Title: Pathogenicity of the omicron variant strain comparison with delta variant strain and seasonal influenza in Japan

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ICMJE Statement

Contributors TS was responsible for the organization and coordination of the study. JK was the chief investigator and responsible for the data setting. YO developed the estimation model. All authors contributed to the writing of the final manuscript.

Abstract

Background: No remarkable mortality attributable to COVID-19 confirmed by PCR test has been observed in Japan.

Object: We sought to quantify excess mortality using the National Institute of Infectious Diseases (NIID) model.

Method: We applied the NIID model to deaths of all causes from 1987 up through the April 2022 for the whole of Japan and up through November 2021 for Tokyo.

Results: Results in Japan show huge number of excess mortality, up to 10 thousands in the two months, in August and September, 2021. On the other hand, in Tokyo, we also substantial excess mortality at the same time, which corresponds to be approximately 9% of the baseline at that time. Moreover, we found the largest number of excess mortality in a month since COVID-19 emerging in February and March 2022 in the whole of Japan, when one month later since the number of newly confirmed patients with omicron variant strain reached the peak.

Discussion and Conclusion: The result in February and March 2022 may indicate the pathogenicity of the omicron variant strain was comparable delta variant strain and stronger than seasonal influenza.

1. Introduction

To date, excess mortality has mainly been used to assess the social effects of influenza activity [1–6]. However, since the emergence of COVID-19, excess mortality attributable to COVID-19 has been attracting attention [7] as a measure of the total effects of the disease because it can reflect cases which have not been identified as polymerase chain reaction (PCR) positive. Especially in Japan, PCR tests administered per capita have been few. Therefore, concern has arisen about the possibility that some deaths caused by COVID-19 have not been recognized heretofore. Moreover, excess mortality related to COVID-19 might be expected to contribute to evaluation of vaccine effects. For these evaluations, the estimated excess mortality without the effects of a vaccine should be regarded as a baseline. Nevertheless, no such a trial has been undertaken to date. This study might be the first trial to measure that figure in Japan.

As of the end of 2021, the COVID-19 outbreak showed about 1.73 million patients and about 1.84 thousand deaths from the outbreak have been reported in Japan. Although Japan has about one third of the population of the U.S., these figures are vastly different in scale from those of the U.S., which has reported 54.8 million cases of morbidity and 826 thousand deaths [8]. In light of the much lower number of patients in Japan, some criticism has arisen that low PCR testing rates might have led to the lower number of documented patients [9]. In this sense, one might regard the number of deaths as reflecting the actual situation in Japan, but with no testing-related bias.

Concerning deaths, the case-fatality rate (CFR) is about 5%. In fact, the CFRs in both countries are not much different. The lower PCR testing in Japan might be related to some problems. Therefore, we specifically examined excess mortality attributable to COVID-19 in Japan, irrespective of the cause of death.

In Japan, excess mortality was estimated using the National Institute of Infectious Diseases (NIID) model [10], which has been the official procedure for more than ten years. It was applied to two data sources: the national monthly deaths of all causes and the respective weekly pneumonia and influenza deaths in the 21 largest cities and their total. The latter is published regularly in Japanese during the influenza season as https://www.niid.go.jp/niid/ja/flu-m/2112-idsc/jinsoku/131-flu-jinsoku.html. Unfortunately, that publication ceased in March 2020 because it is intended for influenza. The first peak in Japan was April 3, 2020[11]: excess mortality cannot be detected until March. Instead, we applied NIID model to the all causes of death in the whole of Japan to evaluate impact of the outbreak of COVID-19.

2. Method

Excess mortality is defined as the difference between the actual number of deaths and an epidemiological threshold. The epidemiological threshold is defined as the upper bound of the 95% confidence interval (CI) of the baseline. The baseline is defined as the number of deaths that are likely to have occurred if an influenza outbreak had not occurred. Therefore, if the actual deaths are fewer than the epidemiological threshold, then excess mortality is not inferred.

The data used for this study were monthly deaths of all causes from 1987 through the April 2022 for the whole of Japan and November 2021 for Tokyo [12]. NIID model, the Stochastic Frontier Estimation [13–19], is presented as

$$log\ D_t=\alpha+\beta T_t+\gamma T_t^2+\Sigma\eta_i M_{it}+\varepsilon_t \quad \text{and} \qquad (1)$$

$$\varepsilon_t=v_t+|\omega_t|\ , \qquad (2)$$

where D_t represents all causes of death in month/year t, T_t denotes the linear time trend, and M_{it} is the dummy variable for a month, which is one if t is the i-th month and otherwise zero. Moreover, v_t and ω_t are stochastic variables as $v_t \sim N(0, \mu^2)$ and $\omega_t \sim N(0,\xi^2)$; they are mutually independent. Although v_t represents stochastic disturbances, ω_t denotes non-negative deaths attributable to influenza. These disturbance terms in this model are parameterized by two parameters: ξ/μ and $(\mu^2+\xi^2)^{0.5}$. If the null hypothesis $\xi/\mu=0$ is not rejected, then the Stochastic Frontier Estimation model is inappropriate.

Study areas were the whole of Japan and its capital, Tokyo. Study period foe estimation was from 1987 to the April 2022 for the whole of Japan and up through November 2021 for Tokyo. We adopted 5% as significant level.

3. Results

Table 1 summarized the estimation results in the whole of Japan and Table 2 for Tokyo. Figure 1 presents observed deaths, the estimated baseline, and its threshold in Japan. Figure 2 specifically depicts the period since emerging COVID-19. We found 12 and 104 excess mortality in August and October, 2020, and 260, 135, 4106, 5853 and 584 in May, June, August, September and October, 2021. In February and March 2022, 9705 and 5396 excess mortality was observed, respectively. These were 0.0, 0.1, 0.2, 0.1, 3.8, 5.5, 0.5, 7.8% and 4.2% of the baseline.

Figure 3 and 4 showed the estimated result in Tokyo. We found 595 excess mortality in August and 150 excess mortality in September 76 in October, 458 in December, 2020, 44 in January, 60 in April, and 762, 942 and 130 in August to October, 2021 which were 6.3, 1.7, 0.8, 4.1, 0.4, 0.6, 8.0, 10.2 and 1.3 % of the baseline.

4. Discussion

This study applied the NIID model to all causes of death to detect excess mortality attributable to COVID-19. We found huge number of excess mortality in August and September, 2021 up to about 10 thousands in the two months in the whole of Japan. We supposed it caused by delt variant strain. At the same time, only 2464 PCR-confirmed death were reported, which was less than quarter of excess mortality. Especially, in Tokyo, we found substantial excess mortality which was approximately 8 and 10% of the baseline at that time.

Moreover, 9705 and 5396 excess mortality in the whole of Japan in February and March, 2022. It was supposed to cause by omicron variant strain. The number of excess mortality at that time was largest number in a month since COVID-19 emerging. Its ratio to base lines in February 2022, 7.8%, was also largest since 2020. However, concerning about total number of excess mortality over several months by the dominated strain, delta variant strain had larger than ten thousands and thus omicron variant strain has almost comparable but slightly smaller than delta variant strain.

Some researchers in Japan have emphasized considerable excess mortality from all causes of death through June 2021 of around 49 thousand at maximum due to COVID-19 [20, 21] using the Farrington algorithm [22] and EuroMOMO [23], which was more than three times larger than the number of death confirmed by PCR test until July, 2021, 53 thousands. Their study measured excess mortalities as the gap between observation and beeline, not threshold as, in prefectures where observation was higher than threshold. Therefore, their estimated too huge excess mortality may seriously mislead the risk participation for COVID-19 among the general population. In particular, in Tokyo, they found 4575 excess mortality until June, 2021. It was more than twice higher than PCR confirmed death in Tokyo, 2211.

At the same time, they also found approximately 60.5 thousands negative excess mortality in Japan until June, 2021 and 3911 negative excess mortality in Tokyo until June, 2021. Conversely, we found only 3 persons as negative excess mortality in February, 2020 in Tokyo, and 751 negative excess mortality in April, 2020, in the whole of Japan, as shown in Figure 2 and 4. Such a huge negative excess mortality in their estimation may doubt validity of their procedures. In particular, they showed that some areas have excess mortality in a week but also have negative excess mortality in a few weeks later. How should we interpret this strange phenomena ? Because they did not provide any interpretation for these phenomena, they probably cannot understand and explain their results.

Their estimated baseline might be upward biased. It probably suggested that their adopted procedure have upper biased for excess mortality comparison with NIID model, which was suggested logically [24]. Moreover, they used only five years to estimate and thus volatility in data might be too small to obtain more appropriate threshold.

Using pneumonia death data instead of total death data might be better to evaluate excess mortality caused by COVID-19. However, application rule of the International Classification of Diseases was revised on January 2017, after which pneumonia deaths decreased by approximately 25%. April 2020 was the fourth April since that of 2017. However, excess mortality in pneumonia death should be our next challenge.

5. Conclusion

We found substantial excess mortality since the outbreak of COVID-19 had emerged in the whole of Japan in the period between August to October 2021, up to 10 thousands. We also substantial excess mortality in Tokyo in the same time, which corresponds to be approximately 9% of the baseline at that time. Moreover, we found the largest excess mortality in a month in February, 2020 and it was supposed to cause by omicron variant strain. It may indicate the pathogenicity of the omicron variant strain was comparable delta variant strain and stronger than seasonal influenza.

The present study is based on the authors' opinions: it does not reflect any stance or policy of their professionally affiliated bodies.

6. Acknowledgement

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7. Conflict of interest

The authors have no conflict of interest to declare.

8. Ethical considerations

All information used for this study was published on the web site of MHLW [12]. Therefore, no ethical issue is presented.

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Table 1 NIID Model estimation results since 1987 until April 2022 in Japan

Explanatory variables	Estimated coefficients	*p*-value
Constant	11.12	<0.0004
Time trend	0.001537	<0.0004
Time trend ^{2}	0.0000009763	0.423
January	0.07075	<0.0004
February	-0.05631	<0.0004
March	-0.01671	0.053
April	-0.1027	<0.0004
May	-0.1247	<0.0004
June	-0.2126	<0.0004
July	-0.1776	<0.0004
August	-0.1710	<0.0004
September	-0.2083	<0.0004
October	-0.1197	<0.0004
November	-0.08768	<0.0004
ξ/μ	2.386	<0.0004
$(\mu^2+\xi^2)^{0.5}$	0.04934	<0.0004

Note: The number of observations was 419. The estimated log likelihood was 915.5. ξ^2 denotes the variance of the non-negative disturbance term. μ^2 is the variance of the disturbance term.

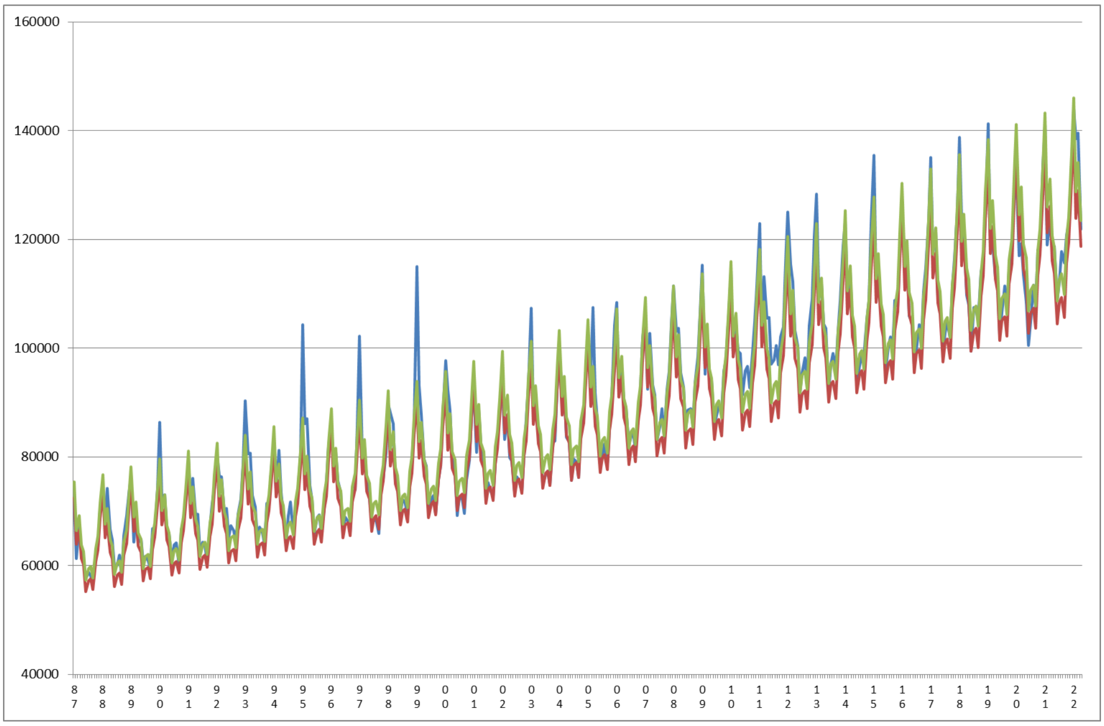
Table 2 NIID Model estimation results since 1987 until August 2021 in Tokyo

Explanatory variables	Estimated coefficients	*p*-value
Constant	8.55	<0.0004
Time trend	0.00186	<0.0004
Time trend ^{2}	$-0.726*10^{-6}$	0.001
January	0.0759	<0.0004
February	0.137	<0.0004
March	0.0292	0.015
April	0.0479	<0.0004
May	-0.0271	0.111
June	-0.0584	<0.0004
July	-0.111	<0.0004
August	-0.0664	<0.0004
September	-0.0719	<0.0004
October	-0.108	<0.0004
November	-0.0253	0.102
ξ/μ	2.44	<0.0004
$(\mu^2+\xi^2)^{0.5}$	0.0 684	<0.0004

Note: The number of observations was 413. The estimated log likelihood was 817.9. ξ^2 denotes the variance of the non-negative disturbance term. μ^2 is the variance of the disturbance term.

Figure 1: Observations of the estimated baseline and threshold since 1987 until April 2022 in Japan

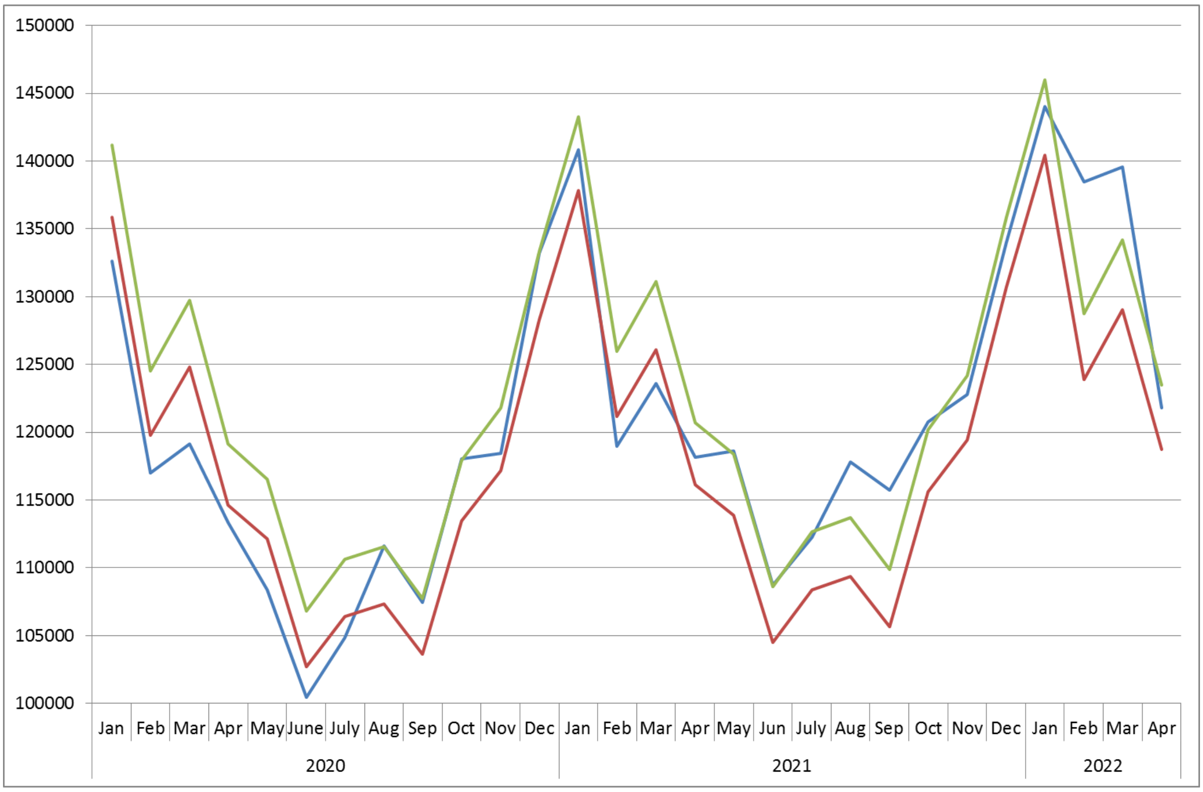
(persons)



Month/Year

Note: The blue line represents observations. The red line represents the estimated baseline. The green line shows its threshold.

Figure 2: Observation of the estimated baseline and threshold since January 2020 in Japan (persons)



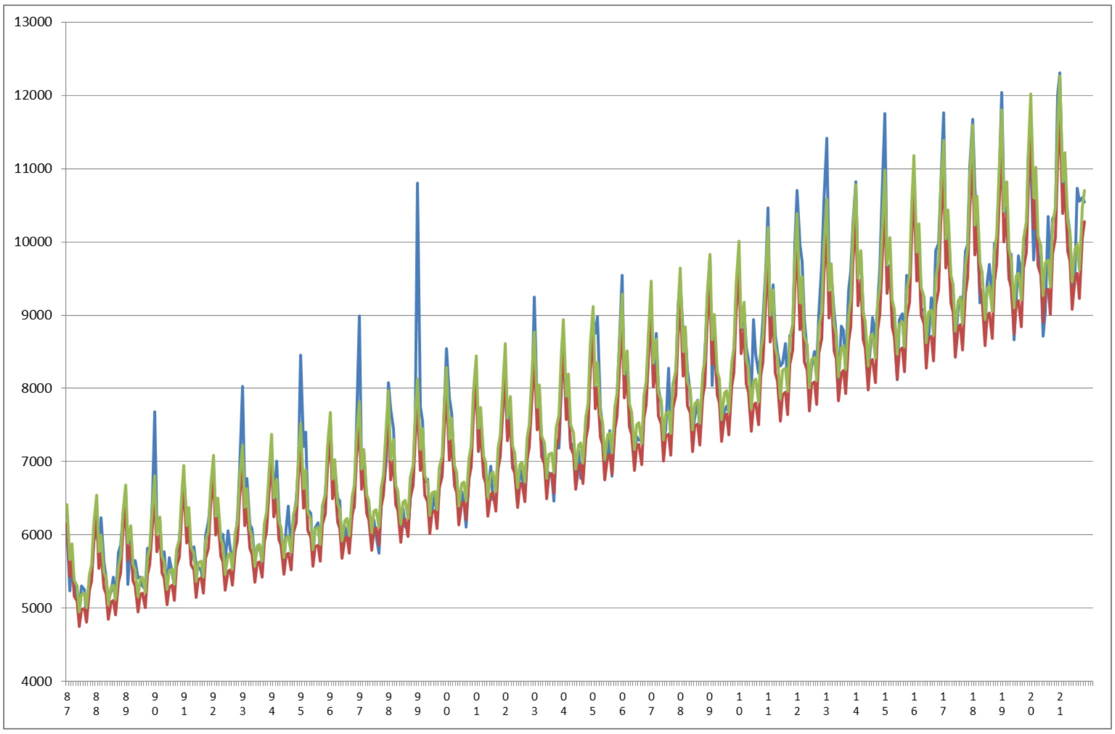
Month/Year

Note: The blue line represents observations. The red line represents the estimated baseline.
The green line shows its threshold.

Figure 3: Observations of the estimated baseline and threshold since 1987 until November

2021 in Tokyo

(persons)



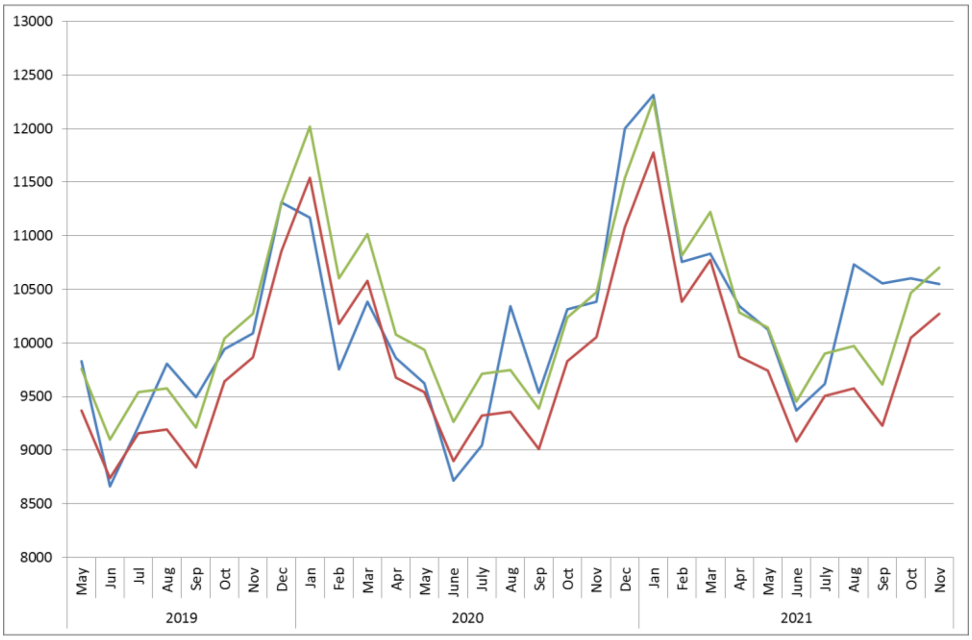
Month/Year

Note: The blue line represents observations. The red line represents the estimated baseline.
The green line shows its threshold.

Figure 4: Observation of the estimated baseline and threshold since May 2019 until

November 2021 in Tokyo

(persons)



Month/Year

Note: The blue line represents observations. The red line represents the estimated baseline. The green line shows its threshold.