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Comparative Clinical Assessment and Risk Stratification of COVID-19 and Influenza Infections in Adults and Children: A Comprehensive Systematic Review and Meta-Analysis

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ABSTRACT

Objective: This study aimed to compare the clinical risks and outcomes of COVID-19 and influenza.
Methods: The search for relevant articles was conducted using both a database search method and a manual search, which involved searching through the reference lists of articles related to the topic for additional studies. The Quality assessment was carried out using the Newcastle Ottawa tool, and the data analysis was conducted using the Review Manager Software (RevMan 5.4.1).
Results: The meta-analysis results indicated that COVID-19 patients had similar lengths of hospital stays (SMD: -0.25; 95% CI: -0.60-0.11; p=0.17). However, COVID-19 patients had significantly higher mortality rates (RR: 0.28; 95% CI: 0.21-0.37; p<0.0001), in-hospital complications (RR: 0.57; 95% CI: 0.50-0.65; p<0.00001), intensive care unit (ICU) admissions (OR: 0.48; 95% CI: 0.37-0.61; p<0.00001), length of ICU stay (SMD: -0.45; 95% CI: -0.83-0.06; p=0.02), and mechanical ventilation use (OR: 0.36; 95% CI: 0.28-0.46; p<0.00001).
Conclusion: The findings suggested that COVID-19 was more severe than influenza. Therefore, "flu-like" symptoms should not be dismissed without a clear diagnosis, especially during the winter when influenza is more prevalent.

Keywords: COVID-19, Risk stratification, Influenza infection.

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Introduction

Coronavirus disease 2019 (COVID-19) is a viral respiratory infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was first found in Wuhan, China, in December 2019 and rapidly spread throughout the world, prompting the World Health Organization (WHO) to declare it a global pandemic on March 11, 2020 [1]. To date, 633,263,617 COVID-19 cases and 6,549,491 deaths have been reported worldwide [2]. Early diagnosis of this disease is a major public health issue because it allows health professionals to employ immediate preventive measures and specific precautions to reduce transmission while also providing appropriate treatments and supportive care to the patients.

Conversely, influenza, also known as the "flu", is a contagious respiratory illness caused by influenza viruses. The disease typically causes mild to severe illness and can occasionally be fatal. The Centers for Disease Control and Prevention (CDC) reported that flu cases in the United States increased from 9 million to 41 million between 2010 and 2020, with 52 thousand deaths [3]. A systematic review and meta-analysis found that children are more likely to contract the flu [4]. In that study, the median incidence rates were 3.9% for elderly adults (65 years and older), 9.3% for children between 0 and 17 years old, and 8.8% for adults aged 18 to 64 years old. These findings indicated that children under the age of 18 had a double risk of contracting the flu compared to adults over the age of 64.

The influenza virus and COVID-19 both exhibit similar primary symptoms. As a result, it is challenging to suspect COVID-19 during the flu season in a specific location where SARS-CoV-2 is not known to be present. Moreover, there is a paucity of systematic reviews that examine in-hospital complications, mortality rates, and other clinical manifestations of COVID-19 and compare them to other highly contagious viral diseases such as influenza. Therefore, the present study aimed to compare the clinical risks and outcomes of COVID-19 to influenza in people of all ages.

Materials and Methods

This systematic review and meta-analysis were in accordance with the PROSPERO database protocol and registration. It was prepared and reported in accordance with the Cochrane Collaboration guidelines, as well as the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

The inclusion and exclusion criteria were applied to studies retrieved via an electronic database and a manual search. Studies that met the following criteria were eligible for inclusion in the present study:

1. Studies written and published in English. The reviewers settled on this criterion to avoid the loss of context and meaning that comes with direct translation of scientific terms.
2. Studies that directly compared the patients with COVID-19 and influenza.
3. Studies with a sufficient pool of participants, i.e., more than 20 patients. This specification was important to enhance the present study's scientific research and statistical power.

Studies were excluded by following the criteria:

1. Articles published in a language other than English
2. Studies either evaluate patients with COVID-19 or influenza only.

Studies were designed as either Systematic reviews and meta-analyses, case reports, letters to the editor, or abstracts without evidence of full articles.

A PRISMA-guided search for studies relevant to our topic was carried out on 6 electronic databases and motor searches, including ScienceDirect, PubMed, Cochrane Library, Embase, Scopus, and Google Scholar. The search criteria employed the Boolean expressions "AND" and "OR" to combine the specific keywords into a detailed search strategy to be used in these electronic databases. The following search strategy was used: ("Clinical assessment" OR "clinical evaluation" OR "Risk stratification" OR "Risk evaluation") AND ("Coronavirus" OR "COVID-19" OR "severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2") AND ("Influenza" OR "seasonal influenza" OR "Flu") AND ("Children" OR "adults"). The other method used to obtain extra studies was reviewing the reference lists of topic-related papers. All retrieved studies were limited to the 2020 to 2022 publication period.

Two reviewers were tasked with gathering and compiling the necessary information from the included studies. The information obtained included the author ID (first author's surname and year of publication), study design, the country in which the study was conducted, participants' characteristics in influenza and COVID-19 groups (age, sample size, and sex distribution), follow-up, and main outcomes. The main outcomes in this study were divided into two categories: risk stratification and clinical evaluation. Risk stratification was determined by comparing the in-hospital complications associated with COVID-19 and influenza and mortality rates, while the clinical assessment was determined by comparing the length of hospital/ICU stay and patients requiring mechanical ventilation (MV). The inconsistencies in the extracted data were resolved through discussions between the two reviewers or by consulting a third reviewer.

Given that the studies included in this review were non-randomized, the methodological quality was assessed using the Newcastle-Ottawa quality assessment tool. A single reviewer independently carried out the quality appraisal process and grouped

each included study into three categories: selection, comparability, and outcomes. The selection category employed 4 assessment criteria, while comparability and outcomes had 1 and 3 assessment criteria, respectively. Based on the assessment criteria, each study was assigned a rating score. A rating score of "1" was used for a fully addressed criterion, whereas "0" was used for a criterion that was either unclear or not entirely addressed. Studies with overall ratings of 0-2, 3-5, and >5 were classified as poor, moderate, and high methodological quality, respectively.

The pooled effect sizes of the main and secondary outcomes were carried out using the Review Manager software (RevMan version 5.4.1). During the meta-analysis, a Risk Ratio (RR) assessment was chosen for the complications and mortality rates, while an odds ratio (OR) assessment was chosen for the MV use. Since the length of Hospital/ICU stays was reported as a mean, their analysis was carried out using the Standard Mean Deviation (SMD).

To account for the expected heterogeneity, we employed the Random effect model for all meta-analyses. This heterogeneity was assessed using I^2 statistics, with scores of 25%, 50%, and more than 70% classified as low, moderate, and high, respectively. A 95% confidence interval (CI) was also employed, and the statistical difference was established as $p<0.05$. The outcomes of all meta-analyses were then presented in forest plots.

Results

520 studies related to our topic were found. Of the 520 articles, 56 were eliminated because they were duplicates, and the remaining 464 had their titles and abstracts screened. Based on the screening criteria, 173 articles were excluded. 234 of the remaining 291 articles were not retrieved, and the rest were evaluated based on the eligibility criteria. The assessment resulted in the inclusion of 9 articles, while the other 48 were excluded as follows: 2 were published in other languages, 42 only included patients with influenza or COVID-19, and 4 were designed as systematic reviews, case reports, letters to the editor, or abstracts without full articles (Table 1). The full selection results are shown in the PRISMA flow diagram (Figure 1).

The evaluation of the studies' quality revealed that only 4 of them were of high quality, while the remaining 5 were of moderate quality. The evaluation revealed that none of the studies had poor methodological quality (Table 2).

Mortality and complications are critical outcomes when evaluating the risk associated with COVID-19 and influenza. A meta-analysis of outcomes from all included studies showed that influenza was significantly associated with a lower mortality risk than COVID-19 (RR: 0.28; 95% CI: 0.21- 0.37; $p<0.00001$) (Figure 2). Similarly, the present meta-analysis demonstrated that COVID-19 was highly associated with in-hospital complications compared to influenza. A subgroup analysis showed that the risk of developing acute respiratory failure was significantly higher for patients with COVID-19 than those with influenza (RR: 0.63; 95% CI: 0.61-0.66; $p<0.00001$). Additionally, the subgroup analysis indicated significantly higher risks of acute kidney failure/injury (RR: 0.73; 95% CI: 0.67 to 0.80; $p<0.00001$), sepsis/septic shock (RR:0.52; 95% CI: 0.33 to 0.83; $p=0.006$), and pulmonary embolism (RR: 0.42; 95% CI: 0.23 to 0.80; $p<0.0001$) among patients with COVID-19 (Figure 3).

Table 1. Study Characteristics

Author ID	Country	Study Design	COVID-19 Group	Influenza Group	Main Outcomes
Zayet *et al.,* 2020 [5]	France	Retrospective observational study	70 patients (29 men and 41 women; average age 56.7±19.3 years)	54 patients (17 men and 37 women; average age 61.3±18.8 years)	The average hospitalization length for patients with COVID-19 and influenza was not substantially different (6.9 5.8 vs. 7.6 6.9 days, respectively; $p=0.667$). The number of COVID-19 and influenza patients requiring IMV was not significantly different (11 (15.7%) vs. 5 (9.3%), respectively; $p=0.499$). The mortality rates for COVID-19 and influenza patients were not different (4 (5.7%) vs. 5 (9.3%), respectively; =1).
Hedberg *et al.,* 2021 [6]	Sweden	Retrospective cohort study	1721 patients (1010 males and 711 females; median age 58 (42-71) years).	2468 patients (1194 males and 1274 females; median age 68 (51-79) years).	The 90-day death rate in the pediatric population was similar for both influenza and COVID-19 patients (6 (1%) vs. 1(1%), respectively). Patients with COVID-19 had significantly longer stays in the ICU as opposed to influenza patients (6 (4-6) days vs. 1 (0-4) days). Adult patients with COVID-19 had a 90-day mortality rate that was significantly higher than patients with influenza (235 (15%) vs. 192 (8%), respectively).

Xie *et al.,* 2020 [7]	United States	Cohort Study	3641 patients (3438 men and 203 women; average age 69.03 (13.4) years)	12676 patients (11,994 men and 682 women; average age 70.25 (12.8) years).	Compared to patients with influenza, COVID-19 patients had a higher mortality risk (16.85 (95% CI: 14.85 to 18.99). COVID-19 patients had a significantly greater need for MV than influenza patients (11.29). (9.62 to 13.14). COVID-19 patients spent significantly more time in the hospital than influenza patients (AOR: 3.00; 2.20 to 3.80 days).
Brehm *et al.,* 2021 [8]	Germany	Prospective observational study	166 patients (111 males and 55 females; median age 59(45-71) years).	255 patients (144 males and 111 females; median age 65 (52; 77) years).	Patients with COVID-19 required IMV significantly more frequently than patients with influenza (52 (31.3) vs. 32 (12.5), respectively; p=0.001). COVID-19 patients stayed in the hospital for longer periods than influenza patients (25.9 (26.6) vs. 17.2 (21.0) days, respectively; p=0.002). COVID-19 patients had a significantly higher rate of deaths than influenza patients (26 [15.9%] vs. 23 [9.0%]; p=0.04).
Cates *et al.,*2020 [9]	United States	Cohort study	3948 patients (3710 males and 238 females; median age 70 (61 – 77) years)	5453 patients (5116 males and 337 females; median age 69 (61 – 75) years)	COVID-19 patients were hospitalized for a significantly longer period than influenza patients (8.6 (3.9-18.6) vs. 3.0 (1.8-6.5) days, respectively; p<0.001). Patients with COVID-19 had an in-hospital mortality rate that was significantly higher than patients with influenza (828 (21.0) vs. 190 (3.8), respectively; p<0.001).
Piroth *et al.,* 2020 [10]	France	Retrospective cohort study	89530 patients (42035 women and 47495 men; average age 65 (20) years)	45819 patients (23701 women and 22118 men; average age 59 (32) years)	Patients with COVID-19 experienced substantially higher in-hospital mortality than patients with influenza (15 104 (16%) vs. 2640 (5%) respectively; p=0.0001). COVID-19 patients had a considerably longer average ICU stay than influenza patients (15 (15) vs. 8 (9) days, respectively; p<00001). MV was more frequently needed by COVID-19 patients in the ICU than influenza patients. (10430/14585 (71·5%) vs. 3004/4926 (61·0%), p<0·0001)
Beatty *et al.,* 2021 [11]	Ireland	Cohort Study	4837 patients	5369 patients	The average length of hospitalization for COVID-19 patients was twice that of influenza patients (17.7 vs. 8.3 days). In-hospital mortality was five times more likely to occur in COVID-19-related cases than in influenza-related cases (OR 5.07, 95% CI 4.29-5.99, P<0.001).
Kanthimathinathan *et al.,* 2021 [12]	United Kingdom	Prospective nationwide cohort study	73 patients (44 boys and 29 girls in the 30 days to 18 years age group)	243 patients (142 boys and 101 girls in the 30 days to 18 years age group)	Patients with COVID-19 required a longer stay in the PICU than those with influenza (11.6 (24.02) vs. 9.2 (12.15) days, respectively.
Talbot *et al.,* 2021 [13]	United States	Observational study	914 patients (423 females and 491 males; aged ≥18 years)	1937 patients (1081 females and 856 males aged ≥18 years)	MV was administered to COVID-19 patients more frequently than it was to influenza patients. (AOR=15.6, 95% CI: 10.7, 22.8, p<0.01). COVID-19's in-hospital mortality was considerably higher than that of influenza. (13.7%, 123/898) vs. (1.4%, 27/1919), p<0.01).

COVID-19: Coronavirus disease 2019; IMV: invasive mechanical ventilation; MV: Mechanical ventilation; AOR: Adjusted Odds Ratio; CI: Confidence Interval; ICU: Intensive Care Unit; PICU: Pediatric Intensive Care Unit.

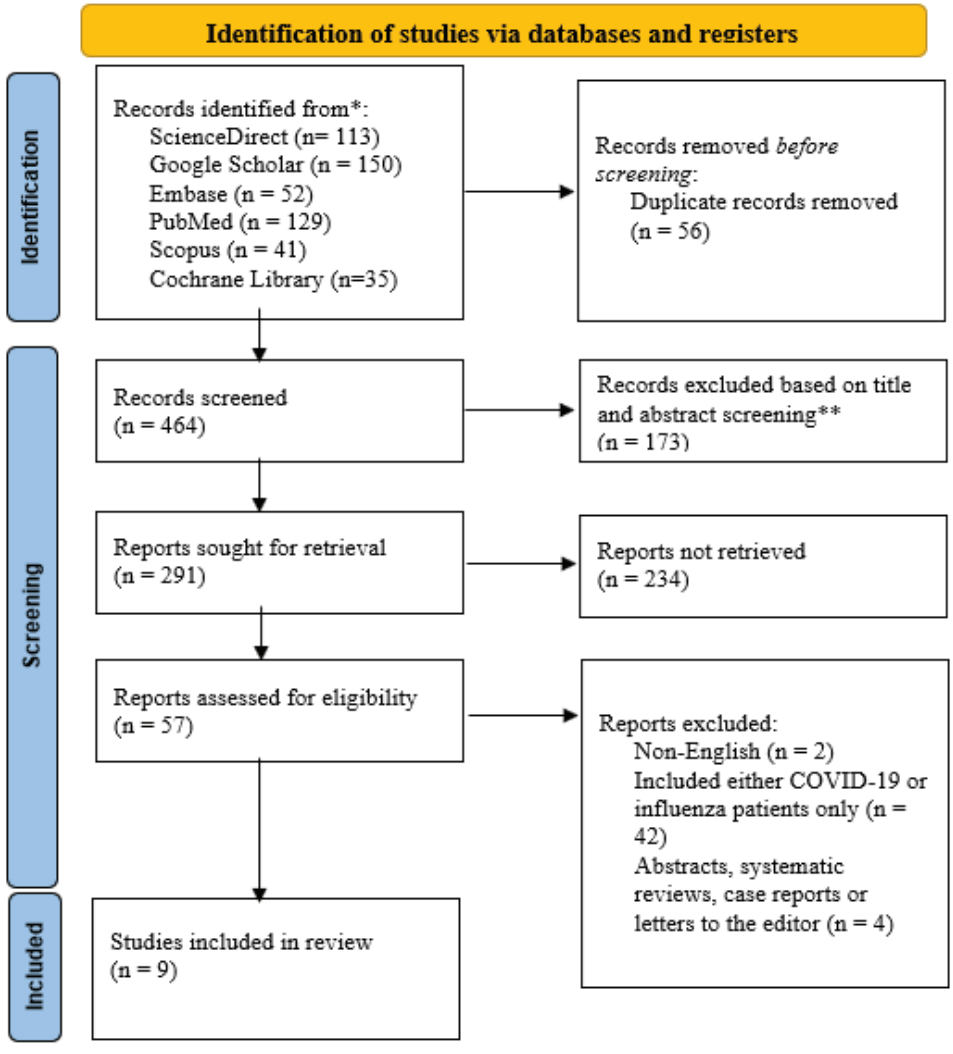

Fig. 1. PRISMA flow diagram

Table 2. Methodological Quality using the Newcastle Ottawa Scale for cohort studies

Author ID	Selection (Maximum 4)	Comparability (Maximum 1)	Outcome (Maximum 3)	Total Score	Quality
Zayet et al. 2020 [5]	4	1	2	7	High
Hedberg et al. 2021 [6]	3	1	2	6	Moderate
Xie et al. 2020 [7]	4	1	2	7	High
Brehm et al. 2021 [8]	3	1	3	7	High
Cates et al. 2020 [9]	4	1	2	7	High
Piroth et al. 2020 [10]	3	1	2	6	Moderate
Beatty et al. 2021 [11]	2	1	3	6	Moderate
Kanthimathinathan et al. 2021 [12]	2	1	2	5	Moderate
Talbot et al. 2021 [13]	3	1	2	6	Moderate

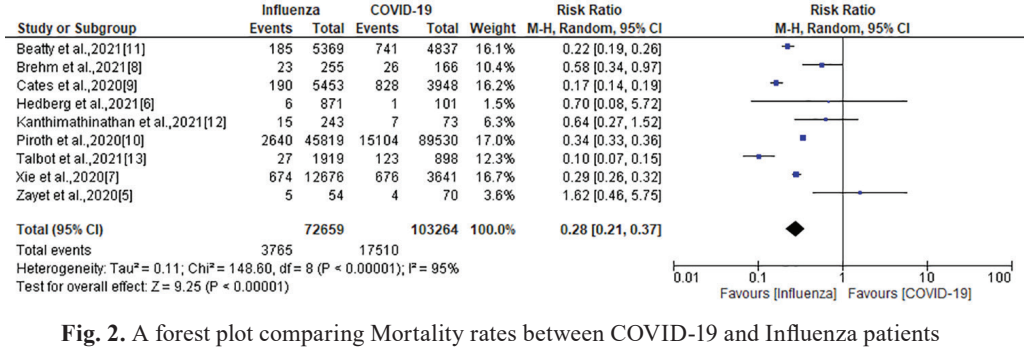

Fig. 2. A forest plot comparing Mortality rates between COVID-19 and Influenza patients

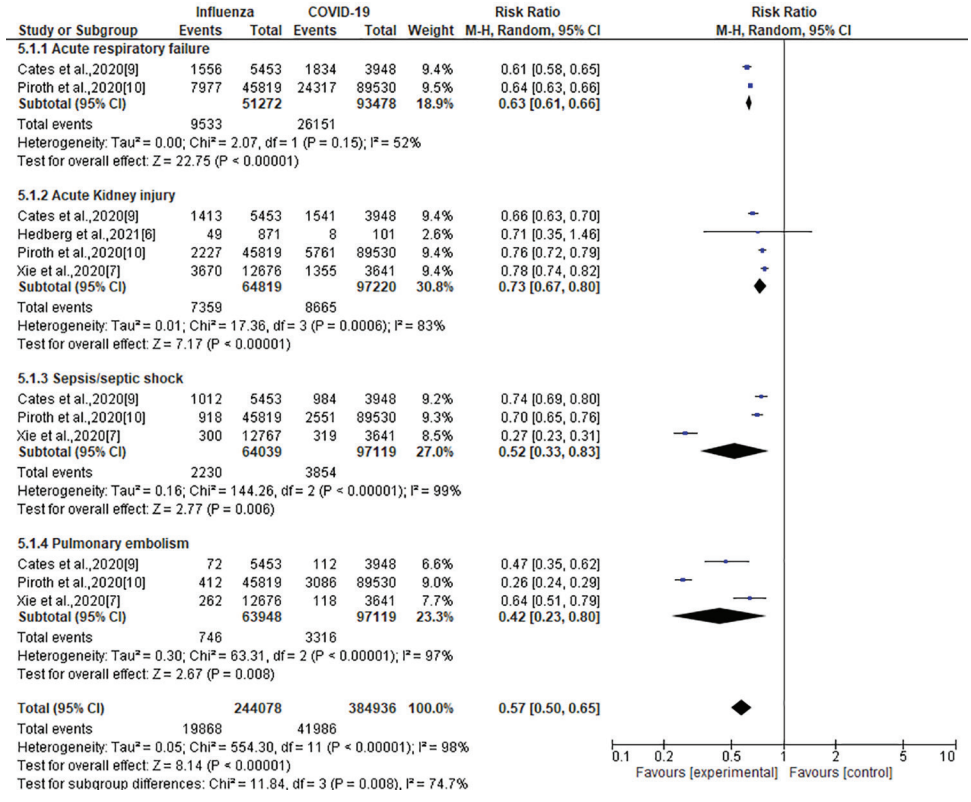

Fig. 3. A forest plot comparing in-hospital complications between COVID-19 and Influenza patients

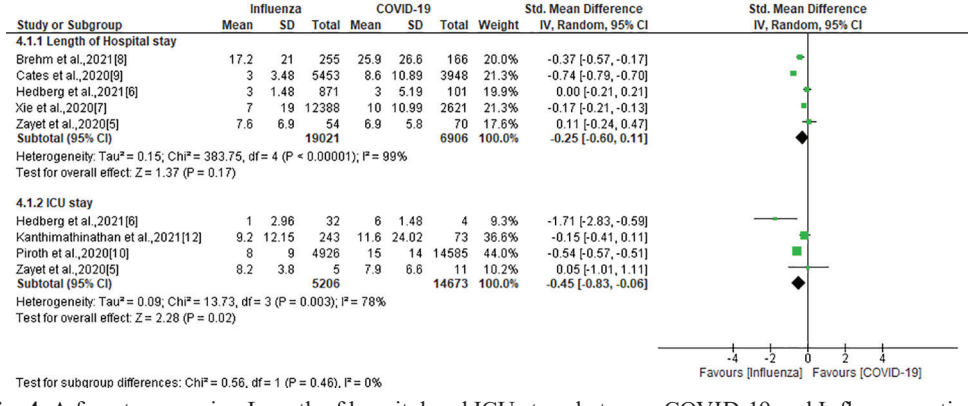

Fig. 4. A forest comparing Length of hospital and ICU stays between COVID-19 and Influenza patients

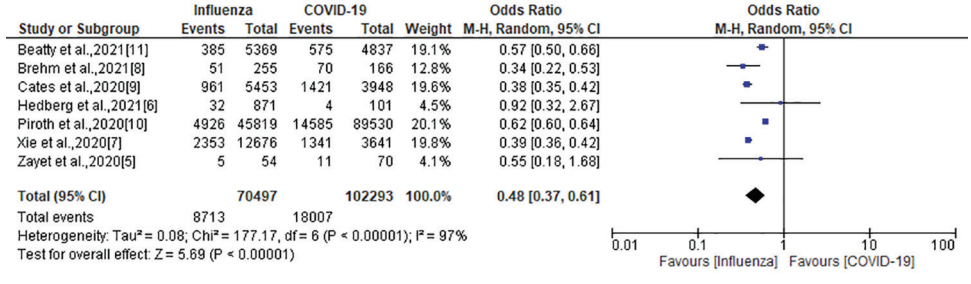

Fig. 5. A forest plot comparing ICU admissions between COVID-19 and Influenza patients

A meta-analysis of outcomes from 5 studies indicated that patients with COVID-19 and influenza had similar lengths of hospital stay (SMD: -0.25; 95% CI: -0.60-0.11; p=0.17) (Figure 4). However, patients hospitalized with these diseases were also likely to develop severe symptoms that necessitate the transfer to the intensive care unit (ICU). The present meta-analysis revealed that the odds of being admitted to the ICU were lower among influenza patients than among COVID-19 patients (OR: 0.48; 95% CI: 0.37-0.61; p<0.00001) (Figure 5). Additionally, COVID-19 patients admitted to the ICU stayed longer than patients with influenza (SMD: -0.45; 95% CI: -0.83-0.06; p=0.02) (Figure 4). Additionally, the analysis indicated that COVID-19 patients were more likely to require mechanical ventilation than influenza patients (OR: 0.36; 95% CI: 0.28-0.46; p<0.00001) (Figure 6).

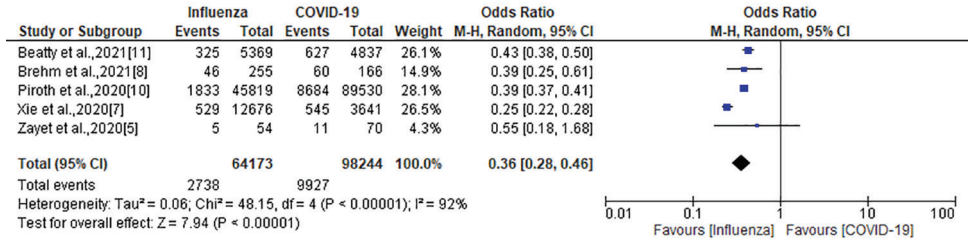

Fig. 6. A forest plot comparing the need for Mechanical use between hospitalized COVID-19 and Influenza patients

Discussion

Research on COVID-19 and influenza risks and clinical outcomes is crucial because it enables medical professionals to provide the best preventive and supportive care to patients suffering from these diseases. The present study found that, while COVID-19 and influenza patients had similar durations of hospital stay, COVID-19 patients were at a higher risk of mortality, in-hospital complications, ICU admissions, mechanical ventilation use, and longer ICU stays.

According to the findings of the present study, COVID-19 patients had a threefold higher mortality rate than influenza patients (17% [17510/103264] vs. 5.2% [3765/72659], respectively). These findings were in agreement with a Danish nationwide cohort study that found that the 30-day mortality rate for hospitalized COVID-19 patients was three times that of influenza patients (RR: 3.00; 95% CI: 2.65-3.39; $p<0.001$) [14]. Similar findings were reported by a comparative study conducted in the United Kingdom, which found that COVID-19 patients had a significantly higher mortality rate (42% vs. 24% for COVID-19 and viral types of pneumonia, respectively) [15]. Cobb and colleagues also noted that patients with COVID-19 had significantly higher hospital mortality rates than patients with influenza ($p=0.006$) [16]. Further statistical analysis revealed that the relative risk (RR) for mortality was twice as high in COVID-19 patients as in influenza patients (adjusted RR: 2.13; 95% CI: 1.24-3.63; $p=0.006$). The high mortality rate among COVID-19 patients observed in these studies appeared to support the notion that COVID-19 is a more severe illness than influenza. Furthermore, the high mortality rate in COVID-19 patients could be attributed to a spontaneous influx of patients over a short span of time, which caused constraints in the medical structure and forced healthcare providers to prioritize patients based on clinical status and prognosis. In contrast to the findings of these studies, Tang and colleagues reported higher mortality rates among patients with H1N1-induced acute respiratory distress syndrome (ARDS) than those with COVID-19-induced ARDS [17]. The disparity in this study could be attributed to several factors. First, the study used data from two hospitals, which might not have accounted for the differences in local practice patterns and other factors. Secondly, the study only included patients with ARDS, meaning that the study only accounted for critically ill patients. The study also revealed that about 36% of patients were still in the hospitals at the completion of the study, which might have led to an underestimation of in-hospital mortality.

The mortality rates among patients with COVID-19 and influenza could be associated with various risk factors. The first factor associated with mortality rates was age. Beatty and colleagues discovered that mortality rates increased with age. That study found no significant differences in mortality rates between COVID-19 and influenza patients under the age of 40. However, in participants over the age of 40, the COVID-19 group had significantly higher mortality rates, with ORs increasing from 2.27 (95% CI 1.4-3.61, $p=0.001$) in the 40-60 year age bracket to 4.99 (95% CI 3.54-7.03, $p=0.001$) in the 85 and older age [11]. Xie *et al.,* similarly found higher mortality rates among older patients [7]. Besides, overall mortality increased from 9.3% in the group of people under 65 years old to 19.4% in the group of people between 65 and 75 years old, and 27.8% in the group of people over 75 years old. Talbot and colleagues also contributed to similar findings, showing that the mortality rates increased with age [13]. Another study evaluating patients with different subtypes of influenza showed that age was highly associated with mortality rates [18]. In that study, influenza A (H1N1) patients who were 65–74 years old and ≥75 years old had a higher risk of death (AOR: 2.46, 95% CI: 1.22-4.97- 2.13, 95% CI: 1.05-4.30, respectively). Similar to patients with influenza A, patients with influenza B had a higher risk of death if they were 65 to 74 years old or older than 75 years old (AOR: 27.42, 95% CI: 4.95-151.93-15.96, 95% CI: 3.01-84.68, respectively).

Additionally, studies have demonstrated the impact of race and sex on the mortality rates of COVID-19 and influenza patients. According to a study by Talbot and colleagues, non-Hispanic African American patients had a higher risk of dying in the hospital than non-Hispanic White patients (AOR=58.6; 95% CI: 13.3-258.8; $p<0.01$ vs. AOR=16.6; 95% CI: 9.1-30.4; $p=0.08$, respectively) [13]. However, the study attributed the disparities in the mortality rates between the different races to undiagnosed and untreated comorbid conditions. The study indicated that in-hospital death was higher among men than women (AOR=26.3, 95% CI: 11.8-

58.7, $p<0.01$ vs. AOR=16.5, 95% CI: 8.3-32.6, $p=0.02$, respectively). Similarly, a previous case series study reported that sex could be an independent factor for COVID-19 severity and mortality. According to their findings, men had a 2.4 times increased risk of death than female patients [19]. On the other hand, Price-Haywood and colleagues investigated how race affected mortality rates among COVID-19 patients and discovered that race was not on its own a significant risk factor for in-hospital mortality. (hazard ratio: 0.89; 95% CI: 0.68-1.17) [20].

The present study also showed that patients with COVID-19 were at a higher risk of developing in-hospital complications. The higher risk of pulmonary embolism among the patients with COVID-19 was consistent with the findings of Fauvel and colleagues, who reported that of the 1240 COVID-19 hospitalized patients referred for a computed tomography pulmonary angiography, 103 (8.3%) patients were found to have developed pulmonary embolism [21]. It is also important to highlight that the present study employed acute respiratory failure to account for respiratory complications and found that COVID-19 patients were at a higher risk of acute respiratory failure than influenza patients. However, evidence suggested that the risk of other respiratory complications differed between studies. For example, Cates and colleagues reported that COVID-19 patients had a 19-fold higher risk for ARDS and a 3.5-fold higher risk of pneumothorax than influenza patients. However, influenza patients were 3 times more likely to develop asthma than COVID-19 [9]. The risk of other non-respiratory complications, such as sepsis and acute kidney injury, was also reported to be high among patients with COVID-19. This increased risk of acute kidney failure/injury among Influenza and COVID-19 was also supported in previous studies [22, 23]. The increased risk of sepsis among COVID-19 patients could be explained by the dysregulated response system in these patients [24].

Other studies found that less common but severe complications, such as hematological and neurologic complications and bacteremia, could occur in influenza and COVID-19 patients. Cates and colleagues reported that the risk of cerebral ischemia was twice as high in the COVID-19 group than in the influenza group [9]. These results were consistent with a United States study which showed that the odds of developing stroke were 7.6 times higher in COVID-19 patients than in influenza patients [25]. Similarly, Xie and colleagues found that the risk for stroke was higher among COVID-19 patients (AOR: 1.62; 95% CI: 1.17-2.24). However, Piroth *et al.,* [10] reported that the risk of developing ischemic stroke was similar in both COVID-19 and influenza patients (0.8% vs. 0.9%, respectively; $p=0.097$). Although the present study did not involve patients being treated or vaccinated against COVID-19 or influenza, it is important to note that some vaccinations might also result in complications. A recent case report of a patient receiving the *Pfizer*-BioNTech COVID-19 mRNA vaccine showed that the patient developed signs and symptoms of acute pericarditis 10 days after the vaccination. A diagnosis made on the patient confirmed that the patient had developed an acute pericarditis, which included pericardial perfusion and typical pain [26].

The complications reported in COVID-19 and influenza patients could be attributed to various risk factors, including age, sex, and race/ethnicity. Cates *et al.,* conducted a statistical analysis to show the effect of race on the risk of developing in-hospital complications and found that Black Hispanic and non-Hispanic patients were at a higher risk of developing sepsis and renal, neurologic, and respiratory complications than White patients. However, the study reports that the difference between these races could not exclusively be related to underlying comorbidities or age; however, other factors such as social, environmental, economic, and structural inequalities could have accounted for the differences. On the other hand, a prospective cohort study in the United Kingdom of COVID-19 patients found that the complication rates were comparable across all the racial groups but were higher among black patients than white patients (57.8% [1433 of 2480] vs. 49.1% [26431 of 53780], respectively) [27]. Further statistical analysis showed that complication rates increased with age, with patients over 50 having a higher complication rate than patients in the 19-49 age group (51.3% vs. 38.9%, respectively). Male patients also seemed to develop more complications than females. The study also stated that when the age, sex, and comorbidities were adjusted, the male sex became an independent predictor for developing complications. Pre-existing comorbidities were also found to be associated with an increased risk of complications. the study reported that patients with some existing comorbidities in a particular organ were at a higher risk of developing complications affecting that organ. A prospective study of influenza patients reported that those with pre-existing comorbidities and patients aged ≥50 years were more likely to suffer in-hospital complications [28].

The findings of the present study suggested that the severity of COVID-19 and influenza was associated with the number of patients being admitted to the ICU. This study showed that patients with COVID-19 were more likely to be referred to the ICU and stay longer than those with influenza. This finding was supported by a previous study, which reported that COVID-19 patients had significantly higher proportions of ICU admissions than influenza patients (29% vs. 6%, $p=0.034$) [29]. Similarly, a German cohort study reported that ICU admissions were substantially higher among COVID-19 patients than among influenza patients (21% vs.13%, respectively) [30]. Contrary to these results, other studies found no significant differences in ICU admissions between COVID-19 and influenza patients. For example,

Zayet and colleagues reported similar proportions of ICU-admitted patients with COVID-19 and influenza (15% and 9%, respectively; p=0.458) [5]. The results also indicated that the mean stay in the ICU was not statistically different between the two groups (p=0.924). Similarly, Cobb and colleagues showed an insignificant difference in the length of ICU stay between COVID-19 and influenza patients (p=0.22) [16]. The difference in these studies could be attributed to the fact that they mostly included patients with severe influenza and COVID-19.

It is important to note that several other factors might have influenced the ICU admissions in both COVID-19 and Influenza patients. Sadeghi and colleagues conducted a univariate analysis of risk factors associated with ICU admission and found that age was significantly associated with the increased risk of ICU admission among COVID-19 patients (OR: 1.02; 95% CI: 0.89-0.89; p=0.03) [31]. This finding was evident in a German cohort study that reported the highest percentage of COVID-19 ICU admissions among patients in the 70-89 age group (64%) and the lowest percentage in the 20-49 age group (<1%) [30]. Pre-existing comorbidities have also been associated with an increased risk of ICU admission. Sadeghi and colleagues reported that patients with a history of kidney diseases or cancer were at a higher risk of being admitted to the ICU (P=0.04, OR=2.54, 95% Cl=1.00-6.41 and p<0.001, OR=3.15, 95% Cl=1.39-7.15; respectively) [31]. Other comorbidities, such as hypotension, diabetes mellitus (Type 2), chronic kidney diseases, and heart failure have also been associated with an increased risk of ICU admissions [30]. Additionally, a Colombian multivariate study found that COVID-19 patients with pre-existing ischemic heart disease (OR: 3.24; 95% CI: 1.16-9.00) and chronic obstructive pulmonary disease (OR:2.07; 95% CI:1.09–3.90) were more likely to be admitted [32]. However, some pre-existing comorbidities, such as acquired immunodeficiency syndrome (AIDs), had some intriguing results. Piroth and colleagues reported that patients with HIV did not seem to be more affected by either COVID-19 or influenza. This finding was attributed to the fact that virologically controlled HIV patients (antiretroviral treated) seem not to have a significantly higher risk of developing severe COVID-19, as shown in countries with low antiretroviral rates [33]. However, this does not imply that HIV patients are at a lower risk of developing severe COVID-19 due to the potentially preventive property of antiretroviral therapy [34].

Previous research also found that among influenza patients, sex and weight might influence ICU admission rates. A Dutch study evaluated the risk factors associated with ICU admission and reported that patients with a body mass index (BMI) greater than 30 were at a higher risk of being admitted to the ICU (p=0.04) [35]. Similarly, Martinez and colleagues reported that obesity was associated with ICU admission, especially for patients with influenza A. However, other studies found no association between ICU admission and obesity [36, 37]. The disparities in the findings of these studies could be attributed to the fact that based on age, obesity is usually accounted for determining whether severe cases of influenza should be admitted to the ICU. Martinez *et al*., found a significant association between sex and ICU admission for patients with type A influenza, with male patients being admitted to the ICU more frequently than female patients [18]. Moreover, the study explained that seasonal influenza vaccination was associated with reduced ICU admission among patients with Influenza A. However, further analysis showed that the statistical power was insufficient to associate the vaccine with a reduced risk of ICU admission in Influenza B patients.

The findings of this systematic review and meta-analysis were subject to various limitations, including significant heterogeneity in the analysis of the main outcomes. However, this heterogeneity was to be expected considering that the study comprised participants with different v COVID-19 and influenza variants. The heterogeneity also had no effect on the results of the present meta-analysis since the majority of the studies included in this study had a good methodological quality, implying that the publication bias was minimized. Some included studies might have under-detected or misclassified some of the patients' characteristics, such as comorbidities, thereby introducing bias in the outcomes that were dependent on these characteristics [10]. Additionally, the present study only included studies published in English. Due to this criterion, numerous papers written in other languages that could have been used to improve the statistical power and the scientific research of the current study were excluded. Some of the studies had relatively small sample sizes compared to other studies, which could have influenced the results of our meta-analysis [5]. The study also allowed the inclusion of both adult and pediatric patients. However, during the meta-analysis, the studies were not grouped based on the patient's age, which made it difficult to properly differentiate the risk of COVID-19 and influenza in adult and pediatric patients.

In summary, this study has suggested that the number of patients hospitalized with COVID-19 and influenza was similar. However, the findings indicated that COVID-19 hospitalized patients had an increased risk for mortality, in-hospital complications, ICU admissions, need for mechanical ventilation, and length of ICU stays. Based on these findings, we could conclude that COVID-19 was more severe than influenza, and caution should be taken when dismissing COVID-19 as a "flu-like" illness, especially during the winter season when influenza is more common. Therefore, clinical evaluation of the "flu-like" symptoms must be performed to differentiate between influenza and COVID-19 and

reduce the risk associated with these viral diseases. The included and previous studies reported that various risk factors, including age, sex, race, and pre-existing comorbidities, influence the mortality rates, ICU admissions, and complication rates. However, future studies require to carry out extensive scientific research to sufficiently understand the effect of these factors on patients with COVID-19 and influenza.

Declaration

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References

1. Organization WH. Coronavirus disease 2019 (COVID-19): Situation Report, 51: World Health Organization; 2020. *Google Scholar*. 2020.
2. WHO. WHO Coronavirus (COVID-19) Dashboard. 2022 [November 18, 2022.]. Available from: https://covid19.who.int.
3. CDC: Burden of Influenza.: Centers for Disease Control and Prevention.; 2022 [November 18, 2022]. Available from: https://www.cdc.gov/flu/about/burden/index.html.
4. Tokars JI, Olsen SJ, Reed C. Seasonal Incidence of Symptomatic Influenza in the United States. *Clin Infect Dis*. 2018;**66**(10):1511-8.
5. Zayet S, Kadiane-Oussou NJ, Lepiller Q, Zahra H, Royer PY, Toko L, et al. Clinical features of COVID-19 and influenza: a comparative study on Nord Franche-Comte cluster. *Microbes Infect*. 2020;**22**(9):481-8.
6. Hedberg P, Karlsson Valik J, van der Werff S, Tanushi H, Requena Mendez A, Granath F, et al. Clinical phenotypes and outcomes of SARS-CoV-2, influenza, RSV and seven other respiratory viruses: a retrospective study using complete hospital data. *Thorax*. 2022;**77**(2):154-63.
7. Xie Y, Bowe B, Maddukuri G, Al-Aly Z. Comparative evaluation of clinical manifestations and risk of death in patients admitted to hospital with covid-19 and seasonal influenza: cohort study. *Bmj*. 2020;**371**:m4677.
8. Brehm TT, van der Meirschen M, Hennigs A, Roedl K, Jarczak D, Wichmann D, et al. Comparison of clinical characteristics and disease outcome of COVID-19 and seasonal influenza. *Sci Rep*. 2021;**11**(1):5803.
9. Cates J, Lucero-Obusan C, Dahl RM, Schirmer P, Garg S, Oda G, et al. Risk for In-Hospital Complications Associated with COVID-19 and Influenza - Veterans Health Administration, United States, October 1, 2018-May 31, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;**69**(42):1528-34.
10. Piroth L, Cottenet J, Mariet AS, Bonniaud P, Blot M, Tubert-Bitter P, et al. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. *Lancet Respir Med*. 2021;**9**(3):251-9.
11. Beatty K, Hamilton V, Kavanagh PM. Just a bad flu? Tackling the "infodemic" in Ireland through a comparative analysis of hospitalised cases of COVID-19 and influenza. *Public Health*. 2021;**194**:19-24.
12. Kanthimathinathan HK, Buckley H, Lamming C, Davis P, Ramnarayan P, Feltbower R, et al. Characteristics of Severe Acute Respiratory Syndrome Coronavirus-2 Infection and Comparison With Influenza in Children Admitted to U.K. PICUs. *Crit Care Explor*. 2021;**3**(3):e0362.
13. Talbot HK, Martin ET, Gaglani M, Middleton DB, Ghamande S, Silveira FP, et al. Coronavirus disease 2019 (COVID-19) Versus Influenza in Hospitalized Adult Patients in the United States: Differences in Demographic and Severity Indicators. *Clin Infect Dis*. 2021;**73**(12):2240-7.
14. Nersesjan V, Amiri M, Christensen HK, Benros ME, Kondziella D. Thirty-Day Mortality and Morbidity in COVID-19 Positive vs. COVID-19 Negative Individuals and vs. Individuals Tested for Influenza A/B: A Population-Based Study. *Front Med (Lausanne)*. 2020;**7**:598272.
15. Richards-Belle A, Orzechowska I, Gould DW, Thomas K, Doidge JC, Mouncey PR, et al. COVID-19 in critical care: epidemiology of the first epidemic wave across England, Wales and Northern Ireland. *Intensive Care Med*. 2020;**46**(11):2035-47.
16. Cobb NL, Sathe NA, Duan KI, Seitz KP, Thau MR, Sung CC, et al. Comparison of Clinical Features and Outcomes in Critically Ill Patients Hospitalized with COVID-19 versus Influenza. *Ann Am Thorac Soc*. 2021;**18**(4):632-40.
17. Tang X, Du RH, Wang R, Cao TZ, Guan LL, Yang CQ, et al. Comparison of Hospitalized Patients With ARDS Caused by COVID-19 and H1N1. *Chest*. 2020;**158**(1):195-205.
18. Martínez A, Soldevila N, Romero-Tamarit A, Torner N, Godoy P, Rius C, et al. Risk factors associated with severe outcomes in adult hospitalized patients according to influenza type and subtype. *PLoS One*. 2019;**14**(1):e0210353.
19. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Front Public Health*. 2020;**8**:152.
20. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and Mortality among Black Patients and White Patients with Covid-19. *N Engl J Med*. 2020;**382**(26):2534-43.
21. Fauvel C, Weizman O, Trimaille A, Mika D, Pommier T, Pace N, et al. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. *Eur Heart J*. 2020;**41**(32):3058-68.
22. Nimkar A, Naaraayan A, Hasan A, Pant S, Durdevic M, Suarez CN, et al. Incidence and Risk Factors for Acute Kidney Injury and Its Effect on Mortality in Patients Hospitalized From COVID-19. *Mayo Clin Proc Innov Qual Outcomes*. 2020;**4**(6):687-95.
23. Chow EJ, Rolfes MA, O'Halloran A, Alden NB, Anderson EJ, Bennett NM, et al. Respiratory and Nonrespiratory Diagnoses Associated With Influenza in Hospitalized Adults. *JAMA Netw Open*. 2020;**3**(3):e201323.
24. Li H, Liu L, Zhang D, Xu J, Dai H, Tang N, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses.

Lancet. 2020;**395**(10235):1517-20.

25. Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, et al. Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza. *JAMA Neurol*. 2020;**77**(11):1-7.

26. Zaki HA, Zahran A, Abdelrahim M, Elnabawy WA, Kaber Y. A Case of Acute Viral Pericarditis Complicated With Pericardial Effusion Induced by Third Dose of COVID Vaccination. *Cureus*. 2022;**14**(1):e21207.

27. Drake TM, Riad AM, Fairfield CJ, Egan C, Knight SR, Pius R, et al. Characterisation of in-hospital complications associated with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol UK: a prospective, multicentre cohort study. *Lancet*. 2021;**398**(10296):223-37.

28. Lina B, Georges A, Burtseva E, Nunes MC, Andrew MK, McNeil SA, et al. Complicated hospitalization due to influenza: results from the Global Hospital Influenza Network for the 2017-2018 season. *BMC Infect Dis*. 2020;**20**(1):465. doi: 10.1186/s12879-020-05167-4. PubMed PMID: 32615985; PubMed Central PMCID: PMCPMC7330273.

29. Auvinen R, Nohynek H, Syrjänen R, Ollgren J, Kerttula T, Mäntylä J, et al. Comparison of the clinical characteristics and outcomes of hospitalized adult COVID-19 and influenza patients - a prospective observational study. *Infect Dis (Lond)*. 2021;**53**(2):111-21.

30. Ludwig M, Jacob J, Basedow F, Andersohn F, Walker J. Clinical outcomes and characteristics of patients hospitalized for Influenza or COVID-19 in Germany. *Int J Infect Dis*. 2021;**103**:316-22.

31. Sadeghi A, Eslami P, Dooghaie Moghadam A, Pirsalehi A, Shojaee S, Vahidi M, et al. COVID-19 and ICU admission associated predictive factors in Iranian patients. *Caspian J Intern Med*. 2020;**11**(Suppl 1):512-9.

32. Machado-Alba JE, Valladales-Restrepo LF, Machado-Duque ME, Gaviria-Mendoza A, Sánchez-Ramírez N, Usma-Valencia AF, et al. Factors associated with admission to the intensive care unit and mortality in patients with COVID-19, Colombia. *PLoS One*. 2021;**16**(11):e0260169.

33. Zaki H, Elgassim M, Shaban E, Ahmed A, Ameen AW, Abdurabu M, et al. Comparative Clinical Assessment and Risk Stratification of COVID-19 and Influenza Infections in Adults and Children: A Comprehensive Systematic Review and Meta-Analysis. 2024.

34. Vizcarra P, Pérez-Elías MJ, Quereda C, Moreno A, Vivancos MJ, Dronda F, et al. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. *Lancet HIV*. 2020;**7**(8):e554-e64.

35. Beumer MC, Koch RM, van Beuningen D, OudeLashof AM, van de Veerdonk FL, Kolwijck E, et al. Influenza virus and factors that are associated with ICU admission, pulmonary co-infections and ICU mortality. *J Crit Care*. 2019;**50**:59-65.

36. Braun ES, Crawford FW, Desai MM, Meek J, Kirley PD, Miller L, et al. Obesity not associated with severity among hospitalized adults with seasonal influenza virus infection. *Infection*. 2015;**43**(5):569-75.

37. Taylor G, Abdesselam K, Pelude L, Fernandes R, Mitchell R, McGeer A, et al. Epidemiological features of influenza in Canadian adult intensive care unit patients. *Epidemiol Infect*. 2016;**144**(4):741-50.