



OPEN Prevalence of erectile dysfunction as long-COVID symptom in hospitalized Japanese patients

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Coronavirus disease-2019 (COVID-19) is associated with a wide range of post-acute sequelae. The prevalence of erectile dysfunction (ED) that developed after COVID-19 and the associated underlying factors were analyzed based on a questionnaire survey, COVID-19 Recovery Study II in Japan. A case-control study was conducted with those with or without ED one and two years hospitalized with COVID-19 between March and September 2021. Six hundred and nine Japanese men, with a median age of 48 years, were analyzed. During the study period, 116 subjects (19.0%) had erectile dysfunction. The patients with ED responded with less subjective awareness of recovery and high breathless and fatigue scores compared to those without ED. The patients with ED also showed higher Hospital Anxiety and Depression Scale-D (depression) and the EuroQol 5-dimensions 5-level scores for pain/discomfort and anxiety/depression scores compared before COVID-19 infection. Sleep disturbance was suggested to be associated with erectile dysfunction using an exploratory clustering analysis in the one-year survey. There were no associations of COVID-19 severity, reinfection, vaccination frequency, antiviral treatment for COVID-19 with the presence of erectile dysfunction. It was considered that mental support for the subject with erectile dysfunction as a long-COVID symptom is warranted.

Keywords Coronavirus disease-2019 (COVID-19), Erectile dysfunction, Post-acute sequelae, Sleep disorder, COVID-19 Recovery Study II (CORES II)

Coronavirus disease-2019 (COVID-19) has spread global, and COVID-19 has been associated with a wide range of post-acute sequelae (PASC)¹. The pathogenesis of PASC was considered to be due to inflammation and thrombosis from severe acute respiratory syndrome virus-2 (SARS-CoV-2) infection² and is known to lead to multiorgan disorders.

In male sexual functions, reduced sperm counts and infertility after COVID-19 have also been reported, with hormonal imbalance suspected as the reason^{3,4}. In COVID-19 patients, vascular endothelial damage due to inflammatory cytokines and hypoxia in the acute phase of COVID-19 lead to the progression of ED⁵. Furthermore, ED is affected by physical stress⁶ and psychological stress⁷. Although vaccination and early treatment may generally reduce the incidence of PASC, it is unknown what is protective measures to prevent the development of ED.

This study aimed to analyze the prevalence of ED among COVID-19 survivors, examining underlying factors based on medical history and questionnaires completed one and two years post-infection.

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Subjects and methods

This study was conducted as a secondary analysis of the CORES II (COVID-19 Recovery Study II), a comprehensive long-term post-morbidity symptom surveillance study of COVID-19 hospitalized cases in Japan. The subjects included in the CORES II study were recruited aged 20 years or older and hospitalized with COVID-19 at 20 hospitals in Japan between 20 April and September 2021, during the fourth and fifth waves of the COVID-19 pandemic in Japan, due to the Alpha or delta variant. Study participants were given written consent, and their clinical course, including basic patient information, symptoms on admission, vital signs, and blood exam data, were obtained during hospitalization; a survey was conducted approximately one year after the COVID-19 infection in August–September 2022 ('one-year survey') and two years after the infection in August–November 2023 ('two-years survey'). Only the first infection was recruited for the subjects infected with COVID-19 multiple times.

The participants themselves completed the survey, which was sent and collected by post. Reminders were sent out to increase the response rate. The questionnaire included items from the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) follow-up protocol⁸. It included the following post-acute symptoms including fever ($>37.5^{\circ}\text{C}$), fatigue, sore throat, nasal discharge, cough, dyspnea, chest pain, palpitations, taste disorders, olfactory disturbances, headache, joint pain and swelling, myalgia, muscle weakness, anorexia, nausea and vomiting, abdominal pain, sleep disturbances, poor concentration, brain fog, hair loss, skin rash, eye symptoms, dizziness and erectile dysfunction (for males only) and menstrual changes (for females only), a total of 26 items were obtained. The definition of PASC was 'symptoms present at three months after infection and lasting for more than two months' based on the World Health Organization (WHO) consensus⁹. For the presence of ED, the question was as follows; "Please mark all symptoms that appeared after the COVID-19 infection that you DID NOT have before the COVID-19 infection. If marked, please answer the appearance date and the duration of the symptom" "For the male patients only: the presence of erectile dysfunction (yes/no) [1] appeared at the time of COVID-19 infection or appeared days (days were required to answer) after the COVID-19 infection [2] remained for (days) after COVID-19 infection or remained at the time of this questionnaire." The diagnosis of ED was based on patients' consciousness of ED according to the guidelines in the European Association of Urology^{10,11}.

The Japanese version of EuroQol 5-dimensions 5-level (EQ5D5L)¹² and Hospital Anxiety Depression Scale (HADS)¹³ were calculated. EQ5D5L and HADS were self-report evaluation for the general quality of life and the mental status of the subjects, which were used also in the PASC in the COVID-19 patients¹¹. Similarly, EQ VAS scored 10–100 on the visual analog scale according to the EQ5D5L, subjective symptoms, history of COVID-19 vaccination, history of reinfection of COVID-19, readmission after hospital discharge, mental health status, lifestyle, and its changes, socio-economic status at the one-year and two-years survey. CORES II study was approved by the Ethics Committee on the National Center for Global Health and Medicine (Approval No. NCGM-S-004471) and was supported by MHLW Research on Emerging and Re-emerging Infectious Diseases and Immunization (Program Grant Number JPMH21HA2011 and JPMH23HA2011). Study participants were given written informed consent. This study was conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki.

As a secondary analysis of the CORES II study, male Japanese cases were selected from subjects who completed the one-year and two-year surveys. Among the underlying conditions taken in the CORES II study, cardiovascular involvement⁶, diabetes¹⁴, and smoking⁶, which were considered responsible for ED, were included in the analysis as underlying conditions. This sub-study of the CORES II study was approved by Yokohama City University ethical board. (The approval number was F230900032).

Statistical analysis

Continuous data are presented as means and 95% confidence intervals (CIs) or medians and interquartile ranges (IQRs). Categorical data are presented as numbers and percentages. Data were analyzed using a two-tailed Mann–Whitney U-test for comparisons of two continuous variables and Fisher's exact test for comparisons of categorical data. Statistical analyses were performed with Prism 10 (Version 10.2.2 (341), GraphPad Software, Boston, MA, USA). Hierarchical cluster analysis was performed using Mac Toukei-Kaiseiki Ver. 3.0 software (Esumi, Tokyo, Japan) for exploratory survey of the relationship between long-COVID symptoms. *P* values < 0.05 were considered statistically significant.

Results

Six hundred nine cases were analyzed. The median age was 56 [IQR, 48–63] years old. COVID-19 infection was from 25 March 2021 to 21 September 2021. Of the 609 cases, 116 (19.0%) reported ED symptoms at one-year, two-year, or both surveys. In the one-year survey, 86 respondents reported symptoms of ED, and in the two-year survey, 70 respondents reported symptoms of ED. Forty had symptoms at both one- and two-year surveys. Seventy-nine (68.1%) subjects reported developing ED within 28 days of COVID-19 infection, and 6 (4.3%) developed ED symptoms after 2–5 months after COVID-19 infection. Thirty subjects (25.2%) reported ED symptoms in the two-year survey, while there was no mention of ED symptoms in the one-year survey. Of the 116 patients with ED, 29 (25.0%) showed improvement in ED symptoms during the two-year study period. Amelioration of ED symptoms occurring within one month (15 patients), two months (1 patient), four months (1 patient), and within one year (12 patients). Fifty-seven patients (49.1%) had no apparent improvement of symptoms at two years when the questionnaire was collected. In 30 cases, the time of symptom resolution was not available.

	1 year after COVID-19			2 years after COVID-19		
	ED (+)	ED (–)	P value	ED (+)	ED (–)	P value
Number of subjects	86	523		70	539	
age	55 [49, 62]	56.5 [48, 64]	0.741	61 [54, 73]	55 [48, 63]	<0.001 *
BMI \geq 25	48 (56.4)	297 (55.6)	0.907	38 (54.3)	307 (57.0)	0.702
BMI \geq 30	22 (26.2)	98 (18.7)	0.145	13 (18.6)	107 (19.9)	0.874
admission to ICU	45 (52.3)	217 (41.5)	0.078	37 (52.9)	225 (41.7)	0.095
oxygen administration	80 (93.0)	445 (85.1)	0.062	65 (92.9)	460 (85.3)	0.098
Underlying conditions						
Hypertension	3 (3.5)	21 (4.0)	1.0	4 (5.7)	20 (3.7)	0.507
Diabetes	2 (2.3)	7 (1.3)	0.370	3 (4.3)	6 (1.1)	0.074
Current smoker	44 (51.2)	267 (51.1)	1.0	34 (48.6)	277 (51.4)	0.704
Treatment to COVID-19†	44 (51.2)	310 (59.3)	0.160	36 (51.4)	318 (59.0)	0.248
Reinfection of COVID-19	4 (4.7)	27 (5.2)	1.0	2 (2.9)	29 (5.4)	0.563
vaccine prior to COVID-19 infection	41 (47.7)	221 (42.3)	0.350	35 (50.0)	227 (42.1)	0.248

Table 1. Underlying conditions of subjects with or without erectile dysfunction at the one-year and two years after COVID-19. Data were shown in numbers and percentages. *Statistically significant. †Treatment included remdesivir, sotrovimab or casirivimab/imdevimab. ED, erectile dysfunction; BMI, body mass index; ICU, intensive care unit; COVID-19, coronavirus disease-2019.

	1 year after COVID-19			2 years after COVID-19		
	Patients with ED	Patients without ED	P value	Patients with ED	Patients without ED	P value
Awareness of recovery (scored 1 to 5)	2 [2, 4]	4 [2, 4]	<0.001*	2 [2, 4]	4 [2, 4]	<0.001*
Breathless (scored 1 to 5)	2 [1, 2]	1 [1, 2]	<0.001*	2 [2, 3]	1 [1, 2]	<0.001*
Fatigue (scored 1 to 5)	2 [1, 2]	1 [1, 2]	<0.001*	2 [1, 2]	1 [1, 2]	<0.001*
Overall wealthiness (scored 10 to 100)	70 [50, 80]	80 [65, 90]	<0.001*	70 [60, 85]	80 [70, 90]	<0.001*
HADS-A	5 [2, 9]	3 [1, 6]	<0.001*	5 [1.5, 8]	3 [1, 6]	0.083
HADS-D	6 [3, 10]	4 [1, 7]	<0.001*	7.5 [5, 10]	4 [1, 7]	<0.001*

Table 2. The self-reported recovery of the subjects who participated in this study one year and two years after COVID-19. Data were shown in median and interquartile ranges. *Statistically significant. COVID-19, coronavirus disease-2019; ED, erectile dysfunction; HADS, hospital anxiety and depression scale.

Underlying conditions appeared in the subjects with ED symptom

Table 1 shows the characteristics of subjects with ED symptoms at the one- and two-year surveys. The subjects having ED had significantly lower awareness of recovery (scored from 1 to 5), breathlessness (1–5), and fatigue (1–5) in the one- and two-year surveys. Age was significantly higher in the two-year survey, and HADS-D was significantly lower in the ED group in the one-year survey.

The self-reported recovery of the patients one year and two years after COVID-19, developing ED or not, were shown in Table 2. The patients who developed ED reported were less conscious of recovery, having breathless, fatigue, overall wealthiness, and having lower HADS-D score in both one- and two-year questionnaire. The patients with ED were found to have lower HADS-A compared those without ED in the one-year questionnaire.

The association of other post-acute symptoms with erectile dysfunction

Eighty-six patients who developed ED symptoms in the one-year survey had 9 [IQR, 7–12] symptoms, and 70 subjects with ED symptoms in the two-year survey had 4 [IQR, 2–7] other post-acute symptoms. A hierarchical cluster analysis was performed to explore the association of other post-acute sequelae with ED symptom. The target number of clusters was set at five, as previous studies categorized post-acute symptoms into five clusters^{15,16}. ED, sleep disorder, hair loss, skin rash, and eye symptom were classified in the same symptom cluster in the one-year survey. A similar exploratory analysis in the two-year survey showed that sore throat, rhinorrhea, cough, arthralgia, myalgia, hair loss, skin rash, and ED were classified in the same symptom cluster subgroup (Fig. 1). The symptoms of hair loss and skin rash were presented in the same cluster subgroup of ED at both surveys.

EQ-5D-5L scores in the group with concomitant ED

The characteristic EQ-5D-5L scores of participants with ED were compared between groups with and without ED (Fig. 2). Of the five EQ-5D-5L items, the degree of mobility (Mo) and personal care (Sc) did not differ between groups with and without ED. However, usual activities (Ua) showed more significant deterioration among those

(A) 1 year survey

cluster 1	cluster 2	cluster 3	cluster 4	cluster 5
sore throat	chest pain	sleep disorder	fever	ageusia
rhinorea	palpitation	hair loss	malaise	anosmia
cough	muscle weak	skin rash	shortness of breath	
headache	decreased concent	eye symptom		
arthralgia	brain fog	erectile dysfunction		
myalgia	dizziness			
anorexia				
vomiting				
abdominal pain				

(B) 2 year survey

cluster 1	cluster 2	cluster 3	cluster 4	cluster 5
sore throat	malaise	fever	chest pain	ageusia
rhinorea	shortness of breath	anorexia	palpitation	anosmia
cough	muscle weak	vomiting	headache	
arthralgia	sleep disorder	abdominal pain	brain fog	
myalgia	decreased concent	dizziness		
hair loss	eye symptoms			
skin rash				
erectile dysfunction				

Fig. 1. Hierarchical cluster analysis of the post-acute symptoms in the 1 year and 2 years survey.

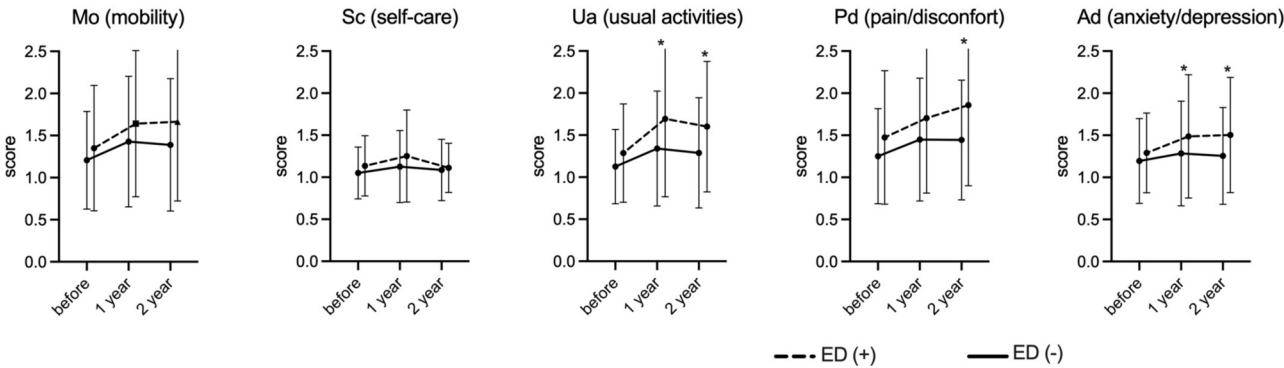


Fig. 2. Changes in the Japanese version of the EQ-5D-5L scores in the patients with ED (dotted line) and without ED (solid line), collected before, one year, and two years after COVID-19 infection. *Statistically significant.

with ED compared with those without ED (0.407 ± 0.788 vs. 0.212 ± 0.586 , $P=0.015$) at one-year and two-year surveys (0.0520 ± 0.583 vs. 0.271 ± 0.721 , $P=0.002$). Pain/discomfort (Pd) was 0.500 ± 1.046 vs. 0.178 ± 0.683 ($P=0.003$), significantly higher in the two-year survey. Anxiety/depression (Ad) scores were significantly worse in one-year (0.209 ± 0.671 vs. 0.0784 ± 0.525 , $P=0.033$) and in a two-year survey (0.271 ± 0.721 vs. 0.052 ± 0.583 , $P=0.002$).

Discussions

The present study showed that 19% of the male patients admitted by COVID-19 developed erectile dysfunction one and two year after COVID-19 in the Japanese cohort. A strong association between ED symptoms and mental distress was suspected. Generally, the prevalence of erectile dysfunction (ED) in men aged 50–59 years was reported to be 18%¹⁷, and increased up to 37 percent in those aged 70–75 years¹⁸. In this study, while the presence of ED symptoms before COVID-19 was not assessed, a certain number of patients recovered from COVID-19 became aware of erectile dysfunction. In the guidelines, the etiology of ED was divided into two categories: primary organic and primary psychogenic¹⁰. For the organic cause, no significant association was found for the age, smoking habit, diabetes, hypertension, dyslipidemia, and obesity, which were generally known as a risk factor for ED in a general population⁸. However, a strong association existed between the psychogenic aspect and ED after COVID-19. The patients who developed ED symptoms reported worsened general conditions and less awareness of recovery. The HADS-A and HADS-D score, which reflects mental quality of life, was also significantly higher in the patients with ED symptom. In patients admitted to the ICU due to severe diseases, a HADS-A ≥ 8 has been used as a guide for anxiety indicators¹⁹. In this study, the median score in the patients with ED was 5, suggesting that those with a lower HADS-A score may be associated with ED symptoms. As such, depression was reported to correlate with ED²⁰. A depression score of HADS-D ≥ 7 is used as an indicator²¹, but lower scores were shown to be associated with developing ED symptoms in COVID-19 patients. In addition, the scores of EQ-5D-5L anxiety/depression (Ad), usual activity (Ua), and pain/discomfort (Pd) were significantly worsened after COVID-19 infection in the patients with ED symptoms compared with those without ED.

It has been suggested that post-acute symptoms can be classified into several clusters according to symptoms. However, changes in sexual desire or capacity did not appear to be strongly associated with other post-acute sequelae in a large previous study¹⁶. Our study suspected an association with sleep disturbance in a one-year survey. It has been reported that the risk of developing ED is approximately three times higher in the presence of sleep disturbance²². Depression, anxiety, and sleep disturbance after COVID-19 infection were suggested characteristics in the patients developing ED.

Long-COVID (or post-acute sequelae) was found in 15% of infected individuals in the origin strain²³. Its frequency has been reported higher in multiple COVID-19 infections²⁴. Conversely, vaccination against COVID-19 was reported protective role for developing long-COVID²⁵. Neuropsychiatric post-acute symptoms such as brain fog and memory impairment were reported to be less common in patients with vaccination²⁶. Early antiviral treatment was reported to possibly reduce the risk of developing long-COVID and readmission with post-acute sequelae²⁷. However, the present study does not suggest a suppressive effect of vaccination or early treatment on developing ED.

Regarding ED symptoms after COVID-19, supportive care and management for depression and sleep disturbances may be more critical. This study did not enquire about ED-specific treatment. One person in the one-year survey and six in the two-year survey had only ED as a post-acute symptom; none of them had seen a doctor or received treatment for ED. In a meta-analysis, the presence of ED was strongly associated with the risk of developing depression (odds ratio 1.39), and depression was associated with a higher risk of developing ED (odds ratio 2.92). The American Urological Association recommends that all men who present with ED undergo an evaluation for potential psychosocial factors (including depression and anxiety)²⁰. The CORES II study also collected information on treatments such as rehabilitation, psychological counseling, and pharmaceutical treatment. However, none of the patients with ED responded to receiving any of these services. Given that ED is strongly associated with depression and anxiety, it is suggested that non-pharmacological interventions possibly improve symptoms. It has been noted that a reduction in the serotonergic transmission system may occur in long-COVID, and serotonin may be a therapeutic option for Long-COVID²⁸. However, serotonin itself inhibits dopamine secretion and causes drug-induced ED, so its use in the treatment of ED as a long-COVID may be controversial.

This study had limitations. This study was a retrospective analysis based self-report questionnaire, thus possibly affected by recall biases. The study did not investigate specific assessment and treatment of ED. For example, this study did not assess patients with the international index of erectile function (IIEF), which helps assess treatment efficacy²⁹. Similarly, the nature of erectile dysfunction, such as severity, nocturnal or morning erection, sexual intercourse erection, or masturbation erection, and the intercourse frequency of those have not been investigated. In this study, we analyzed the subjects admitted to the hospital during the acute phase of COVID-19. It has been reported that the prevalence of post-acute sequelae was higher in hospitalized cases than in outpatients, even in Japanese patients³⁰. Because we are analyzing hospitalized patients in COVID-19, there is a bias toward age groups at risk of hospitalization. In addition, the frequency of post-acute symptoms was lower at 4.3% in outpatients in the Omicron variant era compared to the origin and delta strains, the characteristics of ED symptoms with Omicron strains will be analyzed in another study³¹.

In summary, 19% of COVID-19 hospitalized cases of the original and delta strain COVID-19 showed ED symptom up to 2 years after COVID-19 infection. Anxiety, depression, and sleep disturbances after the post-acute phase of COVID-19 infection suggest that supportive care for the symptoms and quality of life is expected for ED as Long-COVID.

Data availability

The data that support the findings of this study are available from the corresponding author (HK) upon reasonable request.

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Author contributions

H.K. and N.I. contributed to the study design. H.K. performed data collection, statistical analysis, interpretation of data, and drafting and editing the manuscript. H.S., K.O., Y.T., T.Harada, T.Hattori, M.H., Y.M., M.H., and A.I. contributed to data collection. M.K. contributed to the interpretation of data, and editing the manuscript. H.I. and S.F. contributed to the supervision of the analysis. All authors made critical revisions to the manuscript for important intellectual content and approved the final manuscript. All authors meet the ICMJE authorship criteria.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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The COVID-19 Recovery Study II Group

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