Supplementary data

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

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MATERIAL AND METHODS

Study definitions

Severe influenza was defined as infection confirmed by rt-PCR presenting with at least one of the following clinical features: respiratory and/or radiological signs of lower respiratory tract disease (e.g., pneumonia); central nervous system involvement (e.g., encephalopathy or encephalitis); severe dehydration; secondary complications, such as renal failure, multi-organ failure, or septic shock; any other influenza-related condition requiring admission (e.g., myocarditis); or exacerbation of underlying chronic disease, including asthma, chronic obstructive pulmonary disease (COPD), chronic liver or renal failure, diabetes, or other cardiovascular conditions (e.g., congestive cardiac failure) [1].

Community-acquired pneumonia (CAP) was defined in accordance with American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) guidelines [2].

Obese patients were defined as those with a body mass index (BMI) of > 30 kg/m^2.

COPD "exacerbation" was defined according to COPD exacerbation guidelines of the European Respiratory Society/ATS as increased respiratory symptoms, particularly dyspnoea, cough, and increased sputum purulence without pulmonary infiltrates in chest X-ray [3].

Asthma exacerbation was defined as acute or subacute episodes characterized by a progressive increase in one or more typical asthmatic symptoms (dyspnoea, coughing, wheezing, and tightness of the chest) without infiltrates in the chest X-ray [4].

COPD and asthmatic patients with pulmonary infiltrates in chest X-ray were considered as CAP.

Ventilator-associated pneumonia (VAP) was defined according to current International ERS/ESICM/ESCMID/ALAT guidelines among ICU patients who developed a new pneumonic event while mechanically ventilated for at least 48 hours [5].

Shock was defined as the need for vasopressor drugs for 4 hours after fluid replacement at ICU admission[6].

All rt-PCR testing was undertaken in accordance with CDC guidelines [7].

References

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7. World health Organization. CDC protocol of realtime RTPCR for swine influenza A(H1N1) (2009) CDC protocol of realtime RTPCR for swine influenza A(H1N1) 28. Control 1:

RESULTS

TABLES

Table S1. Variables collected during the study

1.- Type of influenza virus	2.- Age
3.- Gender	4.- APACHE II score
5.- SOFA score	6.- Time between onset of Influenza symptoms and hospital admission
7.- Time between onset of Influenza symptoms and diagnosis	8.- Time between Hospital admission and ICU admission
9.- Number of quadrants with pulmonary infiltrates on chest radiograph at ICU admission	10.- Laboratory variables as: Alanine Aminotransferase, Aspartate Aminotransferase, Creatine phosphokinase, white blood cells count, platelets count, serum creatinine, serum urea, CRP, and PCT.
11.- Need of renal replacement therapy	12.- Need of mechanical ventilation and prone therapy
13.- Mechanical ventilation days	14.- Non-invasive ventilation failure
15.- ICU LOS	16.- Presence of organ dysfunction at ICU admission
17.- Presence of shock at ICU admission	18.- Comorbidities (Asthma, COPD, chronic heart disease, chronic renal failure, hematologic disease, pregnancy, obesity, diabetes mellitus, AIDS/HIV, neuromuscular disease, autoimmune disease, and immunodeficiency.
19.- Vaccine data	20.- Bacterial co-infection
21.- Exacerbated COPD	22.- Exacerbated asthma
23.- Co-infection isolated microorganisms	24.- Development of ventilator-associated pneumonia (VAP)
25.- VAP isolated microorganisms	26.- Antibiotic treatment for bacterial co-infection
27.- Duration of antibiotic treatment	28.- Antiviral treatment
29.- Timing of antiviral treatment	30.- Antiviral dose
31.- Duration of antiviral treatment	32.- Type of antiviral treatment (empiric or directed)
33.- Indication for corticosteroid treatment (pneumonia, shock, or others)	34.- Type of corticosteroid treatment
35.- Duration of corticosteroid treatment	35.- Outcome (survival or non-survival)

APACHE II=Acute Physiologic and Chronic Health Evaluation II score. SOFA=Sequential Organ Failure Assessment. ICU=Intensive Care Unit. CRP=C-Reactive Protein. PCT=Procalcitonin. LOS=Length of Stay. COPD=Chronic Obstructive Pulmonary Disease. HIV/AIDS=Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome.

Table S2. Associated factors to receive later antiviral treatment in critically ill patients with influenza pneumonia.

Variable	OR	95% CI	P Value
Age	0.99	0.98-0.99	0.003
Immunosuppression	0.64	0.48-0.86	0.003
Asthma	0.46	0.32-0.64	<0.001
Chronic Obstructive Pulmonary Disease	0.83	0.64-1.07	0.15
Congestive heart disease	0.63	0.46-0.86	0.004
Obesity	1.49	1.18-1.87	0.01

Table S3. Comparison between survivors and non-survivors in critically ill patients with influenza pneumonia.

Variable	Survivors (n=1672)	Non-survivors (n=452)	P value
Demographics characteristics			
Age (years, median)	53 (42-63)	57 (45-68)	<0.001
Male gender (No., %)	1002 (59.9%)	297 (65.7%)	0.025
Disease severity, (No., median)			
APACHE II score	14 (10-20)	20 (15-26)	<0.001
SOFA score	5 (3-8)	8 (5-11)	<0.001
Pulmonary infiltrates	2 (2-4)	3 (2-4)	<0.001
Disease timeline, (days, median)			
Duration of symptom onset to hospital admission	4 (2-6)	4 (2-6)	0.54
Duration of symptom onset to oseltamivir initiation	4 (2-6)	4 (3-6)	0.27
Comorbidities, (No., %)			
Asthma	135 (8.1%)	30 (6.6%)	0.31
COPD	303 (18.1%)	90 (19.9%)	0.38
Congestive heart failure	171 (10.2%)	58 (12.8%)	0.11
Chronic kidney disease	118 (7.1%)	54 (11.9%)	0.001
Immunosuppression	154 (9.2%)	109 (24.1%)	<0.001
Obesity	544 (32.5%)	131 (29%)	0.15
Pregnancy	200 (12%)	36 (8%)	0.02
Complications, (No., %)			
Acute renal failure	377 (22.5%)	231 (51.1%)	<0.001
Mechanical ventilation	1274 (76.2%)	435 (96.2%)	<0.001
Bacterial co-infection	395 (23.6%)	143 (31.6%)	0.001
Septic shock	797 (47.7%)	360 (79.6%)	<0.001
Ventilator-associated pneumonia	104 (6.2%)	66 (14.6%)	<0.001
Treatment			
Early oseltamivir treatment, (No., %)	428 (25.6%)	101 (22.3%)	0.15
Oseltamivir treatment duration (days, median)	8 (6-10)	7 (5-10)	<0.001
High dosage of oseltamivir, (No., %)	676 (40.4%)	197 (34.6%)	0.07
Adjuvant corticosteroids, (No., %)	566 (33.9%)	241 (53.3%)	<0.001

Results are expressed as median (interquartile range) or numbers (%). APACHE=Acute Physiology and Chronic Health disease, SOFA=Sequential Organ Assessment Failure, COPD=Chronic Obstructive Pulmonary Disease.

FIGURE LEGENDS

Figure S1. Timeline of influenza disease in critically ill patients with pneumonia stratified by treatment groups (early and later oseltamivir) and time to outcomes (ICU discharge alive and length of stay of non-survivors).

Timeframes (days) are expressed as medians (and interquartile range). ICU=Intensive care unit. Hospital GAP is the time from onset of illness to hospital admission. Antiviral GAP is the time from illness onset of illness to oseltamivir initiation. ICU GAP is the time from hospital to ICU admission. Timelines showed that all patients received oseltamivir treatment promptly after hospital admission and before ICU admission (which is time zero of follow up).

Figure S2. ICU Mortality rate of early and later oseltamivir treatment according to age

Figure S3. ICU mortality rate of early and later oseltamivir treatment according to the APACHE II score

Figure S4. Love plot of the propensity score matching analysis with unadjusted and adjusted covariates

Figure S5. Forest plot of survival analysis with the cause-specific hazard model for the association of early oseltamivir and 60-day ICU mortality.

APACHE II=Acute Physiology and Chronic Health Evaluation. SOFA= Sequential Organ Failure Assessment. WBC=White Blood Cells. COPD=Chronic Obstructive Pulmonary Disease. HIV/AIDS= Human Immunodeficiency Virus infection and Acquired Immune Deficiency Syndrome.

Figure S6. Forest plot of survival analysis with the cause-specific hazard model for the association of early oseltamivir treatment and probability of 60-day ICU discharge alive.

APACHE II=Acute Physiology and Chronic Health Evaluation. SOFA= Sequential Organ Failure Assessment. WBC=White Blood Cells. COPD=Chronic Obstructive Pulmonary Disease. HIV/AIDS= Human Immunodeficiency Virus infection and Acquired Immune Deficiency Syndrome.

Figure S7. Forest plot of the competing risks analysis for the association of early oseltamivir treatment and probability of 60-day ICU discharge alive.

APACHE II=Acute Physiology and Chronic Health Evaluation. SOFA= Sequential Organ Failure Assessment. WBC=White Blood Cells. COPD=Chronic Obstructive Pulmonary Disease. HIV/AIDS= Human Immunodeficiency Virus infection and Acquired Immune Deficiency Syndrome.

Figure S1

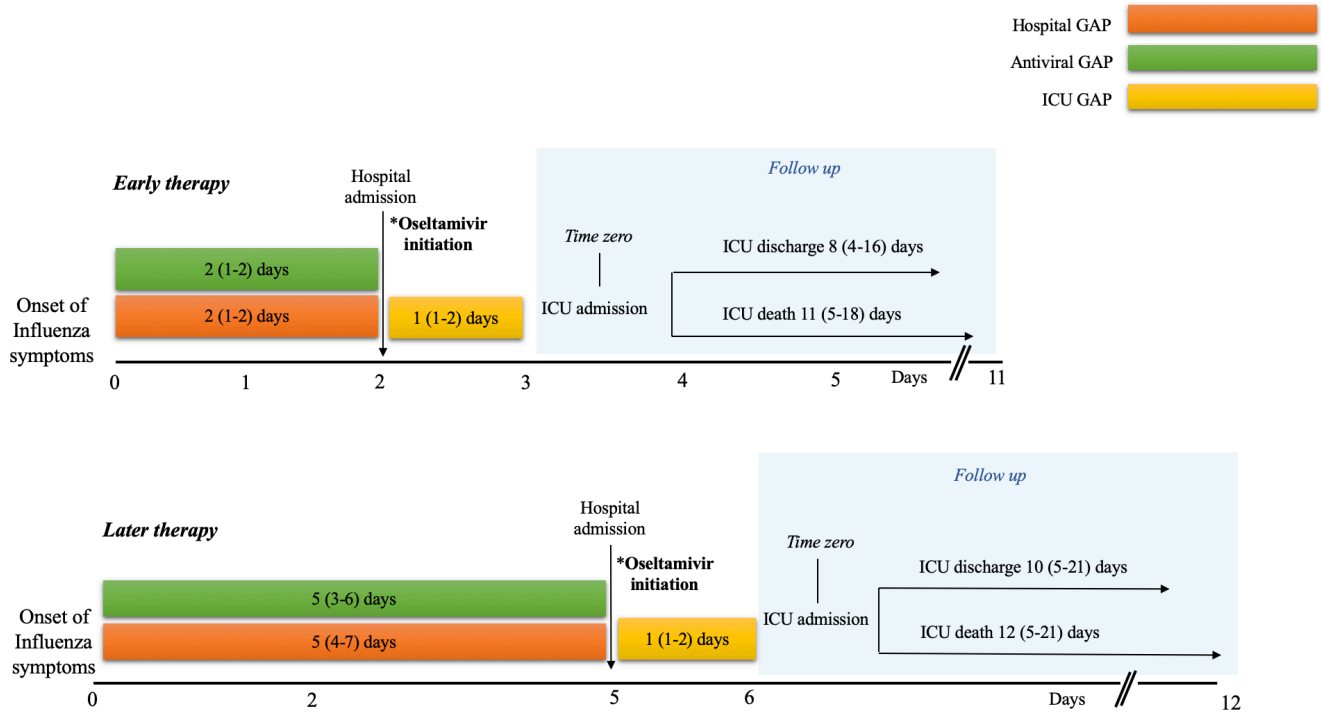

Hospital GAP
Antiviral GAP
ICU GAP
Early therapy
Hospital admission
*Oseltamivir initiation
Follow up
Time zero
ICU discharge 8 (4-16) days
2 (1-2) days
2 (1-2) days
1 (1-2) days
ICU admission
ICU death 11 (5-18) days
Onset of Influenza symptoms
0
1
2
3
4
5
Days
11
Later therapy
Hospital admission
*Oseltamivir initiation
Follow up
Time zero
ICU discharge 10 (5-21) days
5 (3-6) days
5 (4-7) days
1 (1-2) days
ICU admission
ICU death 12 (5-21) days
Onset of Influenza symptoms
0
2
5
6
Days
12

Figure S2

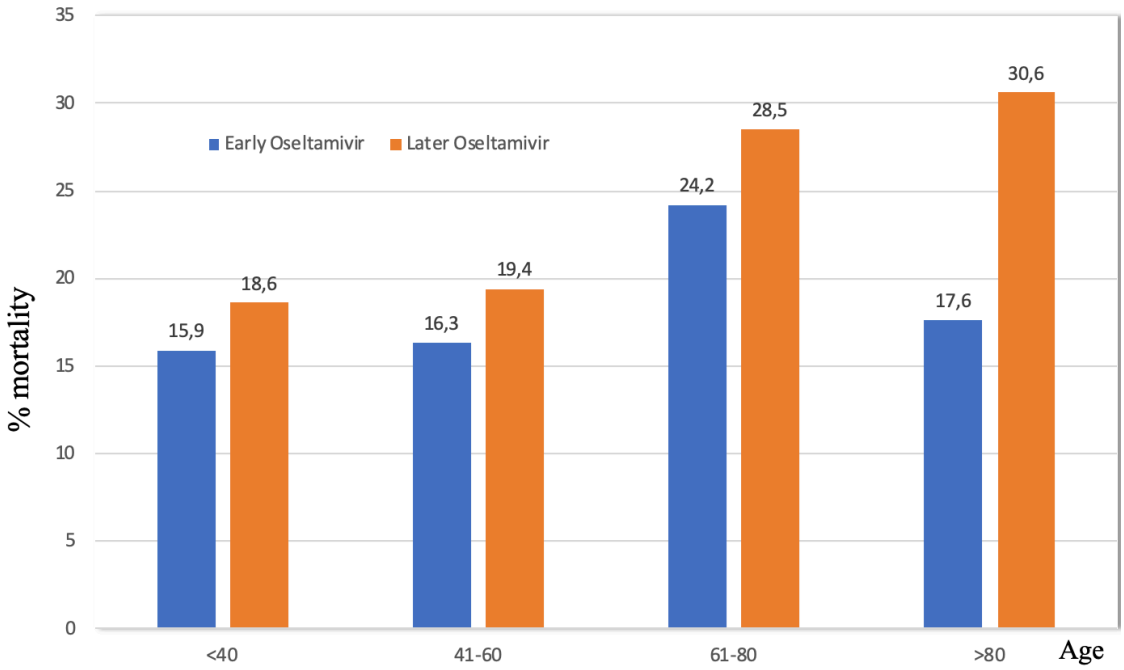

35
30
25
20
15
10
5
0
% mortality
Early Oseltamivir
Later Oseltamivir
15,9
18,6
16,3
19,4
24,2
28,5
17,6
30,6
<40
41-60
61-80
>80
Age

Figure S3

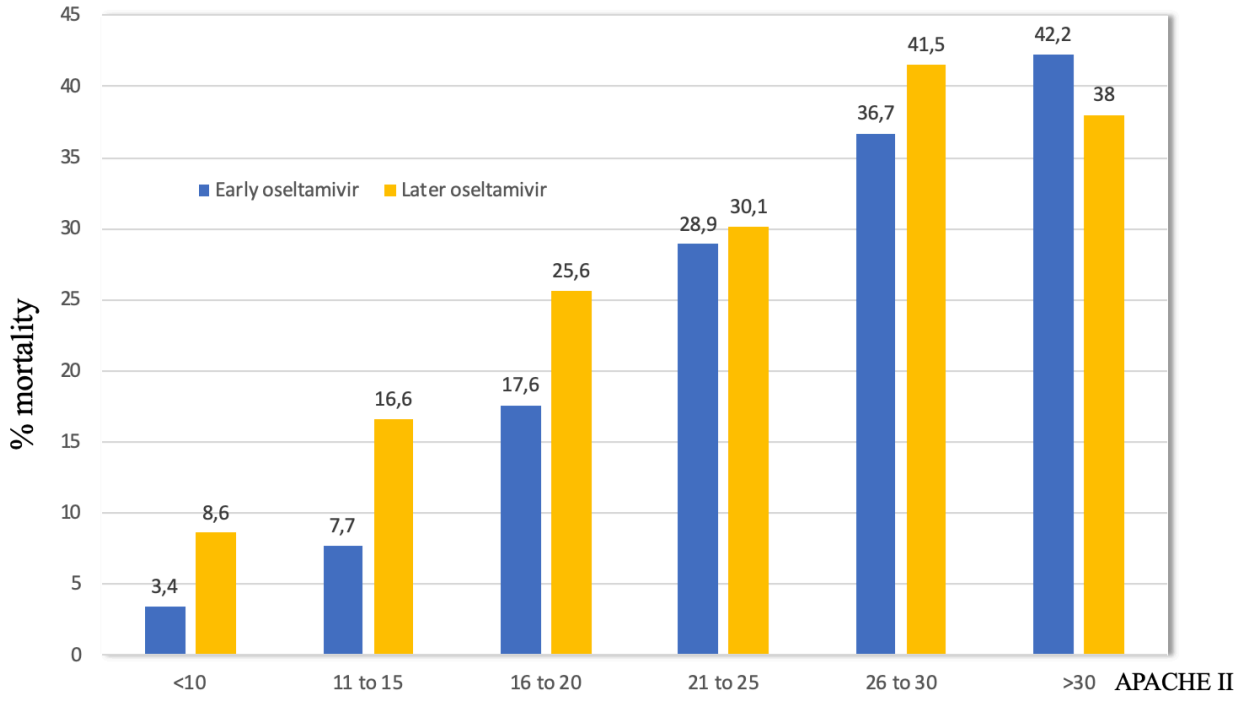

45
40
35
30
25
20
15
10
5
0
% mortality
Early oseltamivir
Later oseltamivir
3,4
8,6
7,7
16,6
17,6
25,6
28,9
30,1
36,7
41,5
42,2
38
<10
11 to 15
16 to 20
21 to 25
26 to 30
>30
APACHE II

Figure S4

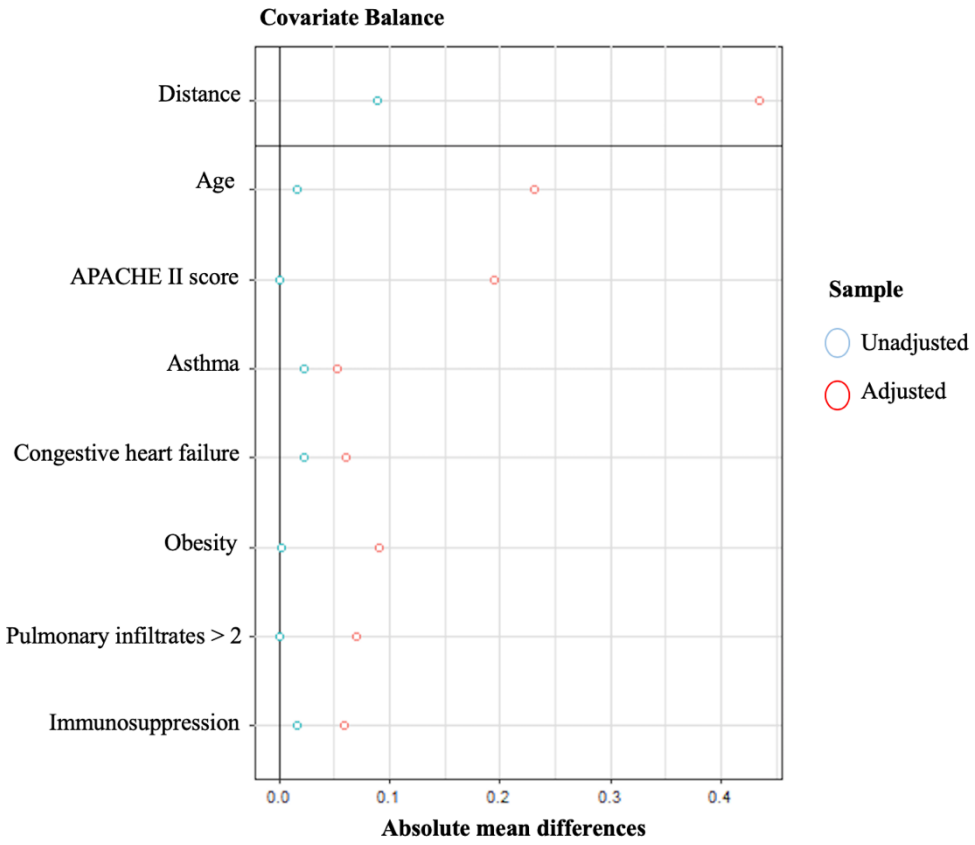

Covariate Balance
Distance
Age
APACHE II score
Asthma
Congestive heart failure
Obesity
Pulmonary infiltrates > 2
Immunosuppression
0.0
0.1
0.2
0.3
0.4
Absolute mean differences
Sample
Unadjusted
Adjusted

Figure S5

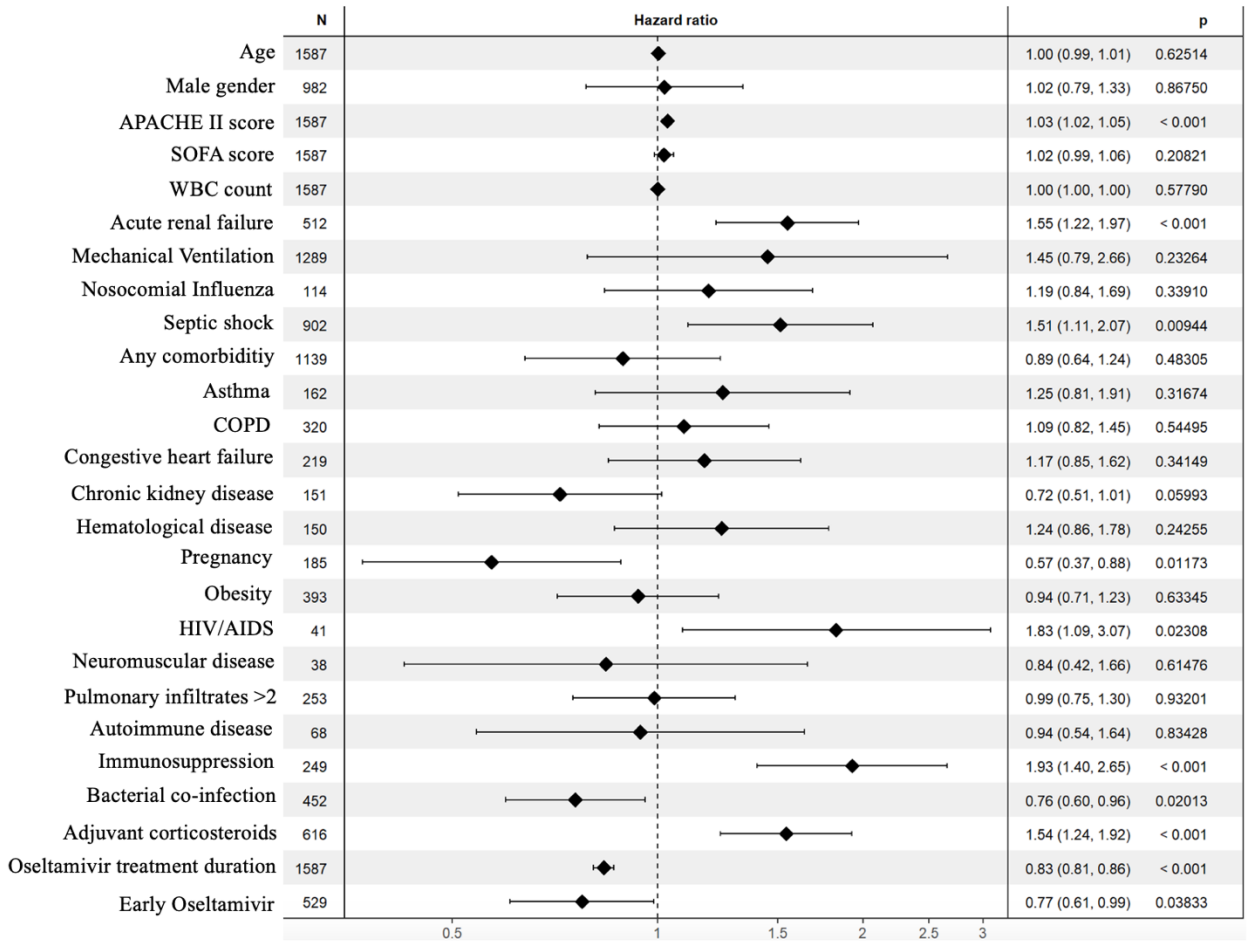

N
Hazard ratio
p
Age 1587 1.00 (0.99, 1.01) 0.62514
Male gender 982 1.02 (0.79, 1.33) 0.86750
APACHE II score 1587 1.03 (1.02, 1.05) < 0.001
SOFA score 1587 1.02 (0.99, 1.06) 0.20821
WBC count 1587 1.00 (1.00, 1.00) 0.57790
Acute renal failure 512 1.55 (1.22, 1.97) < 0.001
Mechanical Ventilation 1289 1.45 (0.79, 2.66) 0.23264
Nosocomial Influenza 114 1.19 (0.84, 1.69) 0.33910
Septic shock 902 1.51 (1.11, 2.07) 0.00944
Any comorbiditiy 1139 0.89 (0.64, 1.24) 0.48305
Asthma 162 1.25 (0.81, 1.91) 0.31674
COPD 320 1.09 (0.82, 1.45) 0.54495
Congestive heart failure 219 1.17 (0.85, 1.62) 0.34149
Chronic kidney disease 151 0.72 (0.51, 1.01) 0.05993
Hematological disease 150 1.24 (0.86, 1.78) 0.24255
Pregnancy 185 0.57 (0.37, 0.88) 0.01173
Obesity 393 0.94 (0.71, 1.23) 0.63345
HIV/AIDS 41 1.83 (1.09, 3.07) 0.02308
Neuromuscular disease 38 0.84 (0.42, 1.66) 0.61476
Pulmonary infiltrates >2 253 0.99 (0.75, 1.30) 0.93201
Autoimmune disease 68 0.94 (0.54, 1.64) 0.83428
Immunosuppression 249 1.93 (1.40, 2.65) < 0.001
Bacterial co-infection 452 0.76 (0.60, 0.96) 0.02013
Adjuvant corticosteroids 616 1.54 (1.24, 1.92) < 0.001
Oseltamivir treatment duration 1587 0.83 (0.81, 0.86) < 0.001
Early Oseltamivir 529 0.77 (0.61, 0.99) 0.03833
0.5
1
1.5
2
2.5
3

Figure S6

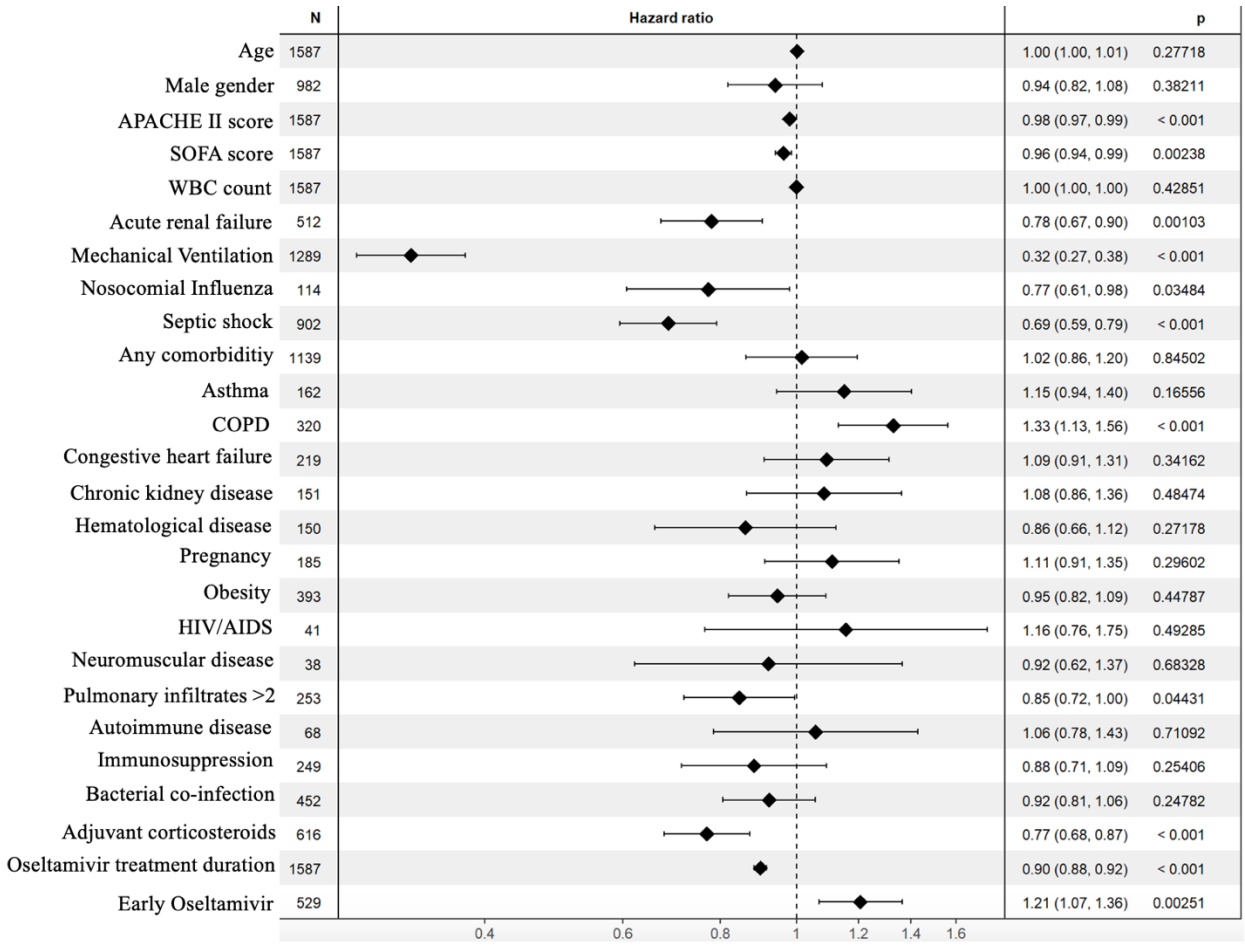
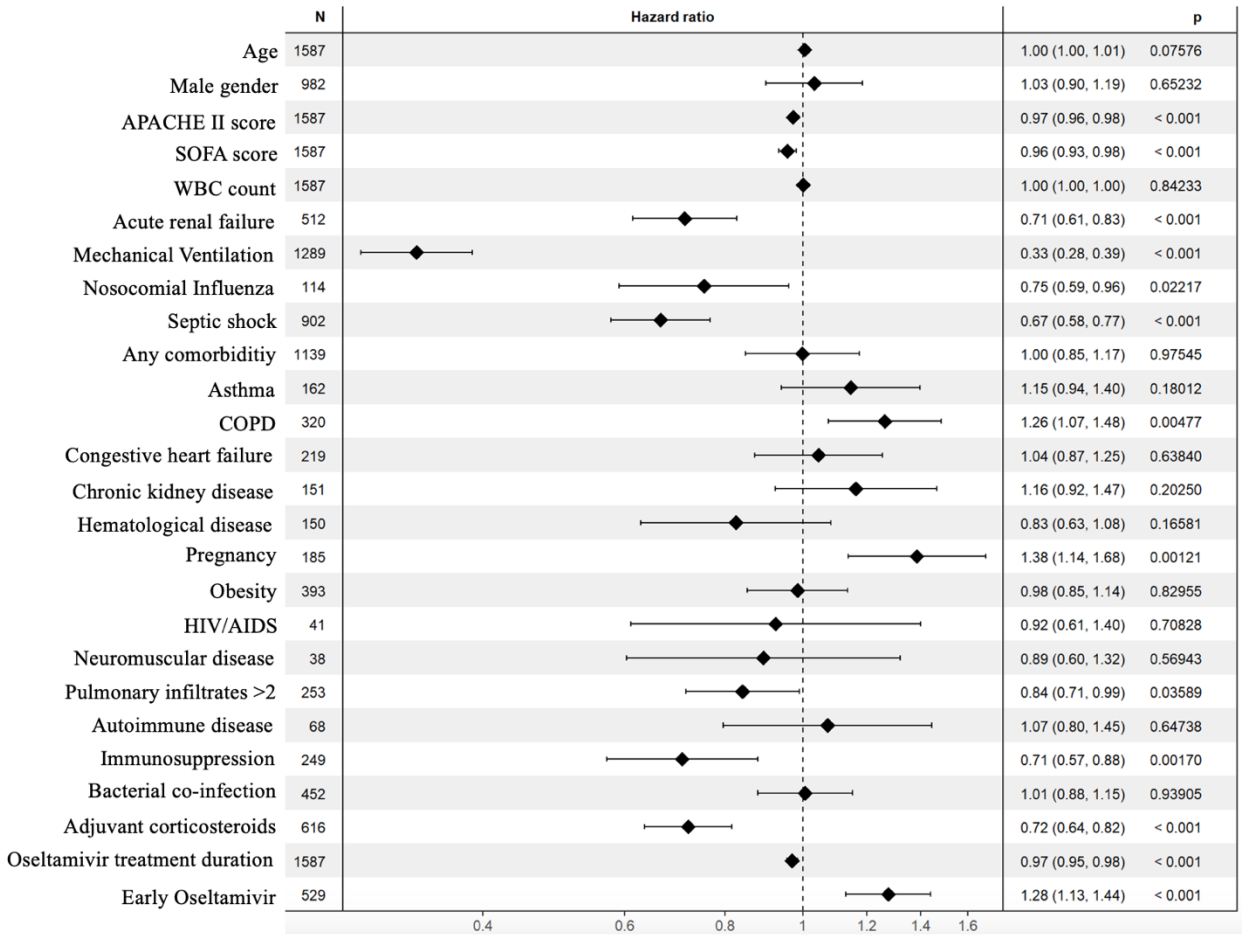

N
Hazard ratio
p
Age 1587 1.00 (1.00, 1.01) 0.27718
Male gender 982 0.94 (0.82, 1.08) 0.38211
APACHE II score 1587 0.98 (0.97, 0.99) < 0.001
SOFA score 1587 0.96 (0.94, 0.99) 0.00238
WBC count 1587 1.00 (1.00, 1.00) 0.42851
Acute renal failure 512 0.78 (0.67, 0.90) 0.00103
Mechanical Ventilation 1289 0.32 (0.27, 0.38) < 0.001
Nosocomial Influenza 114 0.77 (0.61, 0.98) 0.03484
Septic shock 902 0.69 (0.59, 0.79) < 0.001
Any comorbiditiy 1139 1.02 (0.86, 1.20) 0.84502
Asthma 162 1.15 (0.94, 1.40) 0.16556
COPD 320 1.33 (1.13, 1.56) < 0.001
Congestive heart failure 219 1.09 (0.91, 1.31) 0.34162
Chronic kidney disease 151 1.08 (0.86, 1.36) 0.48474
Hematological disease 150 0.86 (0.66, 1.12) 0.27178
Pregnancy 185 1.11 (0.91, 1.35) 0.29602
Obesity 393 0.95 (0.82, 1.09) 0.44787
HIV/AIDS 41 1.16 (0.76, 1.75) 0.49285
Neuromuscular disease 38 0.92 (0.62, 1.37) 0.68328
Pulmonary infiltrates >2 253 0.85 (0.72, 1.00) 0.04431
Autoimmune disease 68 1.06 (0.78, 1.43) 0.71092
Immunosuppression 249 0.88 (0.71, 1.09) 0.25406
Bacterial co-infection 452 0.92 (0.81, 1.06) 0.24782
Adjuvant corticosteroids 616 0.77 (0.68, 0.87) < 0.001
Oseltamivir treatment duration 1587 0.90 (0.88, 0.92) < 0.001
Early Oseltamivir 529 1.21 (1.07, 1.36) 0.00251
0.4
0.6
0.8
1
1.2
1.4
1.6

Figure S7


N
Hazard ratio
p
Age 1587 1.00 (1.00, 1.01) 0.07576
Male gender 982 1.03 (0.90, 1.19) 0.65232
APACHE II score 1587 0.97 (0.96, 0.98) < 0.001
SOFA score 1587 0.96 (0.93, 0.98) < 0.001
WBC count 1587 1.00 (1.00, 1.00) 0.84233
Acute renal failure 512 0.71 (0.61, 0.83) < 0.001
Mechanical Ventilation 1289 0.33 (0.28, 0.39) < 0.001
Nosocomial Influenza 114 0.75 (0.59, 0.96) 0.02217
Septic shock 902 0.67 (0.58, 0.77) < 0.001
Any comorbiditiy 1139 1.00 (0.85, 1.17) 0.97545
Asthma 162 1.15 (0.94, 1.40) 0.18012
COPD 320 1.26 (1.07, 1.48) 0.00477
Congestive heart failure 219 1.04 (0.87, 1.25) 0.63840
Chronic kidney disease 151 1.16 (0.92, 1.47) 0.20250
Hematological disease 150 0.83 (0.63, 1.08) 0.16581
Pregnancy 185 1.38 (1.14, 1.68) 0.00121
Obesity 393 0.98 (0.85, 1.14) 0.82955
HIV/AIDS 41 0.92 (0.61, 1.40) 0.70828
Neuromuscular disease 38 0.89 (0.60, 1.32) 0.56943
Pulmonary infiltrates >2 253 0.84 (0.71, 0.99) 0.03589
Autoimmune disease 68 1.07 (0.80, 1.45) 0.64738
Immunosuppression 249 0.71 (0.57, 0.88) 0.00170
Bacterial co-infection 452 1.01 (0.88, 1.15) 0.93905
Adjuvant corticosteroids 616 0.72 (0.64, 0.82) < 0.001
Oseltamivir treatment duration 1587 0.97 (0.95, 0.98) < 0.001
Early Oseltamivir 529 1.28 (1.13, 1.44) < 0.001
0.4
0.6
0.8
1
1.2
1.4
1.6