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SHORT REPORT

Age-specific Mortality Associated with COVID-19 and Seasonal Influenza in Japan: Using Multiple Population-based Databases

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KEY WORDS

mortality, influenza, SARS-CoV-2, COVID-19

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BACKGROUND

There is considerable interest in comparing the clinical courses of COVID-19 and seasonal influenza. Since the onset of the COVID-19 pandemic, Japan faced 9,431,868 cases and 31,340 deaths as of July 5, 2022 [1]. Comparatively, over 12 million were treated for influenza annually, with a marked reduction in the number of these cases observed during the COVID-19 pandemic [2]. Because the risk of severe clinical course after COVID-19 infections is substantially lower for Omicron variants than for Delta variants, the emergence of Omicron variants raises a controversy about lessening the strict restrictions for COVID-19 [3, 4], and then increases the interest in comparing the clinical courses of COVID-19 and seasonal influenza. To date, only a few studies have investigated the societal burden due to these diseases [5, 6]. Thus, we aimed to compare the differences in the absolute risk of mortality between COVID-19 and seasonal influenza. These estimates are needed to assess the burden of the two diseases on society as a whole in terms of mortality. We focused on COVID-19 related deaths during the Omicron wave because of the ongoing clinical relevance.

METHODS

This was a population-based study using multiple secondary databases, including COVID-19-related deaths, influenza-related deaths, and population in Japan. We identified the COVID-19-related deaths from a publicly available website (data acquired on July 7, 2022) [1]. All patients who died "due to" or "with" COVID-19 are reported by the municipalities. All patients with COVID-19 who died during hospitalization or health

observation are reported irrespective of the time elapsed from the COVID-19 diagnosis, although most cases died within 28 days from diagnosis. The cumulative number of deaths by sex and 10-year age groups is recorded in the database. We identified COVID-19-related deaths reported until January 4, 2022 and those reported until July 5, 2022, and calculated their differences to estimate the number of COVID-related deaths during the recent 26-week period (i.e., the wave of infection due to Omicron variants). The outcome assessment window was selected based on the period of predominance of Omicron variants [7]. Data on sex and/or age were missing for 1,682 patients. Therefore, missing data on sex and/age were imputed by the following formula: $n \times p_{ik}$, where n is the total number of missing data on sex and/or age and p_{ik} is the vector of the proportion of patients who are sex i and age group k relative to the total number of patients without missing data on sex and age.

We calculated the influenza-related deaths using a nationwide claims database that covers almost all claims in Japan [8]. The institutional review board of Nara Medical University reviewed and approved the study protocol for the use of the claims database (approval number: 2831). Patients with influenza were identified by a definitive diagnosis of influenza (ICD-10 code: J09–J11) and/or a prescription of anti-influenza drugs (baloxavir marboxil/laninamivir/oseltamivir/peramivir/zanamivir) between September 1, 2017 and August 31, 2019 (i.e., 2017/18 season and 2018/2019 season). The index date was defined as the initial date of diagnosis and/or prescription. To define the initial case, a patient should not have had a diagnosis of influenza nor a prescription of anti-influenza drugs 90 days prior to the index date. The same patient may have multiple episodes of influenza. All patients with influenza who died within 28 days after the index date were identified by an algorithm to identify deaths based on information about diagnosis and procedural records [9]. The annual number of influenza-related deaths by age group was calculated by dividing the cumulative number of influenza-related deaths by two years. All diagnosis and drug codes used are available in **Supplementary Table 1**.

We identified population size by age group using the Population Estimates in 2020 for COVID-19-related deaths and in 2017 to 2018 for influenza-related deaths [2]. The average population for influenza-related deaths were calculated by dividing the summed population by two years.

The annual number of COVID-19-related and influenza-related deaths and their rate differences with 95% confidence interval (CI) were calculated by age group. To obtain 95% CIs, the approximate standard error of the rate difference was used [10]. Rates are shown as number of deaths per 10 million people per 365 days.

As a sensitivity analysis, we shortened the outcome assessment window to include COVID-related death between March 30, 2022 to July 5, 2022. This outcome assessment window is selected based on the period after an achievement of a high third dose vaccination coverage among elderly (i.e., over 80% of inhabitants aged 65 years or over) since March 28, 2022 [11].

The statistical analysis was performed in R, version 4.0.5 (R Project for Statistical Computing).

RESULTS

During the recent 26-week period, a total of 13,756 COVID-19-related deaths were identified. The annual mortality rate for COVID-19 increased with age, widely ranging from 11 to 17,192 per 10 million people for those aged 10–19 years and ≥80 years, respectively. During the 2017/18 and 2018/19 seasons, a total of 22,876 influenza-related deaths were identified. The annual mortality rate for influenza showed a bimodal distribution, with peaks in those aged 0–9 years and those aged ≥80 years. The annual number of deaths for those aged 0–9 years was 30 fewer per 10 million people in COVID-19 than influenza. The rate differences among those aged 10–29 years were unclear. The annual number of deaths among those aged ≥30 years was significantly higher in COVID-19 than influenza. The rate differences were much higher among those aged ≥70 years than those aged 30–69 years (range: 1,951–9,661 vs. 20–439 per 10 million people, respectively). Data from the period of an achievement of a high third dose vaccination coverage among elderly population produced similar results, but showed smaller differences between COVID-19 and influenza.

DISCUSSION

We observed that the differences in mortality rate between COVID-19 and influenza varied strongly by age. The following limitations of our study should be acknowledged: the time frame for influenza was not limited to the peak-season (usually, December to March) but included the whole year; the number of influenza-related deaths was underestimated due to the low sensitivity of the claims database for out-of-hospital deaths (i.e., 47%) [12], although the algorithms to identify

Table 1 **Annual number of deaths associated with COVID-19 during the recent 26-week period and influenza.**

Age, years	COVID-19 in January 5 to July 5, 2022 (Recent 26-week period)			Influenza in 2017/18 and 2018/19 seasons			Rate difference per 10 million population (95% CI)
	Number of population, in thousand	Number of deaths	Annual number of deaths per 10 million population	Average population, thousand	Average number of deaths	Annual number of deaths per 10 million population	
0–9	9,658	8	17	10,092	47	47	−30 (−48, −12)
10–19	11,083	6	11	11,363	18	15	−5 (−16, 7)
20–29	12,706	15	24	12,536	23	18	6 (−8, 20)
30–39	14,213	37	52	14,814	48	32	20 (1, 39)
40–49	18,342	124	135	18,830	140	74	61 (34, 88)
50–59	16,680	312	374	15,880	256	161	213 (167, 259)
60–69	15,679	701	894	17,343	789	455	439 (366, 513)
70–79	16,254	2,635	3,242	14,827	1,914	1,291	1951 (1815, 2088)
≥80	11,538	9,918	17,192	10,895	8,205	7,531	9661 (9285, 10036)

Abbreviation: CI, confidence interval.

Table 2 **Annual number of deaths associated with COVID-19 during the recent 14-week period and influenza.**

Age, years	COVID-19 in March 30 to July 5, 2022 (Recent 14-week period)			Influenza in 2017/18 and 2018/19 seasons			Rate difference per 10 million population (95% CI)
	Number of population, in thousand	Number of deaths[a]	Annual number of deaths per 10 million population	Average population, thousand	Average number of deaths	Annual number of deaths per 10 million population	
0–9	9,658	7	27	10,092	47	47	−20 (−44, 4)
10–19	11,083	0	0	11,363	18	15	−15 (−23, −8)
20–29	12,706	10	29	12,536	23	18	11 (−8, 31)
30–39	14,213	14	37	14,814	48	32	5 (−17, 26)
40–49	18,342	59	119	18,830	140	74	45 (13, 78)
50–59	16,680	140	312	15,880	256	161	151 (95, 206)
60–69	15,679	312	739	17,343	789	455	284 (196, 372)
70–79	16,254	974	2,226	14,827	1,914	1,291	935 (784, 1086)
≥80	11,538	3,394	10,926	10,895	8,205	7,531	3395 (2992, 3797)

Abbreviation: CI, confidence interval.
[a] A total of COVID-19-related deaths of 4,908 is not equal to a total of covid-related deaths by age of 4,910, because of rounding error related to missing data.

deaths in our study may have a higher sensitivity than those used in the previous study [9, 12]; the definition of death was not uniform due to the different data sources, thus limiting their comparability; the accuracy of using claims data to identify patients with influenza is unknown, although diagnoses for influenza may not have been recorded for other purposes.

The first two limitations may overestimate the annual number of COVID-19-related deaths compare to influenza-related deaths. Even if the true mortality rate

had been the same between COVID-19 and influenza, the study design would have shown a higher mortality rate for COVID-19 than for influenza. However, our results showed that there were small differences in the mortality rate between COVID-19 and influenza among those aged 0–69 years. Therefore, it is unlikely that the annual number of COVID-19-related deaths among those aged 0–69 years was meaningfully higher than that of influenza-related deaths. Our results suggest that elderly population should be prioritized for preventive measures.

CONFLICTS OF INTEREST

Drs Noda and Imamura received a grant from the Ministry of Health, Labour and Welfare to conduct this study. Dr Noda is also a delegate of Japanese Society of Public Health. Dr Okumura is a president of Initiative for Clinical Epidemiological Research that make contracts to support several epidemiological studies with Nara Medical University. No other disclosures were reported.

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AUTHOR CONTRIBUTIONS

Dr Noda had full access to all of the influenza-related data and Dr Okumura had full access to all of the COVID-19-related data in the study. They take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Noda, Okumura.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Okumura.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Okumura.

Obtained funding: Noda.

Administrative, technical, or material support: Noda, Imamura.

Supervision: Kan-o, Taniguchi, Suzuki.

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