学位論文内容の要旨
（Summary of dissertation）

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学 位 論 文 題 名
Infection dynamics of coronavirus disease 2019 (COVID-19)
(新型コロナウイルス感染症の感染動態に関する研究)

Background and Objectives: The first confirmed case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was reported in January 2020, and the transmission of its causative agent, coronavirus disease 2019 (COVID-19) has rapidly spread around the world. In the early phase of the epidemic, knowledge of the confirmed case fatality risk (cCFR) is crucial to characterize the severity and determine the pandemic potential of an emerging infectious disease. To address the risk assessment of COVID-19, *Chapter 1* statistically estimated the cCFR and the basic reproduction number (R_0) of COVID-19 in the early phase of pandemic, using the exported cases which provide an opportunity to estimate the cumulative incidence in mainland China. In addition, *Chapter 2* explored prospective exit strategies by projecting a second wave of the COVID-19 epidemic in Japan with different levels of restriction to suggest a more sustainable strategy than a restrictive guideline. Lastly, the effective reproduction number (R_t) has been used as an essential indicator for assessing the effectiveness of countermeasures during the COVID-19 pandemic. However, conventional methods relying on the reported case counts are unable to provide timely R_t due to the time delay from infection to reporting. Therefore, *Chapter 3* suggested a simple statistical framework for predicting R_t in near real time, using timely accessible data of possible driving factors of COVID-19 transmissions (i.e., human mobility, temperature, and risk awareness).

Chapter 1: Real-time estimation of the risk of death from COVID-19: inference using exported cases

Methods: Using the exponential growth rate of the estimated cumulative incidence from exportation cases and accounting for the time delay from illness onset to death, the cCFR and R_0 were estimated. We modelled epidemic growth either from a single reported index case with illness onset on 8 December 2019 (Scenario 1), or using the growth rate fitted along with the other parameters (Scenario 2) based on data from 20 exported cases reported by 24 January 2020. **Results**: The cumulative incidence in China by 24 January was estimated at 6,924 cases (95% confidence interval [CI]: 4885, 9211) and 19,289 cases (95% CI: 10,901, 30,158), respectively. The latest estimated values of the cCFR were 5.3% (95% CI: 3.5%, 7.5%) for Scenario 1 and 8.4% (95% CI: 5.3%, 12.3%) for Scenario 2. The R_0 was estimated to be 2.1 (95% CI: 2.0, 2.2) and 3.2 (95% CI: 2.7, 3.7) for Scenarios 1 and 2, respectively. **Discussion**: Based on these results, we argued that the current COVID-19 epidemic has a substantial potential for causing a pandemic. The proposed approach provides insights into early risk assessment using publicly available data.

Chapter 2: Projecting a second wave of COVID-19 in Japan with variable interventions in high-risk settings

Methods: We quantified the next-generation matrix, accounting for high- and low-risk transmission settings of SARS-CoV-2. Then, the matrix was used to project the future incidence in Tokyo and Osaka after the first state of emergency is lifted, presenting multiple post-emergency scenarios with different levels of restriction. **Results**: The R_t for the increasing phase, the transition phase and the state-of-emergency phase in the first wave of the disease were estimated as 1.78 (95% credible interval (CrI): 1.73–1.82), 0.74 (95% CrI: 0.71–0.78) and 0.63 (95% CrI: 0.61–0.65), respectively, in Tokyo and as 1.58 (95% CrI: 1.51–1.64), 1.20 (95% CrI: 1.15–1.25) and 0.48 (95% CrI: 0.44–0.51), respectively, in Osaka. Projections showed that a 50% decrease in the high-risk transmission is required to keep R_t less than 1 in both locations—a level necessary to maintain control of the epidemic and minimize the burden of disease. **Discussion**: Compared with stringent interventions such as lockdowns, our proposed exit strategy from restrictive guidelines, with the classification of high- and low-risk settings, allows socioeconomic activities to be maintained while minimizing the risk of a resurgence of the disease.

Chapter 3: Predicting the effective reproduction number of COVID-19: inference using human mobility, temperature, and risk awareness.

Methods: A linear regression model to predict R_t was designed and embedded in the renewal process. Four prefectures of Japan with high incidences in the first wave were selected for model fitting and validation. Predictive performance was assessed by comparing the observed and predicted incidences using cross-validation, and by testing on a separate dataset in two other prefectures with distinct geographical settings from the four studied prefectures (test data). **Results**: The predicted mean values of R_t and 95% uncertainty intervals followed the overall trends for incidence, while predictive performance was diminished when R_t changed abruptly, potentially due to superspreading events or when stringent countermeasures were implemented. In addition, the predictive performance of the best-ranked model on the separate test data indicates the applicability of the proposed model to other geographical settings. **Discussion**: The described model can potentially be used for monitoring the transmission dynamics of COVID-19 ahead of the formal estimates, subject to time delay, providing essential information for timely planning and assessment of countermeasures.

Conclusion: Since the SARS-CoV-2 emerged, it has posed an enormous threat to healthcare systems all around the world. The present dissertation has contributed to a better knowledge of COVID-19 infection dynamics, which is important for controlling the ongoing COVID-19 pandemic and devising a proper COVID-19 response strategy. First, it estimated the risk of death and transmissibility of COVID-19 for the early risk assessment. In addition, it projected the future dynamics of COVID-19 by reconstructing the next-generation matrix accounting for high- and low-risk transmission settings, and quantitatively assessed the impacts of possible exit strategies on the SARS-CoV-2 transmissions in Japan. Lastly, it suggested the statistical framework for providing timely prediction of the effective reproduction number, that can be used before a formal estimate is available. Despite the uncertainty surrounding new SARS-CoV-2 variants, my series of studies can shed light on understanding the infection dynamics of COVID-19 and developing evidence-based response strategies for minimizing the burden of the ongoing COVID-19 pandemic.