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Original Research Article

Clinical Outcomes of Early Versus Delayed Antiviral Therapy in Influenza Patients: A Cohort Study

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Abstract

Background: Influenza remains a significant cause of morbidity and mortality worldwide, with antiviral therapy serving as a cornerstone of management. The optimal timing of neuraminidase inhibitor initiation remains debated, particularly regarding clinical benefit beyond the recommended 48-hour window from symptom onset. This study compared clinical outcomes between early and delayed antiviral therapy in hospitalized influenza patients.

Methods: A prospective cohort study was conducted at tertiary care hospitals, enrolling 386 laboratory-confirmed influenza patients aged ≥18 years. Participants were categorized into early treatment (antiviral initiation ≤48 hours from symptom onset, n=234) and delayed treatment (>48 hours, n=152) groups. Primary outcomes included hospital length of stay, time to clinical improvement, and complications. Secondary outcomes comprised intensive care unit (ICU) admission, mechanical ventilation requirement, and in-hospital mortality.

Results: Mean age was 52.4 ± 16.8 years, with 56.7% having influenza A. Early treatment group demonstrated significantly shorter hospital stay (5.8 ± 2.3 vs. 8.4 ± 3.6 days, $p < 0.001$), faster symptom resolution (4.2 ± 1.6 vs. 6.7 ± 2.4 days, $p < 0.001$), and lower complication rates (18.4% vs. 35.5%, $p < 0.001$) compared to delayed treatment. Early therapy was associated with reduced ICU admission (12.8% vs. 27.0%, $p = 0.001$), mechanical ventilation (8.1% vs. 19.7%, $p = 0.002$), and mortality (3.4% vs. 10.5%, $p = 0.007$). Multivariable analysis revealed early treatment as an independent predictor of favorable outcomes (adjusted OR = 0.42, 95% CI: 0.26-0.68, $p < 0.001$). Benefits were observed across age groups and influenza subtypes, with greatest impact in high-risk patients.

Conclusion: Early antiviral therapy within 48 hours of symptom onset significantly improves clinical outcomes in hospitalized influenza patients, reducing disease severity, complications, and healthcare resource utilization. These findings support aggressive implementation of early treatment protocols and highlight the importance of rapid diagnostic testing and timely therapeutic intervention.

Keywords: Influenza; Antiviral Therapy; Neuraminidase Inhibitors; Treatment Timing; Clinical Outcomes; Oseltamivir; Hospital Length Of Stay.

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Introduction

Seasonal influenza constitutes a major global health burden, causing an estimated 3-5 million cases of severe illness and 290,000-650,000 respiratory deaths annually [1]. Despite widespread vaccination efforts, influenza continues to result in substantial morbidity, healthcare utilization, and economic costs, particularly among vulnerable populations including elderly individuals, young children, pregnant women, and those with chronic medical conditions [2]. The emergence of novel influenza strains and periodic pandemics further underscores the critical importance of effective therapeutic strategies [3]. Neuraminidase inhibitors, particularly oseltamivir and zanamivir, represent

the primary antiviral agents for influenza treatment and prophylaxis [4]. These medications inhibit viral neuraminidase enzyme activity, preventing viral release from infected cells and limiting viral spread within the respiratory tract [5]. Current clinical practice guidelines from major health organizations, including the World Health Organization and the Centers for Disease Control and Prevention, recommend initiating antiviral therapy within 48 hours of symptom onset for optimal efficacy [6]. This recommendation is based on virologic principles demonstrating peak viral replication during the first 48-72 hours of illness and clinical trial data showing maximal benefit with early treatment initiation [7].

Several randomized controlled trials have established that early antiviral therapy reduces symptom duration, viral shedding, and complication rates in outpatient populations [8]. A meta-analysis by Dobson et al. demonstrated that treatment initiated within 48 hours reduced illness duration by approximately one day and decreased lower respiratory tract complications by 44% [9]. Similarly, observational studies in hospitalized patients have shown associations between early treatment and improved outcomes, including reduced mortality [10]. During the 2009 H1N1 pandemic, retrospective cohort studies reported that delayed antiviral therapy was associated with increased risk of ICU admission and death [11].

However, several important questions remain regarding the optimal timing and population-specific benefits of antiviral therapy. First, many patients present to healthcare facilities beyond the 48-hour window, raising questions about potential benefits of delayed treatment [12].

Some studies suggest continued benefit even with later initiation, particularly in severe cases or high-risk patients, while others question clinical significance beyond recommended timeframes [13]. Second, most existing evidence derives from outpatient or pandemic settings, with limited contemporary data from hospitalized patients with seasonal influenza [14]. Third, the impact of treatment timing on specific clinical endpoints such as respiratory failure, secondary bacterial infections, and intensive care requirements requires further clarification [15].

Real-world practice patterns often diverge from guideline recommendations, with studies documenting substantial delays between symptom onset and antiviral initiation [16]. Contributing factors include delayed healthcare seeking, diagnostic uncertainty, limited access to rapid testing, and physician hesitation due to perceived limited efficacy beyond 48 hours [17]. Understanding the magnitude of benefit associated with early versus delayed treatment in contemporary clinical practice is essential for informing treatment decisions, resource allocation, and quality improvement initiatives [18].

Recent advances in rapid diagnostic testing have made timely influenza diagnosis increasingly feasible [19]. Molecular assays, including polymerase chain reaction and rapid antigen detection tests, can provide results within hours, potentially facilitating early treatment decisions [20]. However, optimal integration of these diagnostic capabilities with antiviral prescribing practices requires robust evidence demonstrating clinical benefit [21].

Despite guideline recommendations emphasizing early treatment, gaps persist in evidence regarding the comparative effectiveness of early versus delayed therapy across diverse patient populations, clinical settings, and influenza subtypes [22]. Furthermore, limited data exist examining multiple clinically relevant outcomes simultaneously, including both symptomatic endpoints and serious complications such as respiratory failure and mortality [23].

This prospective cohort study was designed to address these knowledge gaps by comparing clinical outcomes between early (≤48 hours from symptom onset) and delayed (>48 hours) antiviral therapy in hospitalized adult patients with laboratory-confirmed influenza. We hypothesized that early antiviral initiation would be associated with reduced hospital length of stay, faster clinical improvement, fewer complications, decreased intensive care utilization, and lower mortality compared to delayed treatment. Secondary objectives included examining treatment timing effects across patient subgroups defined by age, comorbidity burden, and influenza virus type.

Materials and Methods

Study Design and Setting: This prospective observational cohort study was conducted at tertiary care medical centers.

Study Population and Eligibility Criteria: Adult patients (≥18 years) admitted to hospital wards or intensive care units with laboratory-confirmed influenza were prospectively enrolled. Influenza diagnosis was established through reverse transcription polymerase chain reaction (RT-PCR) testing of nasopharyngeal swabs performed as part of routine clinical care. Inclusion criteria comprised: (1) age ≥18 years; (2) positive RT-PCR test for influenza A or B; (3) hospital admission within 7 days of symptom onset; (4) initiation of neuraminidase inhibitor therapy (oseltamivir, zanamivir, or peramivir); and (5) ability to provide informed consent or availability of legally authorized representative.

Exclusion criteria included: (1) influenza diagnosis based solely on rapid antigen testing without RT-PCR confirmation; (2) receipt of antiviral therapy prior to hospital admission; (3) chronic oseltamivir

prophylaxis; (4) known oseltamivir resistance based on viral genotyping or phenotypic testing; (5) pregnancy; (6) terminal illness with life expectancy <30 days unrelated to acute influenza; (7) previous enrollment in the study during the same influenza season; (8) transfer from another hospital with >24 hours of prior antiviral treatment; and (9) incomplete documentation of symptom onset timing.

Sample Size Calculation: Sample size estimation was based on the primary outcome of hospital length of stay. Assuming mean hospital stays of 6.0 ± 3.0 days in the early treatment group and 8.0 ± 4.0 days in the delayed treatment group, with alpha = 0.05 (two-tailed) and power = 0.85, a minimum of 156 patients per group was required. Anticipating 20% attrition or protocol deviations, we aimed to enroll 380 total participants.

Exposure Definition and Group Assignment: The primary exposure was timing of antiviral therapy initiation relative to symptom onset. Symptom onset was defined as the first appearance of influenza-like illness manifestations including fever, cough, sore throat, myalgia, or malaise, as reported by patients or documented in medical records. Time from symptom onset to antiviral initiation was calculated in hours and categorized as: early treatment (≤48 hours from symptom onset) or delayed treatment (>48 hours from symptom onset). This 48-hour threshold was selected based on current guideline recommendations and existing literature. Treatment timing was verified through medical record review, pharmacy administration records, and patient interviews.

Data Collection: Trained research coordinators collected data using standardized electronic case report forms. Baseline data included demographics (age, sex, race/ethnicity), anthropometrics (height, weight, body mass index), smoking status, vaccination history (influenza vaccine receipt during current season), comorbidities (chronic obstructive pulmonary disease, asthma, cardiovascular disease, diabetes mellitus, chronic kidney disease, immunosuppression, malignancy), baseline vital signs, and laboratory values. Disease severity at presentation was assessed using the Pneumonia Severity Index (PSI) for patients with pneumonia and modified Early Warning Score (MEWS) for all patients. Clinical data collected throughout hospitalization included daily vital signs, supplemental oxygen requirements, laboratory results (complete blood count, comprehensive metabolic panel, inflammatory markers), radiographic findings, antiviral agents administered (type, dose, route, duration), adjunctive therapies (antibiotics, corticosteroids, bronchodilators), and clinical progression. Influenza virus characterization included type (A or B) and subtype when available.

Outcome Definitions

Primary Outcomes:

1. Hospital length of stay: time from admission to hospital discharge, measured in days
2. Time to clinical improvement: time from antiviral initiation to sustained improvement in clinical status, defined as temperature <37.8°C without antipyretics for ≥24 hours plus improvement in respiratory symptoms
3. Complications: composite outcome including pneumonia, acute respiratory distress syndrome (ARDS), secondary bacterial infections, exacerbation of underlying chronic conditions, or new cardiovascular events

Secondary Outcomes:

1. ICU admission during hospitalization
2. Mechanical ventilation requirement (invasive or non-invasive)
3. In-hospital all-cause mortality
4. Viral shedding duration (subset analysis in patients with sequential viral testing)
5. Hospital readmission within 30 days
6. Time to fever resolution
7. Time to hospital discharge readiness (discharge delayed for non-medical reasons documented separately)

Statistical Analysis: Statistical analyses were performed using SPSS version 28.0 (IBM Corp., Armonk, NY) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were calculated for all variables. Continuous variables were assessed for normality using Shapiro-Wilk tests and Q-Q plots. Normally distributed continuous variables were presented as mean ± standard deviation and compared using independent t-tests. Non-normally distributed variables were presented as median (interquartile range) and compared using Mann-Whitney U tests. Categorical variables were presented as frequencies and percentages and compared using chi-square tests or Fisher's exact tests when cell counts were <5.

Multivariable logistic regression analysis was performed to identify independent associations between treatment timing and binary outcomes (complications, ICU admission, mechanical ventilation, mortality), adjusting for potential confounders including age, sex, body mass index, number of comorbidities, influenza vaccination status, baseline disease severity (PSI score or MEWS), and influenza virus type. Results were presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). Multivariable linear regression was used to examine associations with continuous outcomes (hospital length of stay, time to clinical improvement) after adjusting for the same covariates.

Subgroup analyses examined treatment timing effects stratified by age (<65 years vs. ≥65 years), influenza type (A vs. B), presence of high-risk conditions (≥2 comorbidities), vaccination status, and baseline severity (PSI risk classes or MEWS categories). Interaction terms were tested to assess effect modification.

Sensitivity analyses included: (1) analysis restricted to patients with symptom onset <5 days before admission; (2) analysis excluding patients who died within 48 hours of admission; (3) propensity score matching to address potential confounding; and (4) analysis using alternative treatment timing thresholds (24, 36, 72 hours). Statistical significance was set at two-tailed $p < 0.05$. All analyses followed intention-to-treat principles based on initial group assignment.

Results

Study Population and Baseline Characteristics: During the study period, 512 patients with laboratory-confirmed influenza were screened, of whom 386 met eligibility criteria and were enrolled (Figure excluded). The most common exclusion reasons were receipt of antiviral therapy prior to admission (n=64) and inability to confirm symptom onset timing (n=38). Among enrolled participants, 234 (60.6%) received early antiviral treatment (≤48 hours from symptom onset) and 152 (39.4%) received delayed treatment (>48 hours). Median time to antiviral initiation was 36 hours (IQR: 24-42) in the early group and 76 hours (IQR: 58-96) in the delayed group.

Baseline demographic and clinical characteristics are presented in Table 1. The two groups were generally well-balanced regarding most baseline variables. Mean age was 52.4 ± 16.8 years overall, with no significant age difference between groups ($p = 0.421$). The cohort included 56.7% influenza A cases and 43.3% influenza B cases. Influenza vaccination rates were suboptimal at 42.5% overall.

Table 1: Baseline Demographic and Clinical Characteristics by Treatment Timing Group

Characteristic	Early Treatment ≤48h (n=234)	Delayed Treatment >48h (n=152)	p-value
Demographics			
Age (years), mean ± SD	51.8 ± 16.4	53.4 ± 17.4	0.421
Age ≥65 years, n (%)	68 (29.1)	51 (33.6)	0.361
Male sex, n (%)	124 (53.0)	76 (50.0)	0.579
BMI (kg/m²), mean ± SD	28.6 ± 6.2	29.1 ± 6.8	0.478
Current smoker, n (%)	57 (24.4)	43 (28.3)	0.398
Influenza characteristics			
Influenza A, n (%)	135 (57.7)	84 (55.3)	0.650
Influenza B, n (%)	99 (42.3)	68 (44.7)	
Current season vaccination, n (%)	104 (44.4)	60 (39.5)	0.345
Comorbidities			
Chronic lung disease, n (%)	82 (35.0)	58 (38.2)	0.547
Cardiovascular disease, n (%)	76 (32.5)	54 (35.5)	0.549
Diabetes mellitus, n (%)	68 (29.1)	49 (32.2)	0.523
Chronic kidney disease, n (%)	34 (14.5)	27 (17.8)	0.413
Immunocompromised, n (%)	41 (17.5)	31 (20.4)	0.493
Obesity (BMI ≥30), n (%)	94 (40.2)	67 (44.1)	0.458
≥2 comorbidities, n (%)	118 (50.4)	83 (54.6)	0.437
Presentation severity			
Temperature (°C), mean ± SD	38.7 ± 0.8	38.8 ± 0.9	0.287
Respiratory rate (bpm), mean ± SD	22.4 ± 4.6	24.1 ± 5.2	0.001
SpO_2 (%), mean ± SD	93.6 ± 4.2	91.8 ± 5.1	<0.001
MEWS score, mean ± SD	3.2 ± 1.8	4.1 ± 2.1	<0.001
Radiographic pneumonia, n (%)	156 (66.7)	118 (77.6)	0.020
PSI class III-V (if pneumonia), n (%)	89/156 (57.1)	79/118 (66.9)	0.095
Bilateral infiltrates, n (%)	67 (28.6)	58 (38.2)	0.052
Laboratory values			
WBC count (×10³/μL), mean ± SD	9.8 ± 4.3	10.4 ± 4.9	0.213
Lymphocytes (%), mean ± SD	16.4 ± 7.2	15.8 ± 6.9	0.428
CRP (mg/L), median (IQR)	78 (42-124)	96 (58-147)	0.012
Creatinine (mg/dL), mean ± SD	1.1 ± 0.6	1.2 ± 0.7	0.156
Time intervals (hours)			
Symptom onset to admission, median (IQR)	48 (24-60)	84 (72-108)	<0.001
Symptom onset to antiviral, median (IQR)	36 (24-42)	76 (58-96)	<0.001
Admission to antiviral, median (IQR)	6 (3-12)	8 (4-16)	0.034

BMI, body mass index; MEWS, Modified Early Warning Score; PSI, Pneumonia Severity Index; SpO_2, oxygen saturation; WBC, white blood cell; CRP, C-reactive protein; IQR, interquartile range

Primary Outcomes: Patients receiving early antiviral therapy demonstrated significantly superior outcomes across all primary endpoints (Table 2). Mean hospital length of stay was 5.8 ± 2.3 days in the early treatment group compared to 8.4 ± 3.6 days in the delayed treatment group ($p < 0.001$), representing a 31% reduction. Time to clinical improvement was markedly shorter with early treatment (4.2 ± 1.6 vs. 6.7 ± 2.4 days, $p < 0.001$). The composite complication rate was significantly lower in the early treatment group (18.4% vs. 35.5%, $p < 0.001$).

Table 2: Primary and Secondary Clinical Outcomes by Treatment Timing Group

Outcome	Early Treatment ≤48h (n=234)	Delayed Treatment >48h (n=152)	Difference (95% CI)	p-value
Primary outcomes				
Hospital LOS (days), mean ± SD	5.8 ± 2.3	8.4 ± 3.6	-2.6 (-3.2 to -2.0)	<0.001
Time to clinical improvement (days), mean ± SD	4.2 ± 1.6	6.7 ± 2.4	-2.5 (-2.9 to -2.1)	<0.001
Any complication, n (%)	43 (18.4)	54 (35.5)	-17.1% (-26.2 to -8.0)	<0.001
Specific complications				
Pneumonia, n (%)	156 (66.7)	118 (77.6)	-10.9%	0.020
ARDS, n (%)	12 (5.1)	22 (14.5)	-9.4%	0.002
Secondary bacterial infection, n (%)	18 (7.7)	28 (18.4)	-10.7%	0.002
COPD/asthma exacerbation, n (%)	24/82 (29.3)	27/58 (46.6)	-17.3%	0.042
Cardiovascular events, n (%)	8 (3.4)	14 (9.2)	-5.8%	0.018
Secondary outcomes				
ICU admission, n (%)	30 (12.8)	41 (27.0)	-14.2%	0.001
ICU LOS (days), mean ± SD*	4.8 ± 2.6	7.2 ± 4.1	-2.4 (-4.1 to -0.7)	0.008
Mechanical ventilation, n (%)	19 (8.1)	30 (19.7)	-11.6%	0.002
Duration of ventilation (days), mean ± SD†	5.3 ± 3.2	8.9 ± 4.8	-3.6 (-6.1 to -1.1)	0.006
In-hospital mortality, n (%)	8 (3.4)	16 (10.5)	-7.1%	0.007
30-day readmission, n (%)‡	14/226 (6.2)	18/136 (13.2)	-7.0%	0.024
Symptomatic endpoints				
Time to fever resolution (days), mean ± SD	2.8 ± 1.2	4.6 ± 1.9	-1.8 (-2.1 to -1.5)	<0.001
Time to O_2 independence (days), mean ± SD§	3.6 ± 1.8	5.8 ± 2.7	-2.2 (-2.8 to -1.6)	<0.001
Time to discharge readiness (days), mean ± SD	5.4 ± 2.1	7.8 ± 3.2	-2.4 (-2.9 to -1.9)	<0.001
Viral shedding duration (days), mean ± SD‖	4.7 ± 2.1	7.3 ± 3.4	-2.6 (-3.5 to -1.7)	<0.001
Healthcare utilization				
Total hospitalization cost ($), median (IQR)	12,450 (8,200-18,300)	21,800 (14,600-32,400)	-	<0.001
Antibiotic use, n (%)	142 (60.7)	112 (73.7)	-13.0%	0.009
Antibiotic days, mean ± SD¶	4.8 ± 2.6	6.9 ± 3.4	-2.1 (-2.8 to -1.4)	<0.001

LOS, length of stay; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; CI, confidence interval; IQR, interquartile range, *Among patients admitted to ICU; †Among patients requiring mechanical ventilation; ‡Among survivors; §Among patients requiring supplemental oxygen; ‖Subset with serial viral load testing (n=142 early, n=89 delayed); ¶Among patients receiving antibiotics

Multivariable Analysis and Risk Factors: After adjusting for potential confounders in multivariable regression models, early antiviral treatment remained independently associated with improved outcomes (Table 3). Early treatment was associated with significantly reduced odds of complications (aOR = 0.42, 95% CI: 0.26-0.68, $p < 0.001$), ICU admission (aOR = 0.38, 95% CI: 0.22-0.66, $p = 0.001$), mechanical ventilation (aOR = 0.35, 95%

CI: 0.18-0.68, p = 0.002), and mortality (aOR = 0.29, 95% CI: 0.11-0.74, p = 0.010).

Table 3: Multivariable Analysis of Factors Associated with Clinical Outcomes

Variable	Any Complication aOR (95% CI)	ICU Admission aOR (95% CI)	Mechanical Ventilation aOR (95% CI)	In-Hospital Mortality aOR (95% CI)
Treatment timing				
Early (≤48h)	0.42 (0.26-0.68)***	0.38 (0.22-0.66)**	0.35 (0.18-0.68)**	0.29 (0.11-0.74)*
Delayed (>48h)	Reference	Reference	Reference	Reference
Age				
Per 10-year increase	1.24 (1.08-1.42)**	1.31 (1.11-1.55)**	1.28 (1.05-1.57)*	1.47 (1.14-1.89)**
Sex				
Male	1.34 (0.85-2.11)	1.28 (0.74-2.21)	1.42 (0.75-2.69)	1.31 (0.52-3.28)
Female	Reference	Reference	Reference	Reference
BMI category				
Obese (≥30 kg/m²)	1.68 (1.06-2.67)*	1.72 (0.99-2.98)	1.89 (0.99-3.61)	1.24 (0.49-3.14)
Non-obese	Reference	Reference	Reference	Reference
Comorbidity burden				
≥2 comorbidities	2.14 (1.34-3.41)**	2.47 (1.40-4.36)**	2.68 (1.36-5.28)**	3.12 (1.18-8.24)*
0-1 comorbidity	Reference	Reference	Reference	Reference
Vaccination status				
Vaccinated	0.64 (0.40-1.03)	0.58 (0.32-1.04)	0.52 (0.26-1.04)	0.48 (0.18-1.29)
Unvaccinated	Reference	Reference	Reference	Reference
Baseline severity (MEWS)				
Per 1-point increase	1.28 (1.14-1.44)***	1.42 (1.24-1.62)***	1.48 (1.26-1.74)***	1.54 (1.26-1.88)***
Influenza type				
Influenza A	1.43 (0.91-2.25)	1.52 (0.88-2.63)	1.68 (0.88-3.21)	1.84 (0.73-4.63)
Influenza B	Reference	Reference	Reference	Reference
Pneumonia present				
Yes	2.87 (1.64-5.02)***	3.24 (1.58-6.64)**	4.12 (1.56-10.87)**	3.87 (1.12-13.38)*
No	Reference	Reference	Reference	Reference

aOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; MEWS, Modified Early Warning Score; ICU, intensive care unit, *p < 0.05; **p < 0.01; ***p < 0.001

All models adjusted for all variables shown in table plus hospital site and influenza season

Subgroup analyses revealed consistent benefits of early treatment across age groups (<65 years: aOR = 0.44, 95% CI: 0.24-0.80; ≥65 years: aOR = 0.39, 95% CI: 0.18-0.83; p-interaction = 0.782), influenza types (type A: aOR = 0.38, 95% CI: 0.21-0.69; type B: aOR = 0.47, 95% CI: 0.23-0.94; p-interaction = 0.624), and comorbidity burden. However, the absolute benefit was greatest among high-risk patients with ≥2 comorbidities (number needed to treat to prevent one complication = 4.2) compared to those with fewer comorbidities (NNT = 8.7).

Sensitivity analyses using propensity score matching (n=128 matched pairs) confirmed primary findings, with early treatment associated with reduced hospital stay (5.9 ± 2.4 vs. 8.2 ± 3.5 days, p < 0.001) and complications (19.5% vs. 34.4%, p = 0.006). Alternative timing thresholds demonstrated a gradient effect, with greatest benefit at <24 hours, sustained benefit at 24-48 hours, and diminishing but still statistically significant benefit at 48-72 hours.

Discussion

This prospective cohort study of 386 hospitalized adults with laboratory-confirmed influenza demonstrates that early antiviral therapy initiation within 48 hours of symptom onset is associated with substantial improvements in clinical outcomes compared to delayed treatment. Patients receiving early therapy experienced 31% shorter hospitalizations, 40% faster clinical improvement, and 48% fewer complications. Early treatment was also associated with dramatic reductions in ICU admission (52% relative risk reduction),

mechanical ventilation requirements (59% relative risk reduction), and in-hospital mortality (68% relative risk reduction). These benefits remained robust after adjustment for potential confounders and were consistent across patient subgroups, supporting the critical importance of rapid antiviral initiation in influenza management.

Our findings align with and extend previous research demonstrating benefits of early antiviral therapy. A meta-analysis by Muthuri et al. examining 2009 H1N1 pandemic data found that antiviral treatment within 48 hours was associated with reduced mortality compared to later treatment [24]. Similarly, observational studies during seasonal influenza outbreaks have shown associations between early treatment and reduced hospitalization duration [25]. However, much of this evidence derives from pandemic settings or focuses on outpatient populations [26]. Our study provides contemporary data specific to hospitalized patients with seasonal influenza, demonstrating clinically meaningful benefits across multiple relevant endpoints.

The magnitude of benefit observed in our study—a 2.6-day reduction in hospital stay—translates to substantial clinical and economic impact. Given hospitalization costs averaging $15,000-25,000 per influenza admission in our healthcare system, early treatment could yield significant cost savings through reduced length of stay, decreased ICU utilization, and prevention of complications [27]. At a population level, if early treatment were universally implemented for the estimated 400,000 annual influenza hospitalizations in the United States, potential savings could reach billions of dollars annually [28].

The mechanisms underlying early antiviral therapy benefits likely involve interruption of viral replication during peak shedding periods, limiting viral burden and subsequent immunopathology [29]. Neuraminidase inhibitors prevent viral release and spread, and early administration during exponential viral growth phases maximizes impact on total viral load and duration of shedding [30]. We observed a 2.6-day reduction in viral shedding duration with early treatment in our subset analysis, consistent with this mechanism. Reduced viral burden may subsequently attenuate inflammatory responses, as evidenced by lower complication rates and reduced progression to ARDS in early-treated patients [31].

The 48% reduction in complications with early treatment represents a clinically significant finding with important implications. Complications of influenza, including secondary bacterial pneumonia, ARDS, and cardiovascular events, are major drivers of morbidity and mortality [32]. Our study suggests that timely antiviral therapy may interrupt the pathophysiological cascades leading to these complications. The particularly marked reduction in secondary bacterial infections (58% relative risk reduction) supports the hypothesis that early viral suppression preserves respiratory epithelial integrity and immune function, reducing susceptibility to bacterial superinfection [33].

The mortality benefit observed with early treatment, though based on relatively small absolute numbers, is noteworthy. The 68% relative risk reduction in mortality (10.5% vs. 3.4%) translates to a number needed to treat of 14 to prevent one death. This finding is consistent with large observational studies during the 2009 pandemic showing mortality reductions with early oseltamivir treatment [34]. However, as an observational study, we cannot definitively exclude residual confounding despite multivariable adjustment. Potential unmeasured confounders include illness severity perceptions influencing treatment timing, healthcare access factors, or patient behaviors associated with both early presentation and favorable outcomes [35].

Subgroup analyses revealed that while early treatment benefits were observed across all patient categories, the absolute benefit was greatest among high-risk individuals with multiple comorbidities. This finding has important clinical implications, as these patients often present later in their illness course and may be perceived as less likely to benefit from antiviral therapy [36]. Our data suggest that aggressive efforts to achieve early treatment are particularly important in vulnerable populations. Current guidelines already recommend antiviral therapy for all hospitalized patients and high-risk outpatients regardless of illness duration [37], and our findings provide supportive evidence for this recommendation while highlighting the added benefit of early initiation.

The consistency of treatment timing effects across influenza A and B subtypes is clinically relevant, as neuraminidase inhibitors demonstrate activity against both types [38]. Some previous studies suggested differential treatment responses by viral subtype, but our data do not support clinically meaningful differences, suggesting that early treatment should be pursued regardless of viral identification [39].

Our finding that only 60.6% of patients received antiviral therapy within the recommended 48-hour window highlights substantial gaps between guideline recommendations and real-world practice [40]. Barriers to early treatment include delayed healthcare seeking by patients, diagnostic uncertainty, time required for laboratory confirmation, and physician hesitation to prescribe antivirals [41]. The median 48-hour delay from symptom onset to hospital admission among

delayed-treatment patients suggests that patient education regarding early presentation is crucial. Additionally, the 6-8 hour median time from admission to antiviral initiation indicates opportunities for improvement in hospital-based processes [42].

Strategies to improve early antiviral utilization include public education campaigns emphasizing early healthcare seeking for influenza-like illness, expanded access to rapid diagnostic testing (including point-of-care molecular assays), clinical decision support systems prompting early empiric treatment in high-risk patients, and streamlined antiviral prescribing pathways [43]. Some experts advocate for empiric treatment based on clinical presentation during influenza season without awaiting laboratory confirmation, particularly in high-risk patients [44]. Our findings support such approaches, as treatment benefits are time-sensitive.

The suboptimal influenza vaccination rate (42.5%) in our cohort, while concerning, is consistent with national data showing vaccine uptake below 50% in many adult populations [45]. While vaccination remains the primary prevention strategy, our findings underscore the importance of effective treatment options for the substantial proportion of individuals who remain unvaccinated or experience vaccine failure [46]. The trend toward reduced complications in vaccinated versus unvaccinated patients, though not statistically significant in our multivariable model, supports vaccination's potential to reduce illness severity [47].

Several study limitations warrant consideration. First, the observational design limits causal inference despite multivariable adjustment and sensitivity analyses. Randomization to early versus delayed treatment would be unethical given existing evidence, but we cannot completely exclude confounding by unmeasured factors such as healthcare-seeking behavior or social determinants of health. Second, symptom onset timing relied on patient recall, potentially introducing measurement error. However, we excluded cases with unclear onset timing and verified information through multiple sources when possible. Third, the study was conducted at two academic medical centers, potentially limiting generalizability to community hospitals or other healthcare settings. Fourth, we did not assess antiviral resistance patterns comprehensively, though oseltamivir resistance remains rare in seasonal influenza strains [48]. Fifth, we focused on hospitalized patients, and findings may not extrapolate to outpatient populations with milder illness. Sixth, we did not evaluate alternative antiviral agents such as baloxavir marboxil, which has a different mechanism of action and dosing schedule [49]. Finally, the study was conducted during 2021-2023, a period influenced by COVID-19 pandemic effects on healthcare utilization patterns and potentially altered influenza epidemiology [50].

Despite these limitations, this study provides robust, contemporary evidence supporting early antiviral therapy in hospitalized influenza patients. The prospective design, laboratory confirmation of all cases, comprehensive outcome assessment, adequate sample size, and rigorous analytical approach including multivariable adjustment and sensitivity analyses strengthen the findings' validity. The consistency of results across multiple endpoints and subgroups further supports the robustness of our conclusions.

Future research should examine implementation strategies to optimize early antiviral delivery in diverse healthcare settings, evaluate the cost-effectiveness of rapid diagnostic testing coupled with early treatment protocols, investigate the impact of newer antiviral agents with different mechanisms and administration routes, and explore the role of host biomarkers in personalizing treatment decisions [51]. Additionally, studies examining long-term outcomes such as post-influenza functional status and quality of life would provide valuable insights into the full impact of treatment timing [52].

Conclusion

This prospective cohort study demonstrates that early antiviral therapy initiation within 48 hours of symptom onset in hospitalized influenza patients is associated with substantially improved clinical outcomes compared to delayed treatment. Early therapy significantly reduces hospital length of stay, accelerates clinical improvement, decreases complication rates, and lowers risks of ICU admission, mechanical ventilation, and mortality. Benefits are observed across diverse patient populations, with particularly pronounced effects in high-risk individuals with multiple comorbidities. These findings underscore the critical importance of early influenza diagnosis and prompt antiviral treatment as key components of optimal clinical management. Healthcare systems should prioritize strategies to facilitate early treatment delivery, including patient education to promote early presentation, implementation of rapid diagnostic testing capabilities, development of clinical protocols supporting empiric treatment in appropriate patients, and removal of barriers to timely antiviral prescribing.

While influenza vaccination remains the cornerstone of prevention, effective antiviral therapy represents an essential tool for reducing disease burden, and maximizing its benefit requires aggressive pursuit of early treatment initiation. The

substantial clinical and economic benefits associated with early treatment justify continued investment in diagnostic infrastructure, treatment protocols, and healthcare provider education to optimize influenza management and improve patient outcomes.

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