benefits including shortened duration of symptoms, low respiratory tract complication, reduced rate of hospitalization and shorter length of hospital stay [6–8]. Moreover, survival benefit was shown in hospitalized patients [9]. Identification of risk factors associated with severe pneumonia, and timely treatment improved the mortality outcome. The current recommendation is early testing and treatment of hospitalized patients who are suspected to have influenza related pneumonia with antiviral agents [10]. A meta-analysis reported that early treatment within 48h of symptom onset was associated with 55% and 38% reduction in mortality in adults and critically ill patients, compared with late treatment [11]. The overall mortality was not improved when treatments were initiated after 48h of symptoms onset. However, a 35% mortality risk reduction was noted for critically ill adult patients. Each day delay of antiviral initiation, up to a maximum of 5 days, increased the mortality hazard rate. In current practice, treatment is often delayed while awaiting results of laboratory tests [12]. A recent study found that the median time from onset of illness to hospitalization of patients with community-acquired influenza pneumonia was 5 days. Consequently, initiation of oseltamivir 5 days after symptom onset did not yield significant favorable outcomes among hospitalized patients [13]. The impact of initial oseltamivir treatment within 24 h has not been adequately investigated. Hence, the objective in this study is to determine the clinical outcome of early initiation of oseltamivir treatment within 24 h of hospitalization of adult patients with community-acquired influenza related pneumonia.

## Methods

### Study design and population

The study is a retrospective cohort study conducted among adult hospitalized patients in Songklanagarind hospital, an 800-bed university hospital located at the Prince of Songkla University in southern Thailand. Patients aged 18 years or above who were admitted with community-acquired influenza related pneumonia between January 2016 to December 2020 were included in this study.

Records of confirmed influenza cases were retrieved from the hospital information system and laboratory database. The revision of records was based on ICD10 as follows; J110 Influenza with pneumonia, virus not identified and J12 Viral pneumonia, not elsewhere classified. Patients with a diagnosis of influenza pneumonia via: 1. acute lower respiratory tract symptoms, 2. new pulmonary infiltration on chest radiographs and 3. positive samples of influenza virus infection tested by Sofia™ Influenza A + B FIA (Quidel Corporation, CA, USA) rapid influenza diagnostic test and/or VIASURE Flu A, B Real Time RT-PCR Detection Kit (CerTest Biotec S.L.). The viral RNA was extracted by magLEAD 12gC (Precision System Science Co., Matsudo, Japan). The PCR was performed on the CFX96 Touch Real-Time PCR Detection System. The M1 gene was detected at the cut-off threshold of 40 cycles in accordance with the manufacturer's recommendation. Patients with initial bacterial coinfection were excluded from the final analysis. Early oseltamivir treatment was defined as receiving oseltamivir within 24 h from the time of admission. Oseltamivir dosage in this study was divided into high-dose (150 mg twice daily) and standard dose (75 mg twice daily).

## Data collection

Electronic medical records were retrospectively reviewed to obtain demographic data, comorbidities, symptoms onset, respiratory failure, APACHE II score, intensive care unit (ICU) admission, type of influenza, management including time of oseltamivir initiation, dosage, and duration of treatment, and clinical outcomes including 14-day, 30-day, and in-hospital mortality rates. Non-clinical outcomes included length of hospital stay and hospital costs. The patients with respiratory failure were defined as those who required mechanical ventilation during admission. We allocated the patients that received oseltamivir within 24 h in group A and patients that did not receive oseltamivir within 24 h into group B. The databases were accessed for analysis since December 2020 to April 2021.

## Statistical analysis

We compared the clinical characteristics and outcomes of group A and group B. Category variables are presented as number and percentages. Continuous variables are expressed as mean  $\pm$  standard deviation in normal distribution and median  $\pm$  interquartile range (IQR) in non-normal distribution. Fisher's exact test or Chi square was used for category variables. Student's T test or Mann-Whitney U test was employed in regards to the continuous variable.

To compare between survivors and non-survivors, univariate analysis was used, factoring influencing clinical outcomes. Variables with  $P < 0.2$  from univariate or variables with clinical relevance were analyzed using a multivariate logistic regression model. A Cox proportional hazards model was used to analyze independent factors between survivors and non-survivors. A survival analysis between group A and group B, from the time of admission, was performed to assess the clinical outcome in both groups. The time started was defined as the day that influenza pneumonia was diagnosed on admission. The time ended was defined as the date that the patient outcome was documented, or the patient was excluded from the observation frame. All the analyses were performed using R software version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

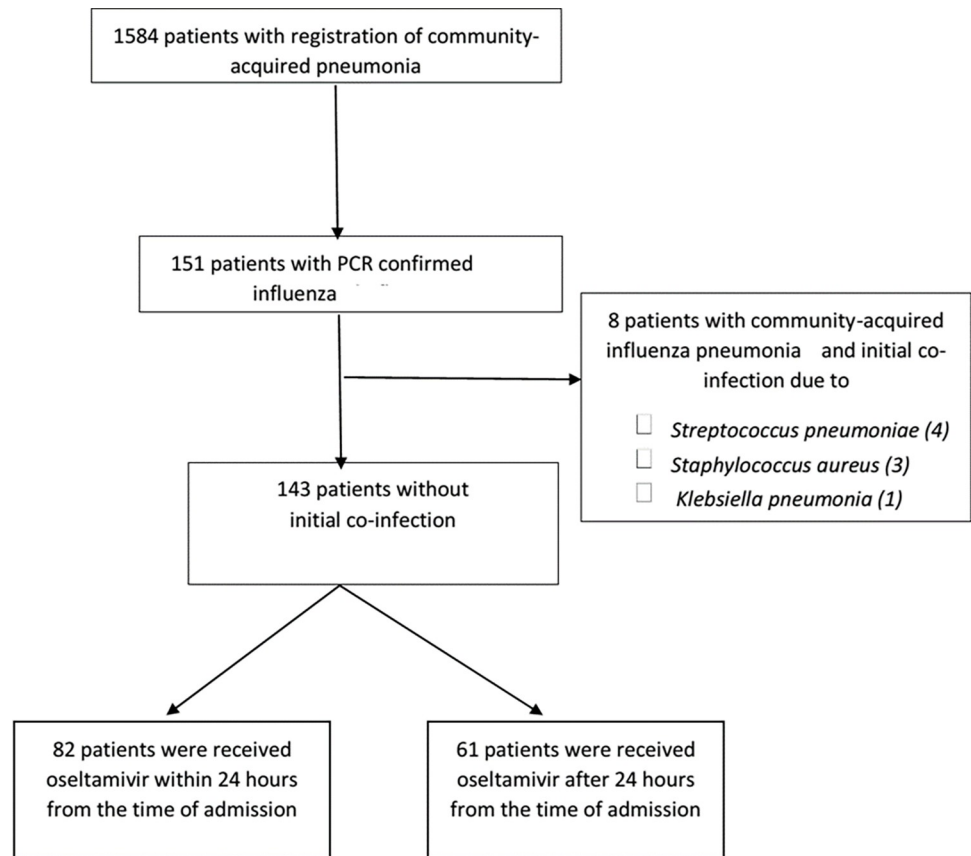
## Ethical statement

Ethical approval was granted by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University with the certification No. PSU EC: 55-141-14-1-3/ Sub 2. The data were fully anonymized before accessed and analyzed. According to the retrospective design of the study and relatively low risk for the participants, the need for informed consent was waived by the ethics committee.

## Results

A total of 1584 patients were registered with community-acquired pneumonia in Songklanagarind Hospital, with 151 (9.5%) patients diagnosed of influenza pneumonia, and 127 (84%) patients had positive results of rapid test following positive result for PCR. There were 24 patients who only had positive PCR results. The study flow chart is presented in [Fig 1](#). Eight patients who had bacterial pneumonia coinfection were excluded, while 143 patients were included in the analysis, consisting of 82 patients (57.3%) that received oseltamivir within 24 h from admission (group A) and 61 patients (46.7%) that received oseltamivir after 24 hours from admission (group B).

Demographic data, comorbidities, clinical characteristic, and treatment are summarized in the [Table 1](#). There were no significant differences in patient characteristics between the two groups. The severity of patients in group A was significantly higher than group B. Higher



**Fig 1. Flow chart of patient enrollment and inclusion in the study.**

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proportion of the patients in group A had respiratory failure and initial ICU admission as well as higher APACHE II score. The median time from symptoms onset until admission in group A and group B was 6 days and 5 days, respectively but these were not statistically significant. The median time for oseltamivir initiation was 8 h for group A and 47 h for group B ( $P < 0.001$ ).

The comparison of outcomes between patients in group A and B is presented in [Table 2](#). The 14-day and 30-day mortality rate were significantly lower in group A ( $P = 0.03$  and  $P = 0.05$ , respectively). However, in-hospital mortality rate was indifferent between group A and group B. Bacterial superimposed infection was significantly lower in group A than in group B ( $P = 0.05$ ). In addition, the non-clinical outcomes (length of hospital stay and hospital cost) were lower in group A than in group B ( $P = 0.05$ ). In subgroup analysis among those who received high dosage of oseltamivir, 14-day, 30-day, in-hospital mortality rate and non-clinical outcomes were indifferent between the patients who received oseltamivir within 24 hours from time of admission and those who did not receive oseltamivir within 24 hours from time of admission. ([S1 Table](#)).

In the subgroup analysis, the outcomes in patients with community-acquired influenza pneumonia who received oseltamivir within 48 h and after 48 h from the time of admission were not different ([S2 Table](#)). Interestingly, receiving oseltamivir within 24 hours from admission improved the mortality outcomes and non-clinical outcomes in patients presenting respiratory failure on admission ([S3 Table](#)). Among the patients without respiratory failure, early

**Table 1. Comparison of clinical features between patients with community-acquired influenza pneumonia who received oseltamivir within 24 h from the time of admission and those that received later than 24 h.**

Parameter	Patients who received oseltamivir within 24 h from the time of admission n = 82(%)	Patients who did not receive oseltamivir within 24 h from the time of admission n = 61(%)	P-value
<b>Demographics</b>			
Age (year), median (IQR)	45 (34,68)	45 (42,68)	0.509
Male sex	56 (68)	39 (64)	0.714
Current smoking	35 (43)	25 (41)	0.974
Comorbidities	64 (78)	42 (69)	0.294
Diabetes mellitus	29 (35)	21 (34)	0.999
Hypertension	33 (40)	31 (51)	0.277
Chronic kidney diseases	9 (11)	4 (7)	0.539
Cardiovascular diseases	14 (17)	7 (12)	0.486
Cerebrovascular diseases	2 (2)	1 (2)	0.999
Hematologic diseases	11 (13)	9 (15)	0.999
Malignancy	2 (2)	1 (2)	0.999
Chronic pulmonary airway diseases	25 (31)	20 (33)	0.912
Immunocompromised status	3 (4)	4 (7)	0.460
Obesity	46 (56)	34 (56)	0.999
<b>Clinical characteristic</b>			
Fever	68 (83)	51 (84)	0.999
Time from onset of symptoms to admission (day), median (IQR)	6(4,8)	5(4,7)	0.762
Respiratory failure at the admission	40 (49)	12 (20)	< 0.001
APACHEII score, median (IQR)	21 (19,24)	18 (16,22)	0.036
Initial admission in intensive care unit	49 (60)	10 (16)	< 0.001
Infection with type A influenza virus	42 (51)	33 (54)	0.864
<b>Treatment</b>			
Initiation of antibiotics within 24 hours	68 (83)	51 (84)	0.999
Time to initiate oseltamivir (hour), median (IQR)	8(4,17)	47(31,59)	< 0.001
Receiving high dosage of oseltamivir	62 (76)	49 (80)	0.641
Duration of oseltamivir(day), median (IQR)	10 (9,14)	10 (9,14)	0.932

IQR, interquartile range; APACHEII, Acute Physiology and Chronic Health Evaluation.

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treatment within 24 hours from admission did not significantly decrease mortality outcome while it significantly shortened the length of hospital stay (S4 Table).

Table 3 presented the factors that influenced 30-day mortality among patients with community-acquired influenza pneumonia. Higher APACHE II score, initial respiratory failure at admission and timing of oseltamivir initiation (within 24 h) were significantly associated with 30-day mortality.

In the subgroup analysis, survival benefit was demonstrated in patients with respiratory failure who received oseltamivir within 24 h (S5 Table). Conversely, the early treatment effect was not revealed in patients without respiratory failure (S6 Table). Survival analysis of patients with community-acquired influenza pneumonia that received oseltamivir within 24 h from admission and those who received it later than 24 h demonstrated borderline different survival with  $P = 0.0579$  by Log rank test (Fig 2). For patients with community-acquired influenza

**Table 2. Comparison of outcomes between patients with community-acquired influenza pneumonia who received oseltamivir within 24 h from the time of admission and those that received later than 24 h.**

Outcome	Patients who received oseltamivir within 24 h from the time of admission n = 82(%)	Patients who did not receive oseltamivir within 24 h from the time of admission n = 61(%)	P-value
Clinical outcomes			
Mortality			
14-day	7 (9)	14 (23)	<b>0.030</b>
30-day	12 (15)	18 (30)	<b>0.050</b>
In-hospital	14 (17)	19 (31)	0.076
After the end of treatment with oseltamivir	7 (9)	7 (11)	0.560
Bacterial superimposed infection	12 (15)	18 (30)	<b>0.050</b>
Non-clinical outcomes			
Length of hospital stay after survival (days) [median (IQR)]	24 (16,34)	32 (20,35)	<b>0.021</b>
Cost (baht) [median (IQR)]			
Total hospital	156,333 (98,456–218,236)	184,882 (101,894–254,569)	<b>0.035</b>
Antimicrobial	23,889 (16,554–28,442)	31,222(27,887–34,002)	< <b>0.001</b>
Non-antimicrobial	136,212 (100,654–199,221)	146,881 (121,488–211,956)	<b>0.039</b>

IQR, interquartile range.

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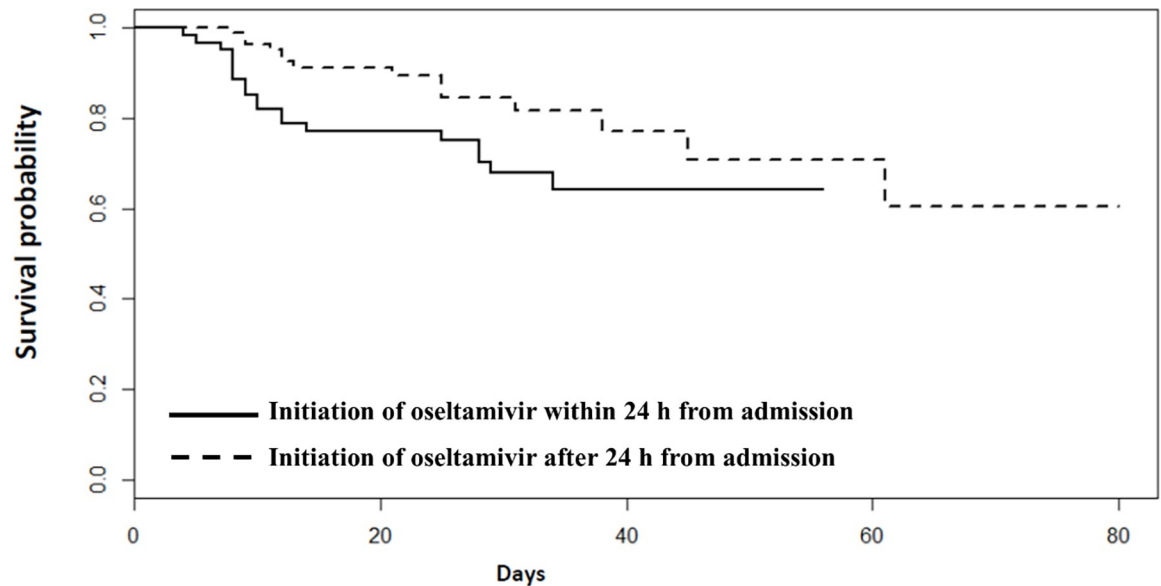
pneumonia and respiratory failure at admission, survival analysis for those who received oseltamivir within 24h of admission and those who received later than 24h demonstrated significant difference ( $P = 0.002$ ) (S1 Fig), whereas for patients with community-acquired influenza pneumonia without respiratory failure at admission, survival analysis for those who received oseltamivir within 24 h of admission and those who received later than 24 h was not significantly different ( $P = 0.200$ ) (S2 Fig).

**Table 3. Factors influencing 30-day mortality among 143 patients with community-acquired influenza pneumonia.**

Variables	Values		Crude OR (95% CI)	Adjusted OR (95% CI)	P-value
	Survivors n = 113(%)	Non-survivors n = 30(%)			
Age (year) [median (IQR)]	45 (42,68)	45 (34,68)	1.19 (0.51,2.75)	1.07 (0.38,2.98)	0.899
Male sex	76 (67)	19 (63)	0.98 (2.38,0.36)	0.83 (2.94,0.24)	0.766
Underlying disease(s)	81 (72)	25 (83)	1.96 (5.55,0.69)	1.56 (5.55,0.43)	0.492
Current smoking	49 (43)	11 (37)	0.75 (1.72,0.33)	1.02 (2.70,0.38)	0.973
Immunocompromised status	6 (5)	1 (3)	0.61 (5.26,0.07)	0.26(3.44,0.02)	0.274
Obesity	59 (52)	21 (70)	2.13 (5.00,0.90)	2.04 (5.88,0.70)	0.178
APACHE II score [median (IQR)]	19 (15,21)	22 (19,22)	1.01 (0.97,1.54)	1.18 (1.03,1.33)	<b>0.048</b>
Initial intensive care unit admission	46 (41)	13 (43)	1.11 (2.44,0.49)	1.61 (4.76,0.53)	0.398
Respiratory failure at the admission	35 (31)	17 (57)	2.94 (6.66,1.28)	4.35(14.28,1.41)	<b>0.008</b>
Infection with type A influenza virus	55 (49)	20 (67)	2.11 (0.91,4.9)	2.12 (0.79,5.71)	0.081
Initiation of oseltamivir within 24 hours	70 (62)	12 (40)	0.41 (0.93,0.18)	0.14(0.47,0.04)	< <b>0.001</b>
Initiation of antibiotics within 24 hours	92 (81)	27 (90)	2.04 (7.69,0.57)	2.04 (9.09,0.47)	0.325
Receiving high dosage of oseltamivir	89 (79)	22 (73)	0.74 (1.89,0.29)	1.01 (3.03,0.33)	0.996
Duration of antimicrobial agents (day) [median (IQR)]	10(9,14)	10(9,14)	1.01 (0.95,1.10)	1.00(0.91,1.04)	0.998

IQR, interquartile range; APACHEII, Acute Physiology and Chronic Health Evaluation; OR, Odds ratio; CI, Confidence interval.

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**Fig 2. Survival between patients with community-acquired influenza pneumonia who received oseltamivir within 24 h from admission and those who received after 24 h from admission.**

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## Discussion

In this study, we provided evidence of clinical and non-clinical benefits of the early initiation of oseltamivir within 24 h from admission among adult patients with community-acquired influenza pneumonia. Significantly lower 14-day and 30-day mortality were observed among patients who received oseltamivir within 24 h from admission. Similarly, significant difference was found among patients with respiratory failure at admission. However, this benefit was not observed among those without respiratory failure at admission. Delayed initiation of oseltamivir even within 48h after admission yielded no beneficial outcome. Our finding underscores that early treatment initiation within 24 h from admission has significant impact on outcome despite 5 days of symptom onset. Notably, mortality was significantly reduced notwithstanding the higher severity among patients who received early treatment.

Although neuraminidase inhibitors are effective against influenza, treatment outcomes are still debated [11, 14–17]. In a recent cohort study, early treatment with oseltamivir within 48 h was associated with lower mortality among critically ill patients that required ICU admission. However, beneficial outcomes were recorded for patients infected with influenza A/H3N2, but not for patients with influenza A/H1N2 and B [18]. The survival benefit of oseltamivir treatment within 5 days from illness onset has been demonstrated in several studies [9, 19–23]. A randomized control trial of empirical oseltamivir treatment within 24 h of hospitalization failed to reduce ICU transfer, re-hospitalization and 30-day mortality. Factors associated with clinical failure were possibly the small sample size of laboratory-confirmed influenza, associated lower respiratory tract infection, and low incidence of influenza [13].

In contrast, our results demonstrated the impact of early oseltamivir treatment within 24h of hospitalization despite the 6 days-interval between symptom onset and admission. Notably, oseltamivir treatment commenced within a median time of 8h in the early treatment group. To the best of our knowledge, this is the first study that demonstrates a survival benefit of early treatment within 24h from admission despite exceeding 5 days post illness onset. Moreover, most of the patients in this study presented with respiratory failure and required ICU

attendance. The results are consistent with an observational study which reported a 33% reduction in ICU mortality following early oseltamivir treatment in critically ill patients [20], while the survival outcomes were insignificant in patients without respiratory failure. This finding agrees with a cohort study which reported that in-hospital mortality was not significantly reduced in patients with  $\text{PaO}_2/\text{FiO}_2 < 200$  following oseltamivir treatment [21]. The incidence of influenza B was relatively high in the study population, but the results showed lesser oseltamivir efficacy on patients infected with influenza B as opposed to those infected with influenza A [24]. However, clinical benefits presented in this study were regardless of the type of influenza.

In this study, high doses of oseltamivir were used for critically ill cases. Although most studies have claimed that high-dose therapy was inadequate for the improvement of survival in a population mainly infected with influenza A [25–28]. Utilization of a high-dose regimen may be beneficial in critically ill cases with influenza B since the  $\text{IC}_{50}$  value was 10 times higher compared with influenza A [29]. Administration of high dose medication was reported to result in high plasma concentration. However, this benefit was not observed in our result. Our study demonstrated the effects of early treatment with oseltamivir in severely ill patients with influenza-related pneumonia. This study was based on analyzing observational data in regards to the treatment of hospitalized patients, differentiating the impact of early treatment between two groups, within 24 and within 48 h from admission. Mortality outcomes were not improved when treatment was initiated within 48 hours from admission.

There were several limitations in this study, that should be acknowledged. Firstly, similar to a previous observational study, a potential selection bias was introduced by different rates of influenza tests in each season [30]. Secondly, the circulating influenza in our studied population was equally proportionate between influenza A and B. Although in Thailand, influenza A is the prevalent type accounting for 76% in the tertiary care hospital system [31]. In a recent systematic review the epidemic strain was influenza A [32]. Our results may not claim an overall benefit in areas where influenza A is predominant. Thirdly, this study was conducted in a single tertiary care center, thus limiting its generalization to other level of healthcare services. Thus, in the setting of a tertiary care and referral center, the patients in this study had relatively severe manifestations with high APACHEII scores and relatively prolonged length of hospital stays. Fourthly, according to the nature of retrospective studies, the data on decision-making processes were insufficient thus an indication bias cannot be excluded. Fifthly, the number of patients in this study was relatively low. In this study, there was a 30-day mortality rate of 31% among the patients who did not receive oseltamivir within 24 h from the time of admission in this study and the enrolment of 143 patients only achieved a 54% power of prediction. Thus, the power of prediction among patients with initial respiratory failure and without initial respiratory failure was only at 55% and at 49%, respectively. Lastly, most of the patients in this study received high dosages of oseltamivir but in subgroup analysis among those who received high dosage of oseltamivir did not demonstrated the favourable outcomes among those who received oseltamivir within 24 hours from admission. Thus, in multivariate analysis, receiving high dosage of oseltamivir was not associated with survival benefit. Then, the results of this study did not inform the appropriate dosing of oseltamivir due to the observed variations.

## Conclusions

Treatment of patients with community-acquired influenza related pneumonia with oseltamivir within 24 h of hospital admission, despite exceeding 5 days from illness onset, led to a significant reduction in 14 and 30-day mortality and favorable non-clinical outcomes, particularly among patients with initial respiratory failure at admission.



## Supporting information

**S1 Fig. Survival between patients with community-acquired influenza pneumonia with respiratory failure at admission who received oseltamivir within 24 h from admission and those who received after 24 h from admission.**

(DOCX)

**S2 Fig. Survival between patients with community-acquired influenza pneumonia without respiratory failure at admission who received oseltamivir within 24 h from admission and those who received after 24 h from admission.**

(DOCX)

**S1 Table. Comparison of outcomes between patients with community-acquired influenza pneumonia at the admission who received high dosage of oseltamivir within 24 h and after 24 h from the time of admission.**

(DOCX)

**S2 Table. Comparison of outcomes between patients with community-acquired influenza pneumonia who received oseltamivir within 48 h and after 48 h from the time of admission.**

(DOCX)

**S3 Table. Comparison of outcomes between patients with community-acquired influenza pneumonia and respiratory failure at the admission who received oseltamivir within 24 h and after 24 h from the time of admission.**

(DOCX)

**S4 Table. Comparison of outcomes between patients with community-acquired influenza pneumonia without respiratory failure at admission who received oseltamivir within 24 h and after 24 h from the time of admission.**

(DOCX)

**S5 Table. Factors influencing 30-day mortality among 52 patients with community-acquired influenza pneumonia and respiratory failure at admission.**

(DOCX)

**S6 Table. Factors influencing 30-day mortality among 91 patients with community-acquired influenza pneumonia and without respiratory failure at admission.**

(DOCX)

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**Writing – review & editing:** Sarunyou Chusri.

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