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Outcomes of non-hospitalized patients with COVID-19 versus seasonal influenza during the fall-winter 2022–2023 period

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Abstract

Background The comparability of outcomes for non-hospitalized COVID-19 outpatients during the Omicron wave to outpatients with influenza remains uncertain. This study aims to compare the outcomes of non-hospitalized outpatients with COVID-19 and seasonal influenza during the fall-winter of 2022–2023.

Methods This is a retrospective cohort study using TriNetX, a collaborative clinical research platform. Non-hospitalized outpatients with COVID-19 and seasonal influenza between 01 October 2022 and 31 January 2023 were selected from TriNetX. Propensity score matching (PSM) was used to compare patients receiving corresponding outpatient antiviral treatments. Hazard ratios (HRs) with 95% confidence intervals (CIs) for the primary outcome—a composite of all-cause emergency department (ED) visits, hospitalizations, or mortality during the 30-day follow-up period—were calculated and compared.

Results After PSM, two well-balanced groups of 9,030 patients each were identified. Non-hospitalized COVID-19 patients had a lower risk of primary composites outcomes including all-cause ED visits, hospitalization, or mortality (5.9% vs. 9.2%, HR, 0.661[95% CI, 0.593–0.737]) compared to the influenza group. In addition, the COVID-19 group demonstrated a reduced risk of all-cause ED visits (4.4% vs. 6.6%, HR 0.683[0.601–0.776]), hospitalization (1.7% vs. 2.9%, HR 0.605[0.495–0.739]) and mortality (0.1% vs. 0.2%, HR 0.176[0.052–0.597]), respectively.

Conclusions This study indicates a lower risk of all-cause ED visits, hospitalization, and mortality in the non-hospitalized COVID-19 patients compared to the seasonal influenza group, supporting the current public health strategy of adjusting COVID-19 management based on approaches used for seasonal influenza.

Keywords COVID-19, Influenza, Ambulatory, Outpatient, Mortality, Outcome

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Introduction

The COVID-19 pandemic has profoundly impacted global health and led to the tragic loss of over 6 million lives since its outbreak in late December 2019 [1, 2]. Despite the adversities, a significant and sustained reduction in mortality has been observed in the recent year [1]. This reduction facilitates the gradual restoration of pre-pandemic norms [1]. Considering the constant mitigation of the pandemic's impact attributed to the changes in SARS-CoV-2 variants, improved immunity levels (either from prior infections or vaccinations), and advancement in care (such as masking, home testing and the development of effective antivirals and treatment strategy), the World Health Organization officially declared an end to the global health emergency of COVID-19 on May 5, 2023 [3]. Following this announcement, several countries have now reclassified COVID-19 on par with seasonal influenza [4–6]. However, a recent study using data from the United States Department of Veterans Affairs revealed a higher risk of death (hazard ratio, 1.61 [95% confidence interval, 1.29–2.02]) for hospitalized patients with COVID-19 compared to those with seasonal influenza [7]. Considering that a significant proportion of COVID-19 cases are managed in outpatient settings, understanding the outcomes of non-hospitalized patients becomes crucial in informing clinical management and public health strategies [8]. Therefore, to address this gap in knowledge, this study aims to compare the outcomes of non-hospitalized patients with COVID-19 and seasonal influenza during the fall-winter of 2022–2023.

Methods

Data source

This retrospective cohort study made use of data from TriNetX, a collaborative clinical research platform known for its real-time electronic medical data collected from over 250 million patients across the Americas, Europe, Middle East, and Africa (EMEA), and Asia-Pacific region (APAC), sourced from more than 120 health-care organizations (HCOs) [9, 10]. TriNetX is compliant with the Health Insurance Portability and Accountability Act (HIPAA) and is certified to the International Organization for Standardization (ISO) 27001:2013 standard. It also maintains an Information Security Management System (ISMS) to ensure the protection of healthcare data and to meet the requirements of the HIPAA Security Rule [11]. As a participating HCO, our institution has authorized access to the patient's deidentified electronic medical records, including their diagnoses, procedures, medications, laboratory data, and genomic information. Moreover, the platform offers built-in analytics tools, empowering researchers to select and match cohorts, analyze event incidence and prevalence, and compare characteristics and outcomes between COVID-19 and influenza cohorts using patient-level data and coding (e.g., International Classification of Diseases, Tenth Revision [ICD-10], Systematized Nomenclature of Medicine [SNOMED], Current Procedural Terminology [CPT] and RxNorm Codes). The requirement for written informed consent was waived owing to the utilization of deidentified aggregate data. The study was approved by the Institutional Review Board of Chi Mei Medical Center (approval number 11202-002).

Patient selection

The study population was divided into two groups based on their status of diagnosis of either COVID-19 or influenza, with participants who had both infections removed. To ensure comparable disease severity, only participants who received outpatient oral antiviral agents within five days after diagnosis were included, namely outpatient nirmatrelvir-ritonavir (NMV-r) or molnupiravir for the COVID-19 group and oseltamivir for the influenza group (Supplemental Table 1) [12–15]. To ensure that our analysis focused on the progression of illness in ambulatory settings rather than including patients diagnosed during hospitalization, we restricted our study to adult patients (aged 18 or older) treated in ambulatory settings, thereby focusing on those not requiring hospital-level care at baseline. Accordingly, patients who were hospitalized within two days before or up to five days after diagnosis were excluded. Moreover, to minimize confounding from the high mortality and hospitalization rates associated with malignant neoplasms, patients with a diagnosis of malignant neoplasm within the past year were excluded. Finally, given that severe hepatic impairment is a contraindication for prescribing NMV-r, we also excluded such participants from both groups to mitigate the baseline characteristic differences.

Covariates

Two groups were matched by demographic characteristics (i.e., age, sex, and ethnicity), lifestyles (i.e., obesity, tobacco use, alcohol abuse, and socioeconomic status), and comorbid conditions using propensity score matching. The corresponding coding used for the listed covariates was listed in Supplemental Table 2 [16, 17].

Outcomes

The primary outcome was a composite of all-cause emergency department (ED) visits, hospitalizations, or death during the 30-day follow-up period from the first date of treatment. Secondary outcomes included all-cause ED visits, hospitalizations, and mortality separately during the follow-up period. All outcomes were identified using codes specified in Supplemental Table 3 [12, 13].

Statistical analysis

The baseline characteristics of the study population were reported as frequency and proportion for categorical variables and as mean ± standard deviation for continuous variables. Propensity score matching was performed using the built-in function of the TriNetX platform. Specifically, the platform provided input matrices for user-selected covariates, which were analyzed through logistic regression for each individual patient based on propensity matching scores. Patients were matched in a 1:1 ratio using the greedy nearest-neighbor algorithm with a caliper width of 0.1 pooled standard deviations. The platform randomized the order of rows to eliminate bias resulting from the nearest-neighbor algorithm. The balance between the two cohorts was evaluated using the standardized mean difference, with a difference greater than 0.1 considered indicative of a significant residual imbalance [18].

Kaplan-Meier survival analysis was applied for the cumulative event-free probability and the differences between groups were analyzed using the log-rank test. We used Cox proportional hazards models to calculate hazard ratios after 1:1 propensity score matching, during which potential confounders—including demographic characteristics, lifestyle factors, and comorbid conditions—were balanced between groups. The hazard ratios, with corresponding confidence intervals, were derived to examine the relative risk of the outcome of interest in the COVID-19 population compared to the influenza group. For prespecified subgroups, we further refined the subgroup populations beyond the original inclusion and exclusion criteria, performed separate 1:1 propensity score matching, and subsequently examined the outcomes within each subgroup: (1) age (18–64 years vs. ≥ 65 years); (2) sex (female vs. male); (3) COVID-19 vaccination status (unvaccinated vs. 1 or 2 doses of vaccine vs. boosted vaccine); (4) influenza vaccination status one year prior to the index date (unvaccinated vs. vaccinated) (5) SARS-CoV-2 infection status (primary infection vs. reinfection); and (6) the choice of anti-COVID-19 agents used (NMV-r vs. molnupiravir). The detailed definitions and coding used in each subgroup were listed in Supplemental Table 4. Stratified analyses, predicated on these subgroups, were executed using Stata 17.0, with preliminary data procured from TriNetX's integrated statistical module. Interaction *p*-values for each subgroup were ascertained using the Wald test.

Results

Patients' characteristics

While TriNetX aggregated real-time electronic medical data from over 250 million patients across 19 countries, our study specifically utilized the Global Collaborative Network, which encompassed records from 14 distinct countries. From a cohort of more than 135 million records between 01 October 2022 and 31 January 2023, a total of 9,383,707 adult participants were recruited. These participants visited the data-contributing HCOs at least twice during the specified time period. Among them, 298,405 and 384,415 patients were diagnosed with COVID-19 and influenza, respectively. Of these, 31,510 (10.6%) and 7,465 (19.4%) patients who had an initial hospitalization between 2 days before and up to 5 days after diagnosis were excluded. Overall, 27,630 patients with COVID-19 and 10,842 patients with influenza were identified by employing our predefined inclusion and exclusion criteria (supplemental Fig. 1). Compared with the influenza group, the COVID-19 group had a higher mean age (58.9 ± 16.2 years versus 45.4 ± 19.5 years, standardized difference [std. diff.]: 0.754). In addition, the COVID-19 group consisted of statistically significant predominantly white and non-Hispanic or Latino (std. diff. ≥ 0.1). Moreover, the COVID-19 group had a higher prevalence of nicotine dependence and more comorbidities (std. diff. ≥ 0.1), including hypertension, dyslipidemia, and heart diseases than the influenza group. After propensity score matching by age at index, sex, race, ethnicity, lifestyle, and comorbid medical conditions, 9,030 matched cases were retained in each group (Table 1). Using propensity score matching methods, two groups of 9,030 patients each were identified and demonstrated good balance (Table 1 and Supplemental Fig. 1). A standardized difference of less than 0.1 was achieved after matching, indicating no significant residual imbalance.

Primary outcome

Non-hospitalized COVID-19 patients had a lower risk of primary composites outcomes including all-cause ED visits, hospitalization, or mortality (5.9% vs. 9.2%, HR, 0.661; 95% CI, 0.593–0.737) compared to the influenza group (Table 2). During the 30-day follow-up, the COVID-19 group had a significantly lower risk of all-cause ED visits, hospitalization, or mortality compared to the influenza group (log-rank test, $p < 0.001$, Fig. 1).

Secondary outcomes

When analyzing individual outcomes within the primary composite outcomes, the COVID-19 group demonstrated a reduced risk of all-cause ED visits (4.4% vs. 6.6%, HR, 0.683; 95% CI, 0.601–0.776), hospitalization (1.7% vs. 2.9%, HR, 0.605; 95% CI, 0.495–0.739) and mortality (0.1% vs. 0.2%, HR, 0.176; 95% CI, 0.052–0.597), respectively (Table 2). Using Kaplan-Meier survival curve analysis, the COVID-19 group had a significantly higher event-free probability of all-cause ED visits, hospitalization, or mortality compared to the influenza group during the 30-day follow-up (all log-rank $p < 0.001$, Fig. 2).

Table 1 Baseline characteristics in COVID-19 and seasonal influenza group before and after propensity score matching

	Before matching			After matching		
	COVID-19 *n* = 27,630	**Influenza *n* = 10,842**	**Std. diff.**	**COVID-19 *n* = 9,030**	**Influenza *n* = 9,030**	**Std. diff.**
Age (Mean ± SD)						
Age at Index (year)	58.9 ± 16.2	45.4 ± 19.5	0.754	48.9 ± 17.4	49.1 ± 18.9	0.006
Sex (%)						
Female	17,047 (61.7)	7,067 (65.2)	0.072	5,794 (64.2)	5,813 (64.4)	0.004
Male	10,579 (38.3)	3,774 (34.8)	0.072	3,233 (35.8)	3,216 (35.6)	0.004
Race (%)						
White	21,641 (78.3)	7,064 (65.2)	0.296	6,370 (70.5)	6,319 (70.0)	0.012
Black or African American	2,717 (9.8)	1,906 (17.6)	0.227	1,277 (14.1)	1,303 (14.4)	0.008
Asian	846 (3.1)	245 (2.3)	0.050	224 (2.5)	236 (2.6)	0.008
American Indian or Alaska Native	78 (0.3)	47 (0.4)	0.025	32 (0.4)	37 (0.4)	0.009
Native Hawaiian or Other Pacific Islander	28 (0.1)	10 (0.1)	0.003	10 (0.1)	10 (0.1)	< 0.001
Unknown Race	2,320 (8.4)	1,571 (14.5)	0.192	1,120 (12.4)	1,126 (12.5)	0.002
Ethnicity (%)						
Not Hispanic or Latino	22,909 (82.9)	7,936 (73.2)	0.236	6,844 (75.8)	6,871 (76.1)	0.007
Hispanic or Latino	2,022 (7.3)	1,062 (9.8)	0.089	892 (9.9)	878 (9.7)	0.005
Unknown Ethnicity	2,699 (9.8)	1,844 (17)	0.214	1,294 (14.3)	1,281 (14.2)	0.004
Lifestyle (%)						
Overweight and obesity	6,703 (24.3)	2,575 (23.8)	0.012	2,182 (24.2)	2,260 (25)	0.020
Nicotine dependence	2,274 (8.2)	1,512 (13.9)	0.183	1,099 (12.2)	1,132 (12.5)	0.011
Alcohol related disorders	560 (2.0)	297 (2.7)	0.047	229 (2.5)	230 (2.5)	0.001
Low socioeconomic status	67 (0.2)	29 (0.3)	0.005	24 (0.3)	23 (0.3)	0.002
Comorbid conditions (%)						
Primary hypertension	13,861 (50.2)	3,750 (34.6)	0.319	3,396 (37.6)	3,469 (38.4)	0.017
Dyslipidemia	14,729 (53.3)	3,352 (30.9)	0.466	3,177 (35.2)	3,214 (35.6)	0.009
Heart disease	7,002 (25.3)	2,221 (20.5)	0.116	1,968 (21.8)	1,972 (21.8)	0.001
Ischemic heart diseases	3,627 (13.1)	1,097 (10.1)	0.094	979 (10.8)	1,002 (11.1)	0.008
Heart failure	1,407 (5.1)	628 (5.8)	0.031	506 (5.6)	525 (5.8)	0.009
Pulmonary hypertension	765 (2.8)	323 (3.0)	0.013	236 (2.6)	259 (2.9)	0.016
Chronic lung diseases	6,350 (23.0)	2,896 (26.6)	0.083	2,348 (25.8)	2,373 (26.1)	0.006
Type 2 diabetes mellitus	5,359 (19.4)	1,742 (16.1)	0.087	1,520 (16.8)	1,562 (17.3)	0.012
With poor control (HbA1c ≥ 9%)	1,149 (4.2)	467 (4.3)	0.007	392 (4.3)	401 (4.4)	0.005
Chronic liver diseases	2,285 (8.3)	773 (7.1)	0.043	660 (7.3)	704 (7.8)	0.018
Chronic kidney disease	2,219 (8.0)	719 (6.6)	0.055	613 (6.8)	612 (6.7)	0.001
Stage 3	1,577 (5.7)	443 (4.1)	0.075	406 (4.5)	394 (4.4)	0.006
Stage 4	230 (0.8)	103 (1.0)	0.013	84 (0.9)	86 (1.0)	0.002
Stage 5	70 (0.3)	55 (0.5)	0.041	38 (0.4)	32 (0.4)	0.011
End stage renal disease	154 (0.6)	133 (1.2)	0.071	91 (1.0)	82 (0.9)	0.010
Cerebrovascular diseases	1,902 (6.9)	582 (5.4)	0.063	534 (5.9)	525 (5.8)	< 0.001

A standardized difference (Std. diff.) of less than 0.1 was considered evidence of good balance

Table 2 The hazard ratio and incidence for comparing matched COVID-19 and influenza groups for the primary composite outcome and its constituents - all-cause emergency department visits, hospitalization, or mortality

Outcomes	**No. (%) of patients with outcome**		**HR (95% CI)**	***P*-value**
	COVID-19 group	**Influenza group**		
Primary outcome				
All-cause ER visit, hospitalization, or mortality	532 (5.9)	829 (9.2)	0.661 (0.593, 0.737)	< 0.0001
Secondary outcome				
All-cause ER visit	393 (4.4)	598 (6.6)	0.683 (0.601, 0.776)	< 0.0001
All-cause hospitalization	152 (1.7)	258 (2.9)	0.605 (0.495, 0.739)	< 0.0001
All-cause mortality	10 (0.1)	18 (0.2)	0.176 (0.052, 0.597)	0.0016

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval

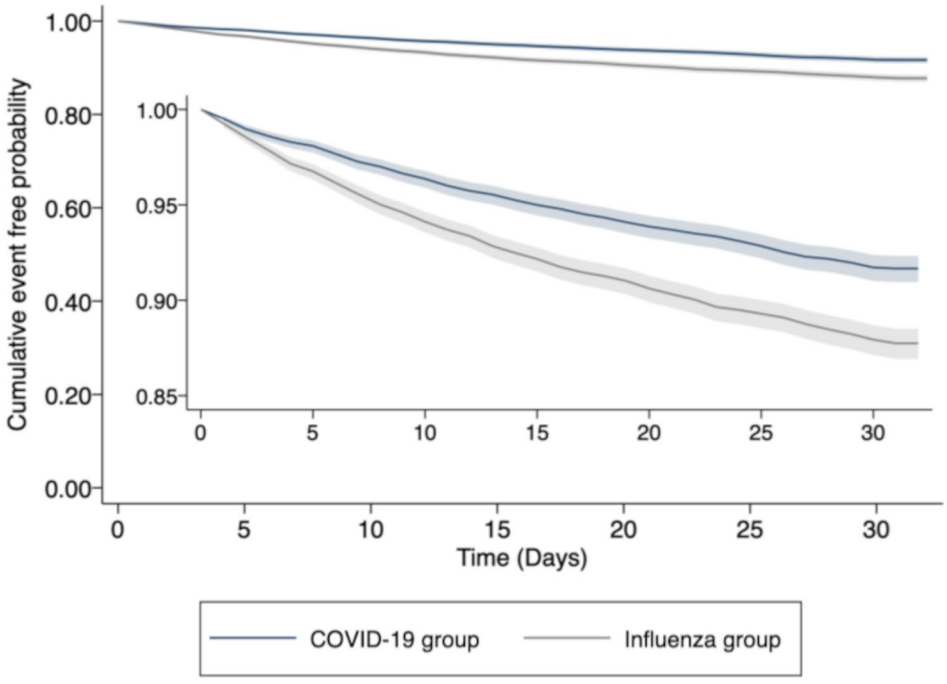

Fig. 1 Cumulative event-free probability plot of the composite outcome of all-cause emergency department visits, hospitalization, or mortality

Stratified analysis

This lower risk of all-cause ED visits, hospitalization, or mortality compared to the influenza group was consistently observed in the stratified analysis according to age (18–64 years: HR, 0.68; 95% CI, 0.59–0.77; ≥ 65 years: HR, 0.62; 95% CI, 0.51–0.77), sex (Female: HR, 0.64; 95% CI, 0.56–0.73; Male: HR, 0.60; 95% CI, 0.50–0.73), COVID-19 vaccine status (unvaccinated: HR, 0.68; 95% CI, 0.61–0.76; 1 or 2 doses of vaccine: HR, 0.67; 95% CI, 0.53–0.84; boosted vaccine: HR, 0.52; 95% CI, 0.42–0.63), influenza vaccine status (absence: HR, 0.82; 95% CI, 0.74–0.90), SARS-CoV-2 infection status (primary infection: HR, 0.66; 95% CI, 0.59–0.74; reinfection: HR, 0.60; 95% CI, 0.51–0.70), and antiviral agents (NMV-r: HR, 0.76; 95% CI, 0.68–0.84; molnupiravir: HR, 0.53; 95% CI, 0.45–0.62) (supplemental Tables 5 and Fig. 3). Interaction *p*-values were determined using the Wald test, with younger age, female sex, unvaccinated COVID-19 status, lack of influenza vaccination, primary COVID-19 infection, and outpatient NMV-r treatment serving as the respective references for each subgroup. Statistically significant interaction *p*-values were not observed in the majority of subgroups, with the exceptions being those who received a COVID-19 booster vaccination. Within the vaccination subgroups, individuals who received the COVID-19 booster vaccination exhibited a statistically superior HR compared to the unvaccinated individuals (interaction *p*-value: 0.0121).

Regarding the secondary outcome, we found that COVID-19 group was associated with a significantly lower risk of all-cause ED visit than influenza group in the all stratified analysis according to age, sex, COVID-19 vaccine status, SARS-CoV-2 infection status, and antiviral agents (supplemental Table 6). Similarly, lower risk of all-cause hospitalization or mortality in the COVID-19 group compared to influenza group were found in all stratified analysis; however, the differences was non-statistically significant in the patients receiving NMV-r for all-cause hospitalization, and adults aged 18–64 years and male for all-cause mortality (supplemental Table 6).

Discussion

This study found that the non-hospitalized COVID-19 patients treated with NMV-r or molnupiravir had a reduced risk of the composite outcome of all-cause ED visits, hospitalization, or death compared to influenza patients treated with oseltamivir during 30-day follow-up. This trend remained consistent across individual secondary individual outcomes and stratified analysis according to age, sex, COVID-19 vaccine status, SARS-CoV-2 infection status, and antiviral agents. These findings lend support to the current strategy of considering COVID-19 on par with seasonal influenza [4–6], thereby advocating for comparable management for SARS-CoV-2 infection in outpatient settings.

Our findings presented an alternative perspective compared to a recent study conducted by Xie et al. [7] Their study primarily focused on hospitalized patients, with approximately 80% of patients being older than 65 years, and more than 95% being male [7]. In contrast,

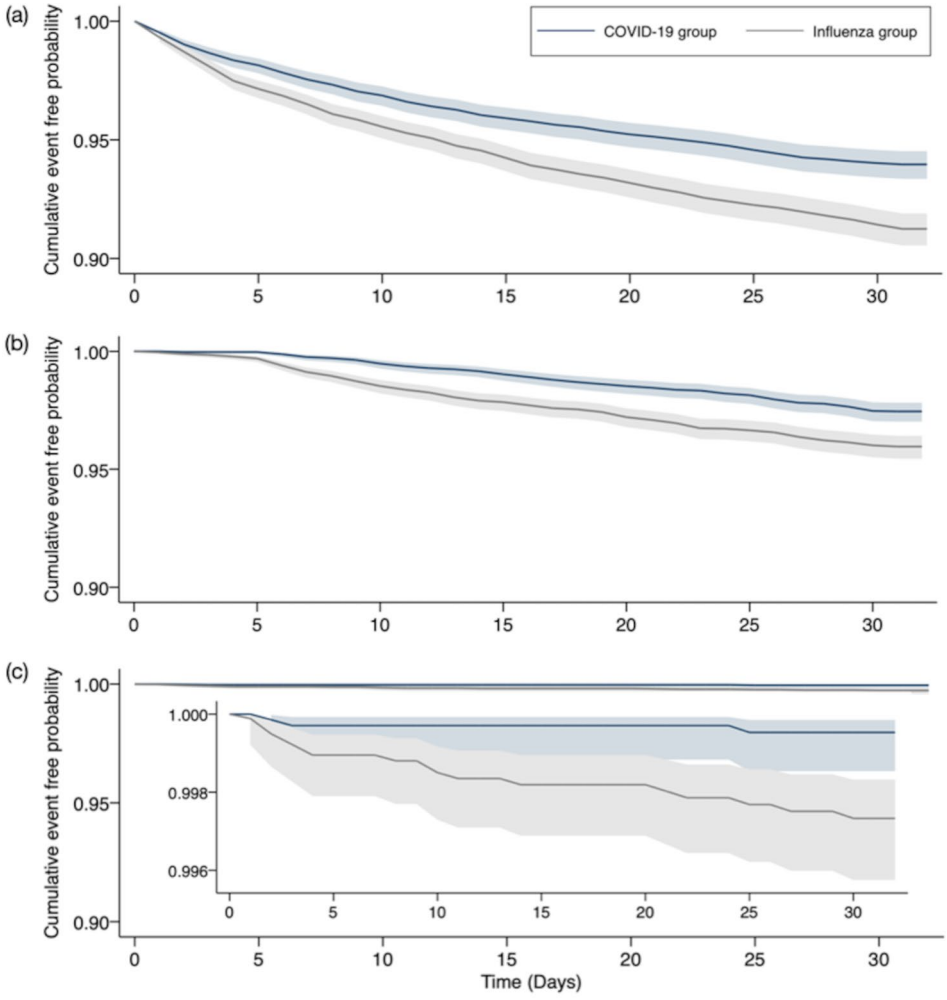

Fig. 2 Cumulative event-free probability plots of all-cause (**a**) emergency department visits, (**b**) hospitalization, and (**c**) mortality

our present study included a younger and well-balanced cohort with a mean age of less than 50 years and 60% of female participants. Additionally, our study enrolled a larger cohort size with 18,060 patients in total and 9,030 patients in each group after PSM whereas Xie et al.'s study [7] recruited 11,399 patients with only 2,403 patients in their influenza group. Furthermore, Xie et al. [7] reported that over 70% of COVID-19 patients did not receive antiviral agents such as NMV-r, molnupiravir, or remdesivir, while more than 88% of influenza patients received oseltamivir. Conversely, all patients included in this study exclusively received outpatient oral antiviral agents for COVID-19 or influenza, which could help balance the severity of these two viral infections. These variations in patient characteristics and antiviral usage rates may account for the divergent findings observed between Xie et al.'s study [7] and the present work. In relation to interaction *p*-values, statistical significance was exclusively noted when comparing individuals who remained unvaccinated for COVID-19 with those who had received a booster vaccination. This underscores the potential of the COVID-19 booster vaccination in reducing the risk of composite outcomes, aligning with the prevailing understanding of the vaccine's protective efficacy.

Our study has several strengths to be emphasized. Firstly, we were able to leverage a large sample size using the TriNetX network, which enhances the statistical power and generalizability of our findings. Second, our study focused on the fall-winter period of 2022–2023, allowing us to capture the most recent trend and pattern in COVID-19 and seasonal influenza. One advantage of our study is the consideration of the engagement of comparable treatment conditions, where both the influenza group and the COVID-19 group received outpatient antiviral agents. In line with the Infectious Diseases Society of America (IDSA) guideline [19] for treating COVID-19, NMV-r and molnupiravir are recommended for patients with mild to moderate symptoms who are at high risk of progressing to severe disease, without the need for supplemental oxygen, and are under ambulatory

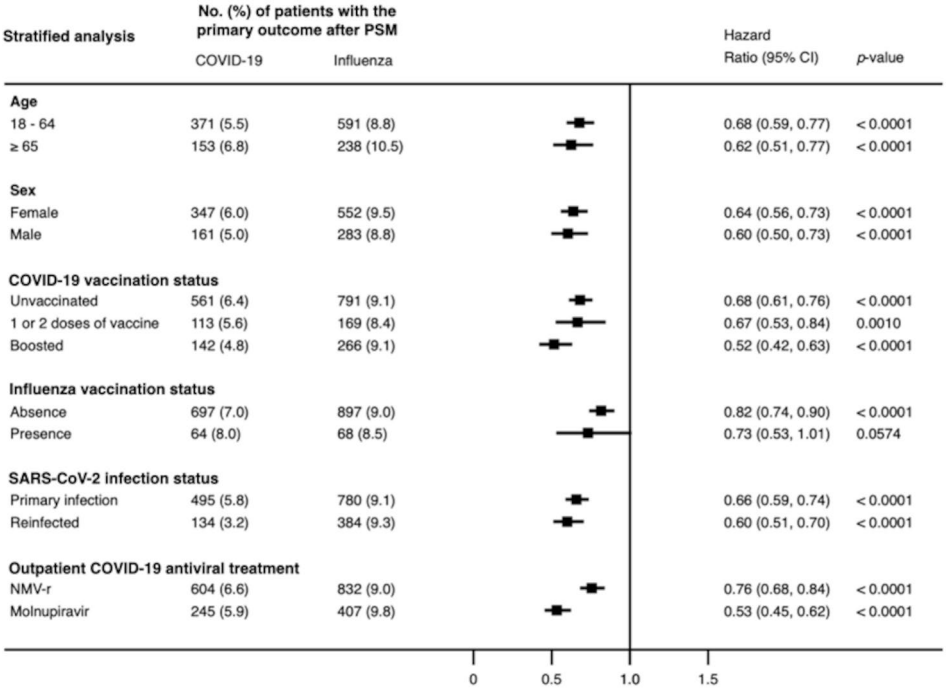

Fig. 3 Hazard ratio, and percentage of the composite outcome of all-cause emergency department visits, hospitalization, or mortality in the subgroup of COVID-19 compared with seasonal influenza

Abbreviations: PSM, propensity score matching; HR, hazard ratio; 95% CI, 95% confidence interval; NMV-r, nirmatrelvir-ritonavir

Stratified analysis was conducted in overall cohort by age (18–65, ≥ 65), sex (female, male), COVID-19 vaccination status (unvaccinated, 1–2 doses of vaccine, and boosted), SARS-CoV-2 infection status (with primary SARS-CoV-2 infection and infection), influenza vaccination status (absence vs. presence) and outpatient COVID-19 antiviral treatment (NMV-r and molnupiravir), compared with overall seasonal influenza.)

care. Remdesivir, which is administered intravenously, is considered less comparable to oseltamivir for influenza, given its distinct intravenous administration method and initiation guidelines, making NMV-r and molnupiravir more analogous in comparison. Additionally, with the prevailing trend of increasing resistance to therapeutic neutralizing monoclonal antibodies, it was no longer recommended for COVID-19. Consequently, participants using off-label neutralizing monoclonal antibodies were not included in the present study. For influenza, the IDSA guideline [20] recommends initiating antivirals promptly after symptom onset in ambulatory patients with uncomplicated cases. By focusing on patients who used oral antiviral medications in outpatient settings for both conditions, we aimed to minimize the disparity between the groups. Another notable strength of our study lies in its specific inclusion criteria, which focused on outpatient settings, providing more meaningful public health strategy insights compared to studies limited to inpatient populations [21, 22]. This distinction is particularly crucial because the majority of SARS-CoV-2 infections occur in outpatient settings. By focusing on outpatients and the study period of fall-winter 2022–2023, we were able to gain valuable insights into the real-world impact and management of COVID-19 in the community. Lastly, propensity score matching methods were employed to achieve a balanced cohort for comparison and mitigate the influence of confounding factors.

However, our findings should be interpreted with caution owing to the following limitations. First, the nature of TriNetX as an electronic medical record database introduces the possibility of coding and uncoding errors, which may impact the accuracy of the data analyzed. For example, home test results were not captured, potentially leading to an underestimation of positive cases. To minimize these issues, we identified both COVID-19 and influenza groups by employing the corresponding antiviral agents in tandem with the diagnostic ICD-10 codes and included only patients who sought ambulatory care and received oral antivirals. This approach aimed to ensure comparability by selecting patients with similar baseline characteristics and disease severity. Second, although the outcomes were assessed using objective measures such as all-cause ED visits, hospitalization, and death instead of relying solely on ICD-10 codes, residual confounding may persist. A limitation of our study is the unavailability of raw data, which prevents us from investigating the specific causes of ED visits, hospitalizations, and mortality. While a range of potential confounders was balanced through propensity score matching, further adjustment of hazard ratios to mitigate residual confounding was not feasible due to the lack of access to

the raw data. Third, our study did not account for other anti-COVID-19 treatments (e.g., remdesivir, systemic corticosteroids, and interleukin-6 blockade) [19, 23–25] nor other anti-influenza treatments (e.g., zanamivir, peramivir, and laninamivir) [20, 26, 27]. According to IDSA guidelines, anti-COVID-19 agents other than NMV-r and molnupiravir were not recommended for outpatients with mild-to-moderate disease and oseltamivir remained the most commonly used anti-influenza agent. Additionally, our study primarily focused on comparing the short-term outcomes between patients with COVID-19 and seasonal influenza. Given that several cohort studies have demonstrated SARS-CoV-2 infection is associated with a higher risk of post-acute sequelae - such as dyspnea, fatigue, palpitations, loss of taste/smell, neurocognitive symptoms, and thromboembolism - compared with influenza [28, 29], our study is limited in its scope for not considering these post-acute sequelae. Therefore, further study is warranted to address the above aspects. Furthermore, our study focused exclusively on comparing COVID-19 and influenza, without considering other epidemic upper respiratory tract infections such as respiratory syncytial virus (RSV) [30]. However, given that targeted antiviral treatments are currently available only for COVID-19 and influenza, incorporating a third epidemic upper respiratory tract infection into the analysis could introduce greater discrepancies in baseline cohort characteristics. Lastly, among the various networks available in TriNetX, we opted for the Global Collaborative Network, as it encompasses the largest number of participants from the most diverse range of countries. However, the country representation is predominately from the Global North, leading to a limited generalizability of the findings due to the skewed ethnicity and race distribution. As per official data from TriNetX, they source medical data from trusted HCOs, predominately academic and community-based HCOs, but details on countries or types of HCOs included in this study could not be provided due to the recent privacy policy implemented by TriNetX. In addition, the built-in analytic tools did not permit PSM by country or region; instead, ethnicity and race were matched. Therefore, we further validated our findings using the US Collaborative Network, which solely comprises medical records from the United States. The outcomes of this network echoed those of the Global Collaborative Network. Specifically, the COVID-19 group exhibited a reduced risk of primary composite outcomes, including all-cause ED visits, hospitalizations, or mortality (7.1% vs. 9.3%, HR, 0.801 [95% CI, 0.728–0.881]), in comparison to the influenza group. Given the consistent trends observed between the US data, which adheres to more standardized criteria for hospitalization and healthcare-seeking behaviours, and the Global Collaborative Network, it reinforces the credibility and applicability of the global results.

Conclusion

Our study indicated a lower risk of all-cause ED visits, hospitalization, and mortality in the COVID-19 group compared to the seasonal influenza group. These findings carry important implications for policymaking and align with the current public health strategy of easing COVID-19 restrictions by adopting approaches used for seasonal influenza. It is crucial to consider these insights when shaping public health policies. However, it is essential to acknowledge and address the limitations of our study when interpreting and applying these findings.

Abbreviations

COVID-19	Coronavirus disease 2019
ED	Emergency department
HCO	Health-care organization
HR	Hazard ratio
ICD-10	International Classification of Diseases, Tenth Revision
NMV-r	Nirmatrelvir-ritonavir
PSM	Propensity score matching

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10833-6.

Supplementary Material 1

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None.

Author contributions

WHH and CCL conceptualized the project. The study design was collaboratively developed by all contributing authors. Data collection was undertaken by BWS, YWT, JYW, THL, PYH, and MHC while data analysis and interpretation were a collective effort of all authors. WHH and CCL drafted the manuscript and all authors contributed to the critical revision of the manuscript, ensuring its intellectual rigor. The final manuscript received unanimous approval from all authors, who also jointly accepted the responsibility for the decision to submit it for publication.

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Data availability

Data available on requet from the authors.

Declarations

Ethics approval and consent to participate

The requirement for written informed consent was waived owing to the utilization of deidentified aggregate data. The study adhered to the Declaration of Helsinki and was approved by the Institutional Review Board of Chi Mei Medical Center (approval number 11202-002).

Consent for publication

Not required.

Competing interests

All authors declared that there was no conflict of interest.

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