Title: Pathogenicity of sublineage BA.5, omicron variant strain comparison with other variant strains of SARS-Cov-2 and seasonal influenza in Japan: Updated until March 2023

Junko Kurita[1],Tamie Sugawara[2], Yasushi Ohkusa[2]

[1] Department of Nursing, Faculty of Sports & Health Science, Daitobunka University, Higashimatsuyama, Saitama, Japan

[2] Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Shinjuku, Tokyo, Japan

Keywords: excess mortality; COVID-19; all cause death; stochastic frontier estimation; NIID model; Tokyo; Japan

*) Correspondence to:

Infectious Disease Surveillance Center, National Institute of Infectious Diseases, 1-23-1 Toyama, Shinjuku-ku, Tokyo 162-8640, Japan

Tamie Sugawara tammy@nih.go.jp

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: Sublineage BA.5 of omicron variant strain recorded the highest peak of morbidity and mortality confirmed with test per day in August for the former and September for the latter, 2022.

Object: We sought to quantify excess mortality using the National Institute of Infectious Diseases (NIID) model for all cause of death to evaluate pathogenicity of sublineage BA.5 of omicron variant strain.

Method: We applied the NIID model to deaths of all causes from 1987 up through the March, 2023 for the whole of Japan and up through November, 2022 for Tokyo.

Results: Results in Japan show that 18845, 14133, 8300, 6702, 18426 and 18404 excess mortality was observed in August 2022 to January 2023,which means 16.8, 13.0,7.0, 13.7 and 12.7 % of the baseline and approximately 72% of total excess mortality during the COVID-19 pandemic. Even in Tokyo, it was 4286 and 39% of total of excess mortality in this pandemic, between August and November, 2022.

Discussion and Conclusion: Results may indicate that its pathogenicity was much stronger than other variant strain and seasonal influenza.

1. Introduction

Since BA.5 sublineage of Omicron variant strain of SARS-CoV-2 emerged, ECDC reported infectivity of BA.5 was higher than BA.2 by 12-13% in Portugal and South Africa [1]. Even in Japan, it was estimated to be increased by 27% point as of July 13, 2022 [2]. Actually, it recorded the highest peak of morbidity per day among COVID-19 outbreak on August 1, 2022. At the same time, mortality confirmed with test positive per day on September 2, 2022.

However, mortality limited test positive patients might not capture the whole impact of COVID-19 outbreak. Thus, excess mortality of all causes of death

Before COVID-19 outbreak, excess mortality has mainly been used to assess the social effects of influenza activity [3–8]. However, since the emergence of COVID-19, excess mortality attributable to COVID-19 has been attracting attention [9] as a measure of the total effects of the disease because it can reflect cases which have not been identified as test positive.

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 March 2023 for the whole of Japan and November 2022 for Tokyo [12]. NIID model, the Stochastic Frontier Estimation [13–19], is presented as

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

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

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, ν_t and ω_t are stochastic variables as $\nu_t \sim N(0, \mu^2)$ and $\omega_t \sim N(0,\xi^2)$; they are mutually independent. Although ν_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 March 2023 for the whole of Japan and up through November, 2022 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, March, May -July 2022, 9705, 5396, 337, 748 and 2214 excess mortality was observed, respectively. These were 0.0, 0.1, 0.2, 0.1, 3.8, 5.5, 0.5, 7.8, 4.2, 0.3, 0.7 and 2.0 % of the baseline.

Especially, in August 2022 to January 2023, 18845, 14133, 8300, 6702, 18426 and 18404 excess mortality was observed, which means 16.8, 13.0,7.0, 13.7 and 12.7% of the baseline. In these six months, 84811 excess mortality were observed. It means that approximately 74% of total excess mortality during the COVID-19 pandemic was occurred in this six months. Finally, the excess mortality was not observed in March, 2023.

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. Additionally, there were 1427, 1201, 166, 228, 184, 212, 2069, 970, 703 and 543 excess morality in February to November, 2022. It mean 13, 11, 1.6, 2.3, 1.0, 2.2 , 21.0, 10.2, 6.8 and 5.1% of the baseline. The largest excess mortality in Tokyo during the COVD-19 pandemic was 2069, which was more than 20% of the baseline and

18.9% of total of excess mortality in this pandemic, in August 2022.

4. Discussion

We found huge number of excess mortality in August 2022 to January 2023 up to about 85 thousands in the whole of Japan. We supposed it caused by sublineage BA.5 of omicron variant strain. At the same time, only 35 thousand test-confirmed death were reported, which was 41.2% of excess mortality in the same period.

Note that pathogenicity was measured by number of excess mortality in all causes and not by case-fatality rate (CFR). Usually, patients who finally died fighting illness for a while. The length of period until death from infection were different patient by patient. Moreover, the concept of excess mortality does not identify who was counted as excess mortality. Therefore, we cannot define CFR for excess mortality precisely. However, because of highest peak of the number of patients with BA.5 was recorded, we can suppose CFR of BA.5 might be comparable with delta or sublineage BA.1 of omicron variant strain.

Actually, CFR of COVID-19 were estimated as 0.06% in 2020 when Wuhan original strain dominated, 1.08% in 2021 when alpha and delta variant strain dominated, 0.31% in 2022 when omicron variant strain dominated. CFR was defined as excess mortality in this study divided by newly confirmed patients including asymptomatic cases [19]. On the other hand, CFR for influenza was estimated 0.05-0.35% in 2011/2012-2018/2019 seasons. In particular, it was higher than 0.3% in 2011/2012 and 2012/2013 season. Following was 0.15% in 2014/2015 season. After that, it was lower than 0.1%. Therefore, CFR of Wuhan original strain was comparable with lower CFR of influenza, CFR of omicron variant strain was comparable with higher CFR of influenza and CFR of alpha and delta variant strain was remarkable higher than influenza.

Recently, international comparison of excess mortality caused by COVID-19 was published [20]. In this article, it reported 112 thousand excess mortality in Japan. It was about six times larger than the number of deaths confirmed COVID-19 infection. Conversely, we found about 27 thousand excess mortality in the same period. It was slightly larger than the number of deaths confirmed COVID-19 infection, however, it was almost comparable. In this sense, the international comparison may underestimate the baseline and overestimate excess mortality. It is well known bias in the careless estimation foe excess mortality [21]. Hence, international comparison might be less precise estimation than this study. Overestimation of excess mortality might mislead to inappropriate policy or counter measures and inflate its disease burden.

5. Conclusion

We found substantial excess mortality since the outbreak of COVID-19 had emerged in the whole of Japan in August 2022 to January, 2023, up to 85 thousands when delta variant strain prevailed. Even in Tokyo, it occupied 39% of total of excess mortality in this pandemic, between August and November 2022. These observations may indicate its pathogenicity was much stronger than other variant strain and 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

We acknowledge Dr. Nobuhiko Okabe, Kawasaki City Institute for Public Health, Dr.Kiyosu Taniguchi, National Hospital Organization Mie National Hospital, and Dr.Nahoko Shindo, WHO for their helpful support.

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.

9. References

1) European Centre for Disease Prevention and Control. Epidemiological update: SARS-CoV-2 Omicron sub-lineages BA.4 and BA.5. https://www.ecdc.europa.eu/en/news-events/epidemiological-update-sars-cov-2-omicron-sub-lineages-ba4-and-ba5 [accessed on October 22, 2022]

2) National Intitute of Infectious Diseases. Updated Situation of COVID-19 Outbreak (July 13,2022) https://www.niid.go.jp/niid/ja/2019-ncov/11309-covid19-ab90th.html (in Japanese) [accessed on October 20, 2022]

3) Lin HC, Chiu HF, Ho SC, Yang CY. Association of influenza vaccination and reduced risk of stroke hospitalization among the elderly: a population-based case-control study. Int J Environ Res Public Health 2014; 11: 3639-49.

4) Asghar Z, Coupland C, Siriwardena N. Influenza vaccination and risk of stroke: Self-controlled case-series study. Vaccine. 2015; 33: 5458-63.

5) Riedmann EM. Influenza vaccination reduces risk of heart attack and stroke. Hum Vaccin Immunother 2013; 9: 2500.

6) Kwok CS, Aslam S, Kontopantelis E, Myint PK, Zaman MJ, Buchan I, Loke YK, Mamas MA. Influenza, influenza-like symptoms and their association with cardiovascular risks: a systematic review and meta-analysis of observational studies. Int J Clin Pract. 2015;69:928-37.

7) Muhammad S, Haasbach E, Kotchourko M, Strigli A, Krenz A, Ridder DA, Vogel AB, Marti HH, Al-Abed Y, Planz O, Schwaninger M. Influenza virus infection aggravates stroke outcome. Stroke. 201142 783-91.

8) Assad F, Cockburn WC, Sundaresan TK. Use of excess mortality from respiratory diseases in the study of influenza. Bull WHO 1973; 49: 219-33.

9) Sugawara T, Ohkusa Y. Comparison of Models for Excess Mortality of Influenza Applied to Japan. Journal of Biosciences and Medicines, 2019, 7, 13-23. doi:10.4236/jbm.2019.76002

10) Kurita J, Sugawara T, Ohkusa Y. Mobility data can explain the entire COVID-19 outbreak course in Japan. medRxiv 2020.04.26.20081315; doi: https://doi.org/10.1101/2020.04.26.20081315

11) Ministry of Health, Labour and Welfare. Preliminary statistics on demographicshttps://www.mhlw.go.jp/toukei/list/81-1a.html (in Japanese) [accessed on January 16, 2022]

12) Aiger AD, Lovell K, Schmitidt P. Formulation and estimation of stochastic frontier production function models. Journal of Econometrics 1977; 21-37.

13) Jondrow J, Lovell K, Materov S, Schmidt P. On the estimation of technical inefficiency in the stochastic frontier production function model. Journal of Econometrics 1982; 233-9.

14) Li T, Rosenman R. Cost inefficiency in Washington Hospitals: A stochastic frontier approach using panel data, Health Care Management Science 2001; 4: 73-81.

15) Newhouse JP. Frontier Estimation: How useful a tool for health economics? Journal of

Health Economics 1994; 13: 317-22.

16) Shelton Brown H. Managed care and technical efficiency. Health Economics. 2003; 12: 149-58.

17) Jacobs R. Alternative methods to examine hospital efficiency: Data envelopment analysis and stochastic frontier analysis. Health Care Management Science. 2001; 4: 103-15

18) Rosko MD. Cost efficiency of US hospitals: A stochastic frontier approach. Health Economics. 2001; 539-51.

19) Ministry of Labour, Health and Welfare. Deta kara wakaru -shingata koronau uirusu kansenshou jouhou- Kansensha doukou (in Japanese) [Visualizing the data: information on COVID-19 infections: COVID-19 trend] https://covid19.mhlw.go.jp/ [accessed on April 14, 2023]

20) COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. Lancet. 2022 ;399:1513-36.

21) Sugawara T, Ohkusa Y. Comparison of Models for Excess Mortality of Influenza Applied to Japan. Journal of Biosciences and Medicines, 2019, 7, 13-23. doi:10.4236/jbm.2019.76002

Table 1 NIID Model estimation results since 1987 until March 2023 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 426. 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.

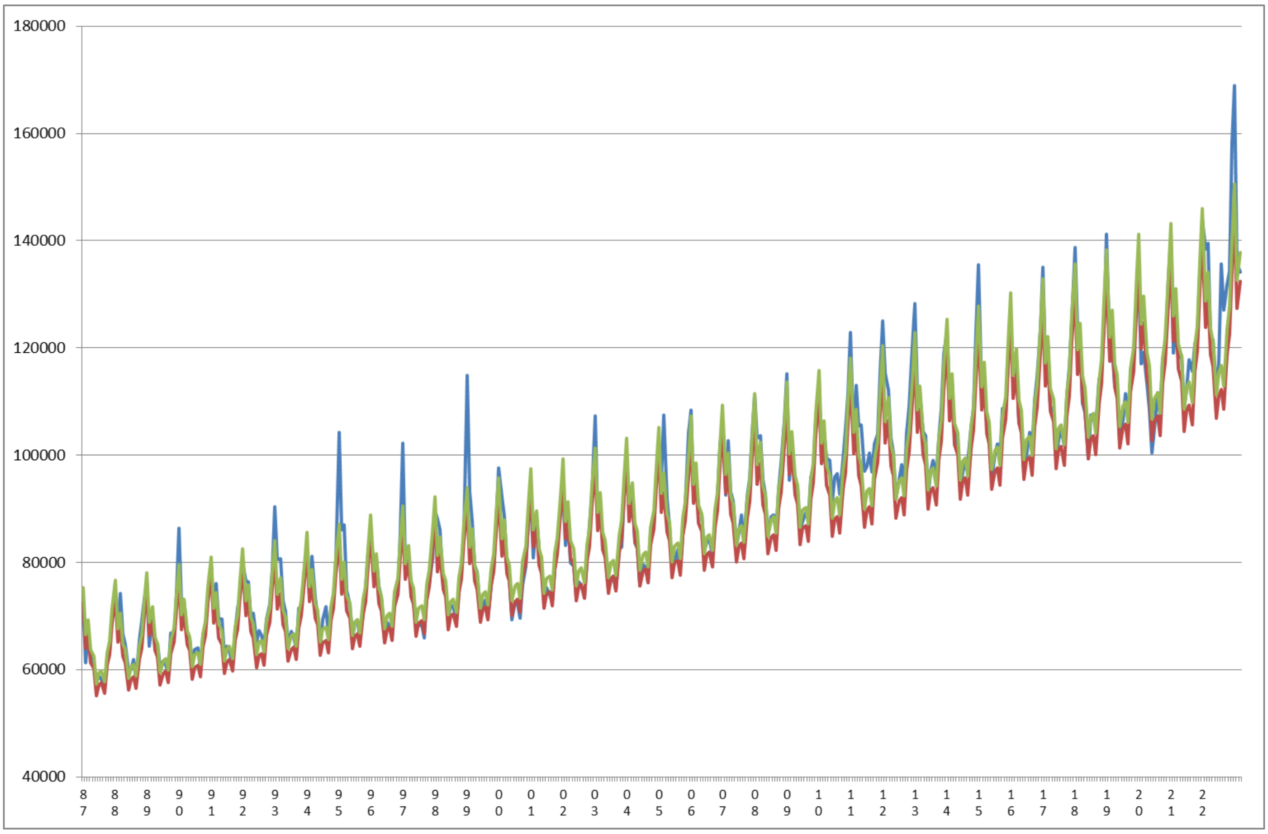
Table 2 NIID Model estimation results since 1987 until November 2022 in Tokyo

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
$(\mu^2+\xi^2)^{0.5}$	0.0684	<0.0004

Note: The number of observations was 425. 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 March 2023 in Japan

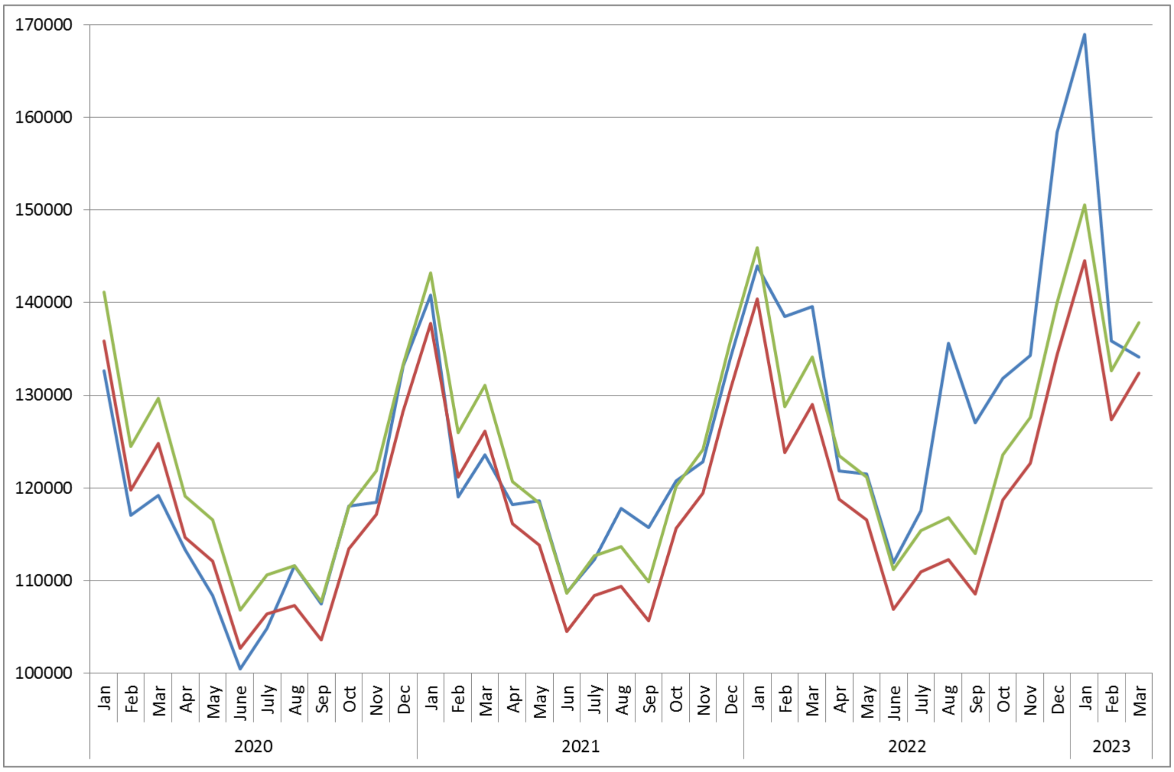
(persons)



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)

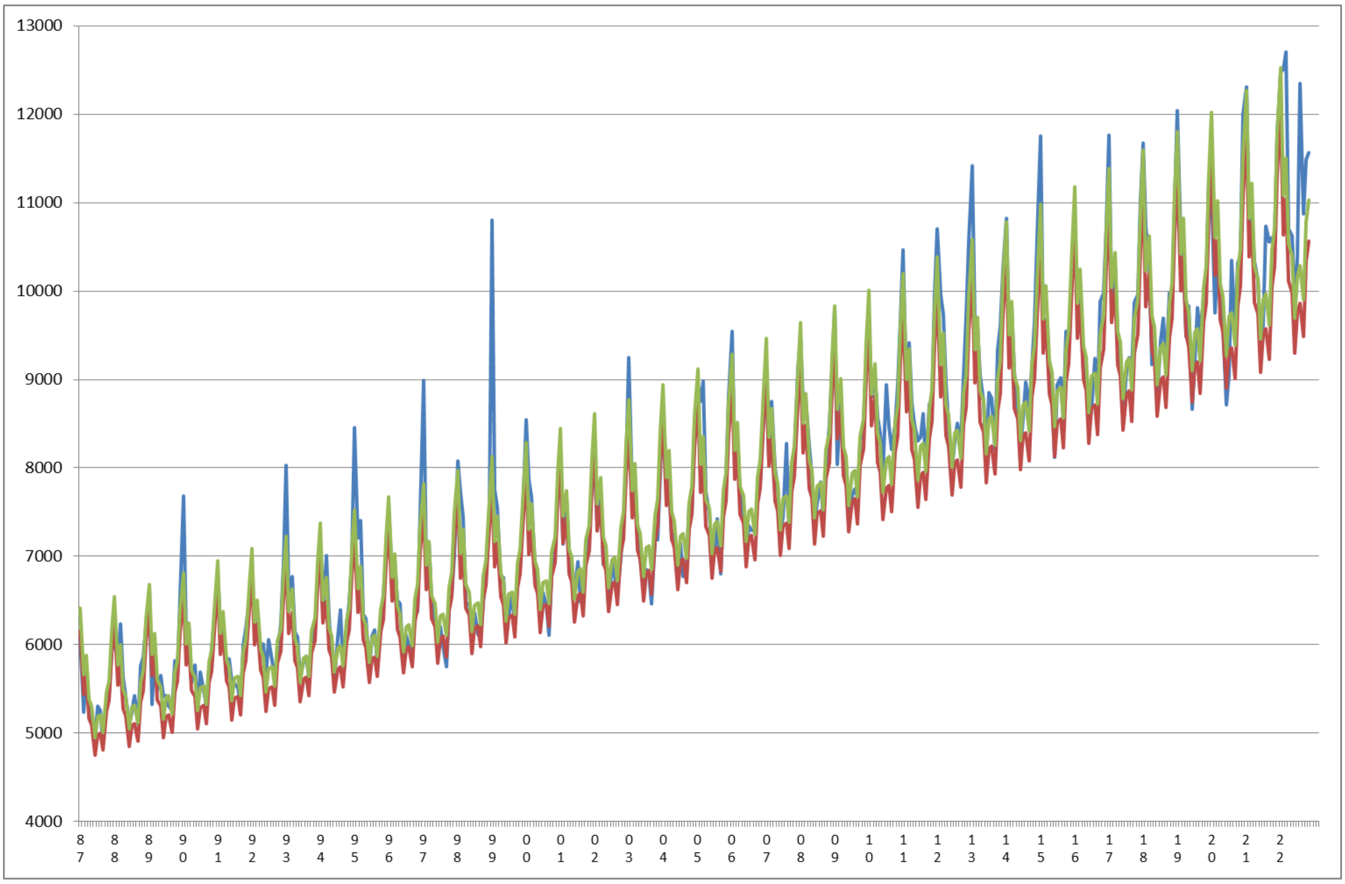


Month/Year

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, 2022 in Tokyo

(persons)

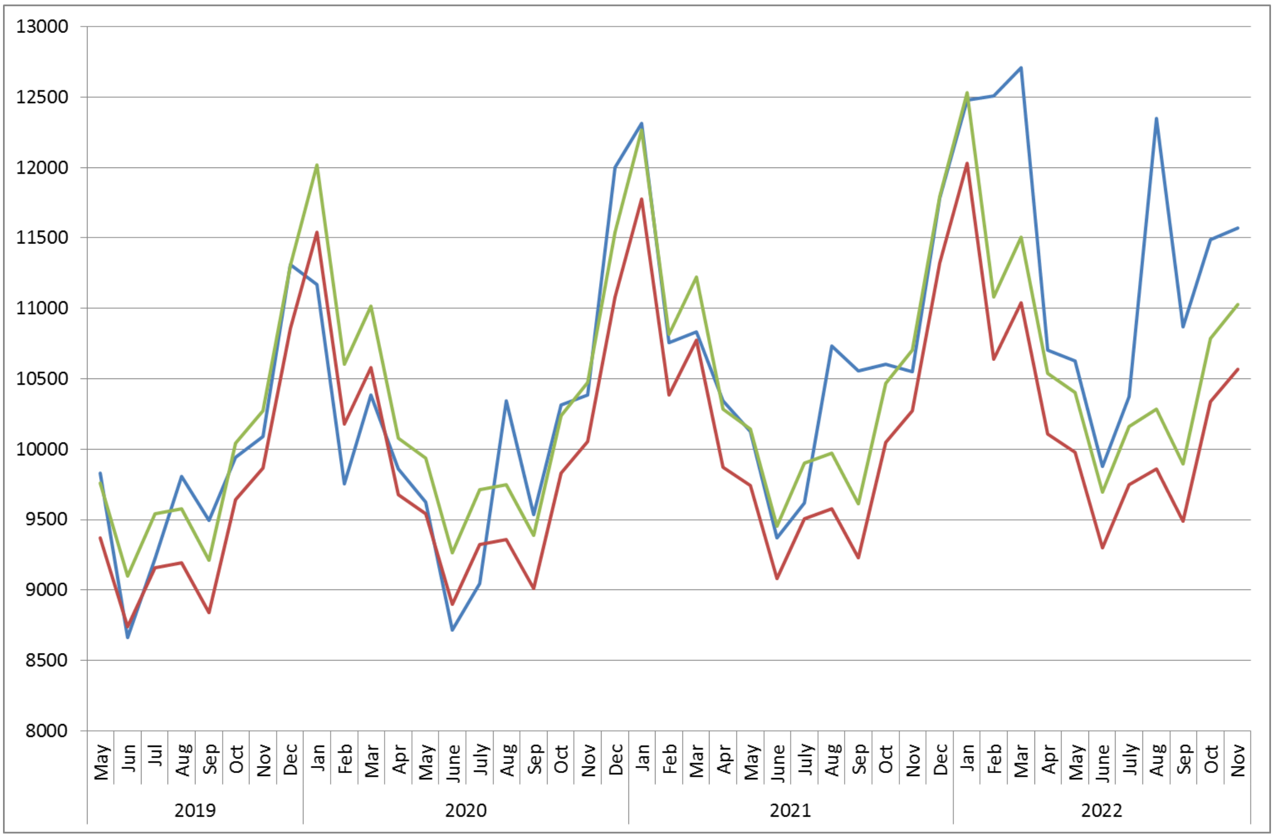


Month/Year

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, 2022 in Tokyo

(persons)



Month/Year

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