

Cardiovascular considerations during the COVID-19 pandemic: A focused review for practice in Japan

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Abstract: The COVID-19 pandemic is continuing to have drastic consequences for patients, healthcare workers, and the health system. Its cardiovascular implications have been well described in previous studies, but original reports from Japan are sparse. Validating overseas findings in the Japanese clinical settings is crucial to improve local COVID-19 care and to clarify the pandemic's impacts in the country. This review of available literature demonstrates that in Japanese patients and clinical settings too, there is a close relationship between COVID-19 and the cardiovascular system including cardiovascular complications. On the contrary, secondary effects on cardiovascular practice including service disruptions, telemedicine, and epidemiological changes in Japan have been relatively small.

Keywords: COVID-19, Japan, cardiovascular complications, health system, epidemiology

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic is now entering its third year. Case fatality rates are lower than they were at the start of the pandemic, as more people around the globe are being vaccinated and less severe variants have become predominant. However, total infections worldwide have soared to over 400 million as of February 2022, continuing to exert extensive effects on our health and well-being. Even though Japan ranks the lowest among G7 nations in COVID-19 cases and deaths, the country is struggling on its own to apply lessons from overseas in the Japanese context.

An important consideration when drawing on global scientific literature regarding COVID-19 is that most previous studies do not take into account geographical and ethnic differences. The severity of COVID-19 is determined by a number of host factors like the baseline health condition and vaccination status, which have significant regional disparities. In addition, recent studies have suggested that genetic background may also be a determinant of severity (1,2). To provide more appropriate care in Japanese clinical settings, we must clarify the unique characteristics in Japanese cases.

Apart from infected individuals, the pandemic has had widespread collateral effects on society. Changes to the epidemiology of diseases and the healthcare system have resulted not only from the overwhelming rise in COVID-19 admissions but also from the lifestyle changes of the entire population.

Such secondary consequences are observed across the globe but vary greatly in each region, depending on factors like public health policies, media coverage, and economic activities. Even though the direct burden from infections seems to be relatively small in Japan, collateral impacts on the non-infected population need to be taken into account to evaluate the comprehensive effects of the pandemic.

The close association between COVID-19 and the cardiovascular system and cardiovascular practice in general has been described previously (3). Here in this review, we will reinvestigate this association with an aim to be embraced in the Japanese context. We will first discuss the relationship between COVID-19 and the cardiovascular system, referring to unique findings in Japanese patients and clinical settings. Then, we will broaden our perspective to collateral consequences of the pandemic, depicting changes in clinical practice and epidemiology of cardiovascular diseases in Japan.

Role of cardiovascular comorbidities on the clinical course

Previous reports from around the world have shown that cardiovascular risk factors including male sex, advanced age, diabetes, hypertension, and obesity also pose a risk for poor prognosis in COVID-19 patients. Not surprisingly, cardiovascular comorbidities are also a predictor of severe illness. In one of the largest multinational cohort studies of over 20,000 patients, the adjusted risk ratio for in-hospital mortality was 1.19

for heart failure and 1.41 for severe heart failure (New York Heart Association (NYHA) class III/IV) (4).

In Japanese COVID-19 patients too, cardiovascular comorbidity was confirmed to be one of the risk factors for severity along with age, diabetes, obesity, and chronic respiratory disease (5). The CLAVIS-COVID registry was organized by the Japanese Circulation Society to investigate the prognosis of hospitalized COVID-19 patients with prior cardiovascular diseases and/or risk factors. From the analysis of this extensive registry, the following observations have been made: the risk of complications was higher in those with multiple cardiovascular diseases or risk factors (6), statin users had lower severity (7), and increased lactate dehydrogenase (LDH) levels were associated with in-hospital mortality (8). Also, the 4C Mortality Score, developed based on UK cohorts predicting poor outcomes, was validated in Japanese cohorts as well (9). These results are compatible with findings in foreign studies. On the contrary, the threshold for increased mortality in obese patients was body mass index (BMI) of 30 in Japan, whereas in other countries the number was 40 (10). This suggests that even just mild obesity may predispose the patients to a poorer outcome in

the Japanese population. In conclusion, predicting prognosis based on a cardiovascular standpoint is appropriate in the Japanese population as well, but there are probably subtle differences that need further investigation.

Cardiovascular complications

Various types of cardiovascular complications may occur during the course of COVID-19, including arterial and venous thrombosis (*i.e.*, acute coronary syndrome, pulmonary embolism, and venous thromboembolism (VTE)), arrhythmias, and myocardial damage. According to a multicenter cohort study of over 65,000 hospitalized COVID-19 patients from UK healthcare facilities, there was a significant ethnic difference in the incidence of cardiovascular complications (11). Furthermore, compared to reports from other regions of the world, the incidence rates of cardiovascular complications such as thrombosis appear to be lower in Japan (12-15) (Figure 1). According to an analysis of Japan's largest inpatient registry of almost 20,000 COVID-19 patients (COVIREGI-JP), the incidences of cardiovascular complications were 0.59% for deep venous thrombosis, 0.19% for pulmonary embolism, 0.48% for ventricular tachycardia/fibrillation, 0.17% for myocardial ischemia, and 0.098% for myocarditis/pericarditis/cardiomyopathy (14). It is crucial, however, to bear in mind large variations in study settings. Complications may occur depending on the properties of the host (*i.e.*, baseline patient characteristics and vaccination status), the pathogen (*i.e.*, type of variant), and interventions (*i.e.*, prophylactic and supportive therapies) (Figure 2). One of the most critical determinants of complication occurrence is the severity of the infection. Complications occur more frequently in more severe cases. Even within COVID-19 patients that were hospitalized, the severity may vary greatly depending on factors like bed availability. Also, due to publication bias, the incidence rates might have been overestimated in initial reports. Therefore, a significant

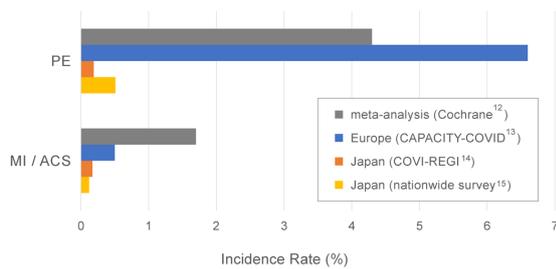


Figure 1. Reported incidence rates of thrombotic complications in hospitalized COVID-19 patients. Data adapted from four studies (12-15). The incidence rates appear to be substantially lower in Japanese cohorts, but differences in study designs and existence of numerous confounding factors make it virtually impossible to determine to what extent ethnic predispositions actually play a role.

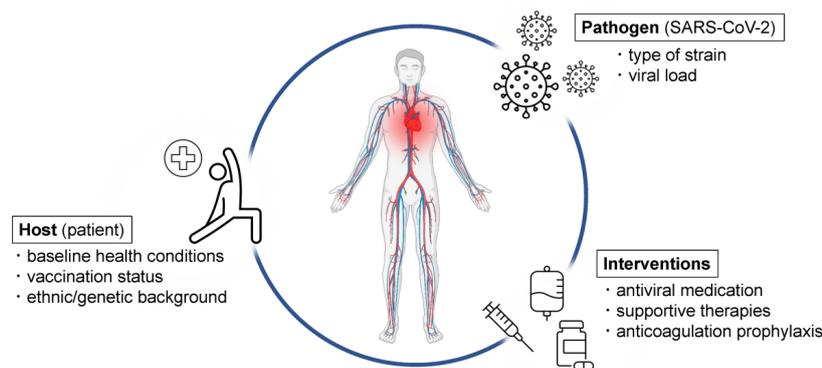


Figure 2. Determinants of cardiovascular complications in COVID-19. The effects of the infection on the cardiovascular system are dictated by various factors regarding the host, the pathogen, and medical interventions.

deviation is inevitable among different studies at different time points. Keeping in mind such pitfalls, we will carefully discuss regional and ethnic differences regarding thrombosis and myocardial damage.

Thrombosis

Apart from COVID-19, it has been previously revealed that thrombosis occurs less frequently in people of Asian descent compared to other races (16). Although the same trend is expected in COVID-related thrombosis, factors other than ethnicity, like disease severity of COVID-19 and thromboprophylaxis, play a similar if not a greater role in its occurrence. In order to reveal ethnic differences, studies of a patient population in one ethnically-diverse region are useful because region-specific variables are standardized to some extent. One such investigation which examined the incidence of thrombotic events among over 20,000 COVID-19 patients revealed that both arterial and venous thrombosis were more common in Black patients than in other races (17). While Asian patients tended to have a lower likelihood of VTE (odds ratio 0.64), the trend was only confirmed in the unadjusted model. On the contrary, in a smaller study of a mixed-ethnicity UK cohort of 613 patients, Asian patients were more likely to present with VTE compared to Caucasian and Afro-Caribbean patients (18). Limited reports thus far point to inconsistent conclusions.

Simple comparisons of incidence rates of thrombotic complications in hospitalized COVID-19 patients in and outside Japan may provoke interesting discussions. In Japan, a nationwide questionnaire-based survey revealed that thrombosis, the majority of which were VTEs, occurred in 1.86% of all hospitalized COVID-19 patients ($n = 6,202$) (15). More specifically, the number was 0.59% in mild or moderate patients, whereas the number was higher at > 13.5% in severe patients. Even when the severity of COVID-19 was accounted for, the numbers were quite low compared to reports from Western countries. Japanese patients may be less likely to develop COVID-19-related thrombosis.

In some clinical guidelines, uniform prophylactic anticoagulation is recommended for hospitalized COVID-19 patients due to the high risk of thrombosis (19). However, there is an ongoing debate whether racial predispositions should be considered for such practice (20). Anticoagulant-induced bleeding occurs more frequently in patients of Asian descent (16); this is the rationale behind non-adoption of routine postoperative anticoagulation for VTE prevention in Asia. In an observational study of 1,784 Japanese cohorts (21), although there was no difference in mortality between anticoagulated and non-anticoagulated COVID-19 patients overall, within the group treated with steroids (an indication of more severe infection), there was a trend towards lower mortality in the anticoagulated

patients. In line with the study, a guideline issued by the Japanese Society of Phlebology and others recommends prophylactic-dose heparin only in patients that require oxygen support (22).

Whether or not there are other unique characteristics regarding COVID-related thrombosis in Japanese patients remains to be answered in future research. Only few studies have been published so far. As an example, despite possibly having lower thrombotic risks overall, in Japanese cohorts too, patients with obesity and severe COVID-19 were especially likely to develop VTE (23). Also, a small single-center study suggested that besides d-dimer, ferritin levels were also helpful biomarkers of thrombosis in COVID-19 patients (24). This may be an original finding in Japanese cohorts.

Myocardial injury

Myocardial injury in the context of COVID-19 infection usually refers to an elevation in cardiac troponin and is associated with disease severity and mortality (25). It is not unique to COVID-19; previous studies have described the same complication in other respiratory infections, including seasonal influenza (26). The primary mechanism is likely to be a mismatch in oxygen supply and demand rather than direct viral invasion into the myocardium. Myocardial injury may prevail in both early and convalescent phases of COVID-19.

Although there is insufficient data to compare its frequency in different populations, studies have confirmed the phenomenon in Japanese patients too. In a study of 209 recently recovered COVID-19 patients, 65% had positive high-sensitive troponin T (27). It is important to note that although the measurements were higher in those who suffered more severe infections, the majority of troponin-positive patients had only a mild illness. Furthermore, an additional analysis of the same patients revealed a decrease in left ventricular global longitudinal strain (LVGLS) on echocardiograms, suggesting that they may have poorer cardiovascular prognosis (28). Although these works are preliminary, these studies remind us to watch out for signs of cardiac dysfunction even after recovery from acute infection.

Secondary effects on cardiovascular practice

Service disruptions

The pandemic has restricted cardiovascular procedures globally, but the impact in Japan seems to have been small compared to other parts of the world (29). The Japanese Circulation Society conducted a nationwide survey in April and August of 2020 to evaluate the pandemic's impact on cardiovascular practice (30,31). According to the reports, transesophageal echocardiograms and diagnostic/therapeutic catheterizations were limited in over half of the

facilities during the first surge of the pandemic. Still, the restriction was much milder after the second surge. Large analyses of claims databases also support the perspective that disruptions in cardiovascular care were minimal or have faded away. According to one study, by September 2020, the number of elective percutaneous coronary interventions (PCIs) recovered to 98% of corresponding months in the previous two years (32). Another investigation showed that the number of physician visits declined only in April 2020 and that prescriptions for major chronic diseases (hypertension, diabetes, and dyslipidemia) were not affected (33). For emergent procedures, over 97% of hospitals managed to perform primary PCIs for ST elevation myocardial infarction (STEMI) even amid sharp COVID-19 surges (34). However, even in Japan, the door-to-balloon time was prolonged due to COVID-19 screening (35,36). Although reports so far have not shown increases in short-term mortality, recent evidence from overseas suggested that such delay resulted in an increase in infarct size and more frequent intramyocardial hemorrhage (37). Further optimization of COVID-19 screening protocols may be necessary.

Telemedicine

Some clinicians see the pandemic as a chance for digital transformation in healthcare. Although ICT-based healthcare entails unsolved issues such as digital divide, it has the potential to improve accessibility and efficiency (38). In the United States, the pandemic has led to a rapid expansion of online medical services, with the number of telehealth visits increasing tenfold in March 2021 compared to the same period in 2020 (39). Similar trends were seen in European countries like the UK, Germany, and France. In Japan, however, the adoption of telemedicine seems to be lagging behind. Although the Ministry of Health, Labor, and Welfare lifted some of the restrictions regarding online visits, the percentage of medical institutions offering virtual services reached a plateau after hitting 15% in June 2020 (40).

For cardiac rehabilitation (CR) also, Japan has been slow to adopt digital technology. According to a nationwide survey of CR facilities, group ambulatory CR was suspended in 70% of the facilities (41). Despite the suspension, only 8% offered remote CR programs, and, what is worse, only 30% of facilities not providing telerehabilitation had specific future plans for implementation. Another report revealed that CR interruption has actually resulted in a deterioration of hemodynamic measures of the patients overall (42).

Telemedicine does not necessarily require cutting-edge technology. For instance, most CR facilities in the UK have continued providing physical activity advice or training mainly by using less sophisticated technologies like telephones and pre-recorded online videos(43).

In Japan too, a study proposed that making use of the country's reliable, high-speed postal service was effective to provide long-term remote electrocardiogram monitoring during the pandemic (44). These examples show that we should not passively wait for a revolutionary platform to emerge but instead actively make the best use of what is currently available.

Epidemiological changes

Functional emergency medical services and high care units are essential parts of acute cardiovascular care. In the early stages of the pandemic, disruption of overwhelmed healthcare systems resulted in a decline in hospitalizations for acute cardiovascular diseases worldwide (45). This section will focus on epidemiological changes of myocardial infarction and heart failure. In Japan during the pandemic, hospital admissions for acute coronary syndromes declined by only 5-10%, even in areas where COVID-19 was most prevalent (46,47). This contrasts with situations in areas hardest hit by the pandemic like the US, Spain, and Latin America, which saw declines of up to -50% (48-50). For heart failure exacerbations too, although a sudden decrease of -3.6% in hospitalizations was observed just after the declaration of the state of emergency in April 2020, there was no deterioration in in-hospital mortality (51). Despite the seemingly minor disruption, the phenomenon demands further investigation. It is speculated that the decreased cardiovascular admissions in Japan is a consequence of reluctance to seek medical attention. Media bias and health illiteracy may have been the root causes that incited excessive fear of viral exposure. Undeniably, it has been previously reported that the health literacy of Japanese people is poorer than that of Europeans (52). The public sector must work harder to deliver accurate and reliable health information to its citizens in comprehensible language.

Another aspect of cardiovascular diseases is that they are strongly associated with lifestyles. As the burden to the healthcare system is gradually being alleviated, impacts of post/with-COVID lifestyle changes on cardiovascular health are becoming more of a concern. For example, according to a recent US study that tracked health measures of more than 464,000 participants, blood pressure increased significantly during the pandemic compared to the previous year (53). The finding is alarming, given that even small rises in blood pressure measurements across a large population increase the long-term incidence of adverse cardiovascular events. In Japan, it appears that some people have adapted well to the pandemic and established healthier lifestyles, whereas others have increased their lifetime cardiovascular risk. For instance, in the working population, promotion of remote work and decreased overall work hours have

generally rendered them physically inactive (54). On the contrary, some people have become more health-conscious and developed healthier dietary habits (55). Effects on health parameters such as blood pressure and glycemic control are inconsistent among different studies (56,57). Future studies are awaited to assess the situation in more detail.

Conclusion

While the majority of publications regarding COVID-19 come from outside of Japan, Japanese patients have been underrepresented in most studies so far. There also remain great regional differences in clinical practice surrounding COVID-19. Thus, conclusions drawn from previous reports from different regions of the world may not always hold true for Japanese patients. We have summarized available scientific literature on the clinical characteristics of Japanese COVID-19 patients and the secondary impacts of the pandemic in Japan from a cardiovascular perspective. Studies from Japan were indeed limited, and knowledge gaps remain to be filled. Further research is called for in order to realize more precise approaches specific to Japanese clinical settings.

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