

Supplementary Materials

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Table S1. Comparison of symptoms between coronavirus disease 2019 (COVID-19) patients and test-negative controls aged ≥ 18 years who were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at a clinic in Tokyo, Japan, between January 2022 and January 2023

Symptoms, no. (%)	Acute phase of illness			Month 1			Month 3			Month 6		
	COVID-19 patients (n=302)	Test-negative controls (n=77)	p-value*	COVID-19 patients (n=302)	Test-negative controls (n=77)	p-value*	COVID-19 patients (n=302)	Test-negative controls (n=77)	p-value*	COVID-19 patients (n=249)	Test-negative controls (n=59)	p-value*
Any	302 (100)	77 (100)	NA	103 (34.1)	7 (9.1)	<0.001	60 (19.9)	7 (9.1)	0.029	35 (14.1)	4 (6.8)	0.190
Fever	253 (83.8)	30 (39.0)	<0.001	5 (1.7)	1 (1.3)	1.000	3 (1.0)	1 (1.3)	1.000	2 (0.8)	0	1.000
Fatigue	231 (76.5)	47 (61.0)	0.009	27 (8.9)	1 (1.3)	0.025	14 (4.6)	0	0.083	10 (4.0)	0	0.218
Post-exertional malaise	49 (16.2)	3 (3.9)	0.003	15 (5.0)	0	0.048	9 (3.0)	0	0.214	5 (2.0)	0	0.587
Joint and muscle pain	92 (30.5)	6 (7.8)	<0.001	5 (1.7)	0	0.588	4 (1.3)	0	0.586	4 (1.6)	0	1.000
Dizziness	13 (4.3)	1 (1.3)	0.317	9 (3.0)	0	0.214	4 (1.3)	0	0.586	3 (1.2)	0	1.000
Cough	180 (59.6)	10 (13.0)	<0.001	38 (12.6)	0	<0.001	6 (2.0)	0	0.606	4 (1.6)	0	1.000
Shortness of breath	33 (10.9)	0	0.001	8 (2.6)	1 (1.3)	0.693	6 (2.0)	1 (1.3)	1.000	3 (1.2)	1 (1.7)	0.575
Sore throat	208 (68.9)	17 (22.1)	<0.001	15 (5.0)	1 (1.3)	0.211	2 (0.7)	0	1.000	2 (0.8)	0	1.000
Headache	131 (43.4)	15 (19.5)	<0.001	10 (3.3)	0	0.224	7 (2.3)	0	0.353	5 (2.0)	0	0.587
Nasal congestion	123 (40.7)	13 (16.9)	<0.001	10 (3.3)	2 (2.6)	1.000	4 (1.3)	2 (2.6)	0.352	3 (1.2)	2 (3.4)	0.245
Taste or smell disorder	41 (13.6)	1 (1.3)	0.001	14 (4.6)	0	0.083	9 (3.0)	0	0.214	5 (2.0)	0	0.587
Hair loss	0	1 (1.3)	0.203	16 (5.3)	2 (2.6)	0.547	13 (4.3)	2 (2.6)	0.745	2 (0.8)	0	1.000
Chest pain	11 (3.6)	0	0.130	3 (1.0)	1 (1.3)	1.000	2 (0.7)	1 (1.3)	0.495	1 (0.4)	1 (1.7)	0.347
Heart palpitations	8 (2.6)	0	0.368	7 (2.3)	1 (1.3)	1.000	5 (1.7)	1 (1.3)	1.000	4 (1.6)	1 (1.7)	1.000
Stomach pain	6 (2.0)	0	0.606	4 (1.3)	1 (1.3)	1.000	3 (1.0)	1 (1.3)	1.000	1 (0.4)	1 (1.7)	0.347
Nausea	8 (2.6)	0	0.368	1 (0.3)	0	1.000	1 (0.3)	0	1.000	0	0	NA

Diarrhea	18 (6.0)	6 (7.8)	0.600	2 (0.7)	2 (2.6)	0.185	2 (0.7)	2 (2.6)	0.185	2 (0.8)	2 (3.4)	0.167
Difficulty concentrating	14 (4.6)	0	0.083	15 (5.0)	0	0.048	10 (3.3)	0	0.224	7 (2.8)	0	0.354
Depression	26 (8.6)	1 (1.3)	0.024	25 (8.3)	2 (2.6)	0.132	16 (5.3)	0	0.050	13 (5.2)	0	0.140
Sleep disorder	15 (5.0)	1 (1.3)	0.211	12 (4.0)	0	0.136	12 (4.0)	0	0.136	11 (4.4)	0	0.132

Abbreviations: COVID-19, coronavirus disease 2019; NA, not applicable

*Fisher's exact test was performed to compare the percentage of individuals reporting symptoms in the acute phase, month 1, 3, and 6 after testing, between COVID-19 patients and test-negative controls for SARS-CoV-2.

Table S2. Comparison of EQ-5D-5L utility scores between coronavirus disease 2019 (COVID-19) patients and test-negative controls aged ≥18 years who were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at a clinic in Tokyo, Japan, between January 2022 and January 2023

	Acute phase of illness			Month 1 to 3			Month 3 to 6			Month 6 to 12		
	COVID-19 patients (n=287)	Test-negative controls (n=67)	p-value*	COVID-19 patients (n=268)	Test-negative controls (n=58)	p-value*	COVID-19 patients (n=296)	Test-negative controls (n=74)	p-value*	COVID-19 patients (n=249)	Test-negative controls (n=59)	p-value*
EQ-5D-5L utility score												
Mean (95% CI)	0.615 (0.586–0.645)	0.874 (0.826–0.921)	<0.001	0.907 (0.888–0.925)	0.976 (0.956–0.996)	0.001	0.961 (0.948–0.974)	0.994 (0.986–1.000)	0.015	0.970 (0.958–0.982)	0.995 (0.987–1.000)	0.056
Percentage of individuals without any problems in each or any of the five dimensions of the EQ-5D, no (%)												
Mobility	82 (28.6)	50 (74.6)	<0.001	221 (82.5)	53 (91.4)	0.114	279 (94.3)	74 (100)	0.030	239 (96.0)	59 (100)	0.218
Self-care	144 (50.2)	56 (83.6)	<0.001	253 (94.4)	57 (98.3)	0.322	294 (99.3)	74 (100)	1.000	246 (98.8)	59 (100)	1.000
Usual activities	56 (19.5)	47 (70.1)	<0.001	209 (78.0)	56 (96.6)	<0.001	278 (93.9)	74 (100)	0.030	237 (95.2)	59 (100)	0.132
Pain/Discomfort	46 (16.0)	44 (65.7)	<0.001	195 (72.8)	55 (94.8)	<0.001	272 (91.9)	73 (98.6)	0.038	232 (93.2)	58 (98.3)	0.214
Anxiety/Depression	156 (54.4)	57 (85.1)	<0.001	216 (80.6)	55 (94.8)	0.006	261 (88.2)	71 (95.9)	0.054	224 (90.0)	57 (96.6)	0.127

Abbreviations: COVID-19, coronavirus disease 2019; CI, confidence interval

*A t-test was used for analyzing continuous variables, while Fisher's exact test was employed for categorical variables.

Table S3. Comparison of symptoms between male and female coronavirus disease 2019 (COVID-19) patients aged ≥18 years who were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at a clinic in Tokyo, Japan, between January 2022 and January 2023

Symptoms, no. (%)	Acute phase of illness			Month 1			Month 3			Month 6		
	Men (n=118)	Women (n=184)	p-value*	Men (n=118)	Women (n=184)	p-value*	Men (n=118)	Women (n=184)	p-value*	Men (n=98)	Women (n=151)	p-value*
Any	118 (100)	184 (100)	NA	37 (31.4)	66 (35.9)	0.457	20 (16.9)	40 (21.7)	0.375	10 (10.2)	25 (16.6)	0.193
Fever	100 (84.7)	153 (83.2)	0.752	0	5 (2.7)	0.161	0	3 (1.6)	0.283	0	2 (1.3)	0.521
Fatigue	79 (66.9)	152 (82.6)	0.002	5 (4.2)	22 (12.0)	0.023	3 (2.5)	11 (6.0)	0.262	2 (2.0)	8 (5.3)	0.323
Post-exertional malaise	16 (13.6)	33 (17.9)	0.341	5 (4.2)	10 (5.4)	0.789	4 (3.4)	5 (2.7)	0.740	2 (2.0)	3 (2.0)	1.000
Joint and muscle pain	29 (24.6)	63 (34.2)	0.095	2 (1.7)	3 (1.6)	1.000	2 (1.7)	2 (1.1)	0.645	2 (2.0)	2 (1.3)	0.647
Dizziness	1 (0.8)	12 (6.5)	0.019	1 (0.8)	8 (4.3)	0.095	0	4 (2.2)	0.159	0	3 (2.0)	0.281
Cough	66 (55.9)	114 (62.0)	0.337	13 (11.0)	25 (13.6)	0.595	2 (1.7)	4 (2.2)	1.000	1 (1.0)	3 (2.0)	1.000
Shortness of breath	6 (5.1)	27 (14.7)	0.008	2 (1.7)	6 (3.3)	0.489	2 (1.7)	4 (2.2)	1.000	2 (2.0)	1 (0.7)	0.563
Sore throat	79 (66.9)	129 (70.1)	0.611	3 (2.5)	12 (6.5)	0.175	0	2 (1.1)	0.522	0	2 (1.3)	0.521
Headache	41 (34.7)	90 (48.9)	0.017	4 (3.4)	6 (3.3)	1.000	3 (2.5)	4 (2.2)	1.000	1 (1.0)	4 (2.6)	0.651
Nasal congestion	38 (32.2)	85 (46.2)	0.017	4 (3.4)	6 (3.3)	1.000	3 (2.5)	1 (0.5)	0.303	2 (2.0)	1 (0.7)	0.563
Taste or smell disorder	8 (6.8)	33 (17.9)	0.006	6 (5.1)	8 (4.3)	0.785	4 (3.4)	5 (2.7)	0.740	2 (2.0)	3 (2.0)	1.000
Hair loss	0	0	NA	4 (3.4)	12 (6.5)	0.298	4 (3.4)	9 (4.9)	0.773	0	2 (1.3)	0.521
Chest pain	1 (0.8)	10 (5.4)	0.055	1 (0.8)	2 (1.1)	1.000	1 (0.8)	1 (0.5)	1.000	1 (1.0)	0	0.394
Heart palpitations	4 (3.4)	4 (2.2)	0.716	4 (3.4)	3 (1.6)	0.438	2 (1.7)	3 (1.6)	1.000	2 (2.0)	2 (1.3)	0.647
Stomach pain	2 (1.7)	4 (2.2)	1.000	1 (0.8)	3 (1.6)	1.000	1 (0.8)	2 (1.1)	1.000	0	1 (0.7)	1.000
Nausea	3 (2.5)	5 (2.7)	1.000	1 (0.8)	0	0.391	1 (0.8)	0	0.391	0	0	NA

Diarrhea	5 (4.2)	13 (7.1)	0.456	1 (0.8)	1 (0.5)	1.000	1 (0.8)	1 (0.5)	1.000	1 (1.0)	1 (0.7)	1.000
Difficulty concentrating	2 (1.7)	12 (6.5)	0.089	1 (0.8)	14 (7.6)	0.007	1 (0.8)	9 (4.9)	0.095	1 (1.0)	6 (4.0)	0.251
Depression	7 (5.9)	19 (10.3)	0.212	4 (3.4)	21 (11.4)	0.017	4 (3.4)	12 (6.5)	0.298	3 (3.1)	10 (6.6)	0.258
Sleep disorder	4 (3.4)	11 (6.0)	0.419	2 (1.7)	10 (5.4)	0.136	2 (1.7)	10 (5.4)	0.136	1 (1.0)	10 (6.6)	0.054

Abbreviations: COVID-19, coronavirus disease 2019; NA, not applicable

*Fisher's exact test was performed to compare the percentage of individuals reporting symptoms in the acute phase, month 1, 3, and 6 after testing between male and female COVID-19 patients.

Table S4. Comparison of EQ-5D-5L utility scores between male and female coronavirus disease 2019 (COVID-19) patients aged ≥18 years who were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at a clinic in Tokyo, Japan, between January 2022 and January 2023

	Acute phase of illness			Month 1 to 3			Month 3 to 6			Month 6 to 12		
	Men (n=110)	Women (n=177)	p-value*	Men (n=105)	Women (n=163)	p-value*	Men (n=114)	Women (n=182)	p-value*	Men (n=98)	Women (n=151)	p-value*
EQ-5D-5L utility score												
Mean (95% CI)	0.672 (0.628–0.715)	0.581 (0.541–0.620)	0.003	0.945 (0.927–0.963)	0.882 (0.855–0.910)	0.001	0.985 (0.976–0.995)	0.946 (0.926–0.966)	0.003	0.990 (0.983–0.998)	0.957 (0.937–0.976)	0.008
Percentage of individuals without any problems in each or any of the five dimensions of the EQ-5D, no (%)												
Mobility	40 (36.4)	42 (23.7)	0.023	94 (89.5)	127 (77.9)	0.020	112 (98.2)	167 (91.8)	0.020	98 (100)	141 (93.4)	0.007
Self-care	63 (57.3)	81 (45.8)	0.069	103 (98.1)	150 (92.0)	0.053	114 (100)	180 (98.9)	0.525	98 (100)	148 (98.0)	0.281
Usual activities	29 (26.4)	27 (15.3)	0.031	90 (85.7)	119 (73.0)	0.016	113 (99.1)	165 (90.7)	0.002	97 (99.0)	140 (92.7)	0.031
Pain/Discomfort	23 (20.9)	23 (13.0)	0.097	84 (80.0)	111 (68.1)	0.036	111 (97.4)	161 (88.5)	0.007	96 (98.0)	136 (90.1)	0.019
Anxiety/Depression	64 (58.2)	92 (52.0)	0.331	94 (89.5)	122 (74.8)	0.003	108 (94.7)	153 (84.1)	0.005	93 (94.9)	131 (86.8)	0.051

Abbreviations: COVID-19, coronavirus disease 2019; CI, confidence interval

*A t-test was used for analyzing continuous variables, while Fisher's exact test was employed for categorical variables.

Table S5. Variance Inflation Factor (VIF) values for explanatory variables in the linear mixed regression analysis of the mean EQ-5D-5L utility score among patients aged ≥ 18 years who were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at a clinic in Tokyo, Japan, between January 2022 and January 2023

Variables	Multivariable regression model	Multivariable regression model with interaction terms
	Variance Inflation Factor values	
Female sex	1.04	5.48
Age	1.43	1.45
Presence of underlying medical condition	1.14	1.14
Timing		
Month 1 to 3	1.46	8.01
Month 3 to 6	1.49	7.67
Month 6 to 12	1.46	7.67
Positive test result for SARS-CoV-2	1.10	5.26
The number of COVID-19 vaccines		
1	1.06	1.07
2	2.53	2.54
3	2.56	2.56
4	1.93	1.93
5	1.29	1.31
Sex, test result for SARS-CoV-2		
Female, positive		6.98
Timing, test result for SARS-CoV-2		
Month 1 to 3, positive		8.51
Month 3 to 6, positive		8.18
Month 6 to 12, positive		8.06

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019.

Table S6. Results of generalized estimating equations for the mean EQ-5D-5L utility score among patients aged ≥ 18 years who were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at a clinic in Tokyo, Japan, between January 2022 and January 2023

Variables	Multivariable model		Multivariable model with interaction terms	
	β (95% CI)	p-value	β (95% CI)	p-value
Sex				
Men	Reference		Reference	
Women	-0.050 (-0.080 to -0.020)	0.001	0.043 (0.006 to 0.080)	0.023
Age	0.0003 (-0.001 to 0.002)	0.657	0.0006 (-0.0009 to 0.002)	0.416
Presence of underlying medical condition	-0.0005 (-0.046 to 0.045)	0.984	-0.001 (-0.046 to 0.043)	0.951
Timing				
Acute phase of illness	Reference		Reference	
Month 1 to 3	0.339 (0.302 to 0.376)	<0.001	0.117 (0.066 to 0.167)	<0.001
Month 3 to 6	0.385 (0.346 to 0.425)	<0.001	0.131 (0.078 to 0.184)	<0.001
Month 6 to 12	0.397 (0.356 to 0.438)	<0.001	0.133 (0.080 to 0.187)	<0.001
Test result for SARS-CoV-2				
Negative	Reference		Reference	
Positive	-0.113 (-0.144 to -0.082)	<0.001	-0.275 (-0.350 to -0.200)	<0.001
The number of COVID-19 vaccines				
0	Reference		Reference	
1	-0.054 (-0.302 to 0.195)	0.672	-0.078 (-0.314 to 0.158)	0.519
2	0.008 (-0.043 to 0.060)	0.754	0.001 (-0.052 to 0.054)	0.968
3	0.024 (-0.027 to 0.076)	0.356	0.025 (-0.028 to 0.077)	0.357
4	0.060 (-0.002 to 0.120)	0.051	0.062 (0.0007 to 0.124)	0.047
5	0.078 (-0.002 to 0.158)	0.057	0.069 (-0.006 to 0.144)	0.073
Sex, test result for SARS-CoV-2				
Female, positive			-0.118 (-0.169 to -0.067)	<0.001
Timing, test result for SARS-CoV-2				
Month 1 to 3, positive			0.280 (0.214 to 0.346)	<0.001
Month 3 to 6, positive			0.320 (0.251 to 0.390)	<0.001
Month 6 to 12, positive			0.330 (0.259 to 0.400)	<0.001

Abbreviations: CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019.

Table S7. Sensitivity analyses for missing data in the linear mixed regression model with interaction terms for the mean EQ-5D-5L utility score among patients aged ≥ 18 years who were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at a clinic in Tokyo, Japan, between January 2022 and January 2023

Results of complete case analysis			
Variables	Multivariable regression model with interaction terms		
	β (95% CI)		p-value
Sex			
Men	Reference		
Women	0.032 (-0.045 to 0.110)		0.411
Age	0.001 (-0.001 to 0.002)		0.264
Presence of underlying medical condition	-0.008 (-0.056 to 0.039)		0.728
Timing			
Acute phase of illness	Reference		
Month 1 to 3	0.125 (0.072 to 0.178)		<0.001
Month 3 to 6	0.144 (0.091 to 0.196)		<0.001
Month 6 to 12	0.144 (0.092 to 0.197)		<0.001
Test result for SARS-CoV-2			
Negative	Reference		
Positive	-0.186 (-0.257 to -0.115)		<0.001
The number of COVID-19 vaccines			
0	Reference		
1	-0.115 (-0.289 to 0.059)		0.197
2	-0.006 (-0.053 to 0.042)		0.818
3	0.007 (-0.041 to 0.055)		0.774
4	0.041 (-0.038 to 0.121)		0.309
5	NA		
Sex, test result for SARS-CoV-2			
Female, positive	-0.093 (-0.178 to -0.008)		0.032
Timing test result for SARS-CoV-2			
Month 1 to 3, positive	0.187 (0.130 to 0.245)		<0.001
Month 3 to 6, positive	0.216 (0.159 to 0.274)		<0.001
Month 6 to 12, positive	0.227 (0.170 to 0.285)		<0.001
Results of the LOCF method			
Variables	Multivariable regression model with interaction terms		
	β (95% CI)		p-value
Sex			

Men	Reference	
Women	0.029 (-0.023 to 0.081)	0.275
Age	0.0003 (-0.001 to 0.001)	0.583
Presence of underlying medical condition	0.003 (-0.033 to 0.038)	0.873
Timing		
Acute phase of illness	Reference	
Month 1 to 3	0.101 (0.060 to 0.142)	<0.001
Month 3 to 6	0.120 (0.080 to 0.160)	<0.001
Month 6 to 12	0.120 (0.080 to 0.161)	<0.001
Test result for SARS-CoV-2		
Negative	Reference	
Positive	-0.201 (-0.253 to -0.149)	<0.001
The number of COVID-19 vaccines		
0	Reference	
1	-0.046 (-0.176 to 0.084)	0.487
2	0.010 (-0.027 to 0.047)	0.600
3	0.021 (-0.017 to 0.058)	0.274
4	0.051 (-0.0001 to 0.101)	0.051
5	0.056 (-0.040 to 0.153)	0.252
Sex, test result for SARS-CoV-2		
Female, positive	-0.087 (-0.145 to -0.029)	0.003
Timing test result for SARS-CoV-2		
Month 1 to 3, positive	0.176 (0.130 to 0.221)	<0.001
Month 3 to 6, positive	0.226 (0.181 to 0.271)	<0.001
Month 6 to 12, positive	0.236 (0.191 to 0.281)	<0.001

In the primary analysis using a linear mixed regression model, no imputation was performed for missing data, and the analyses were conducted using all available data. To ensure the robustness of our findings, sensitivity analyses were carried out using (1) complete case analysis and (2) the last observation carried forward (LOCF) method.

Abbreviations: CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; NA, not applicable; LOCF, last observation carried forward.

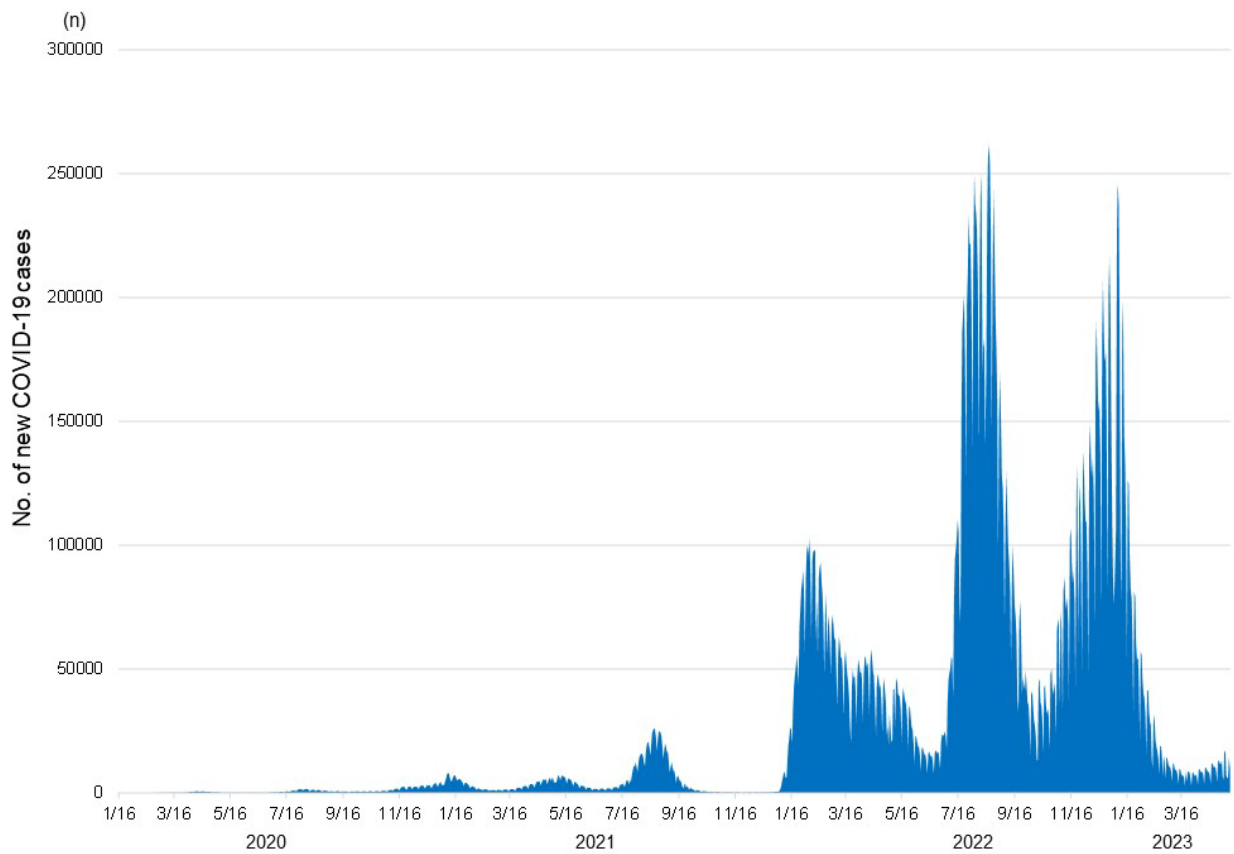


Figure S1. Number of confirmed coronavirus disease 2019 (COVID-19) cases in Japan from March 2020, through March 2023

X-axis: calendar day; Y-axis: the number of new COVID-19 cases per day.

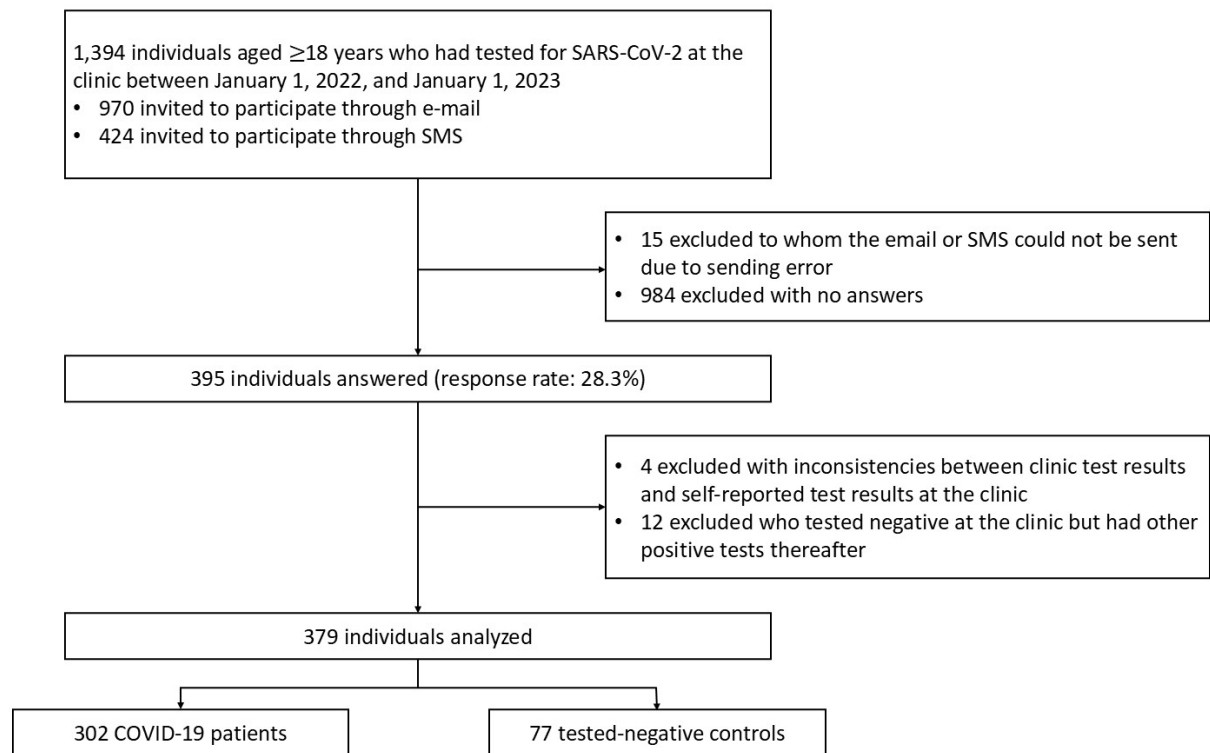


Figure S2. Study flowchart

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SMS, short message service

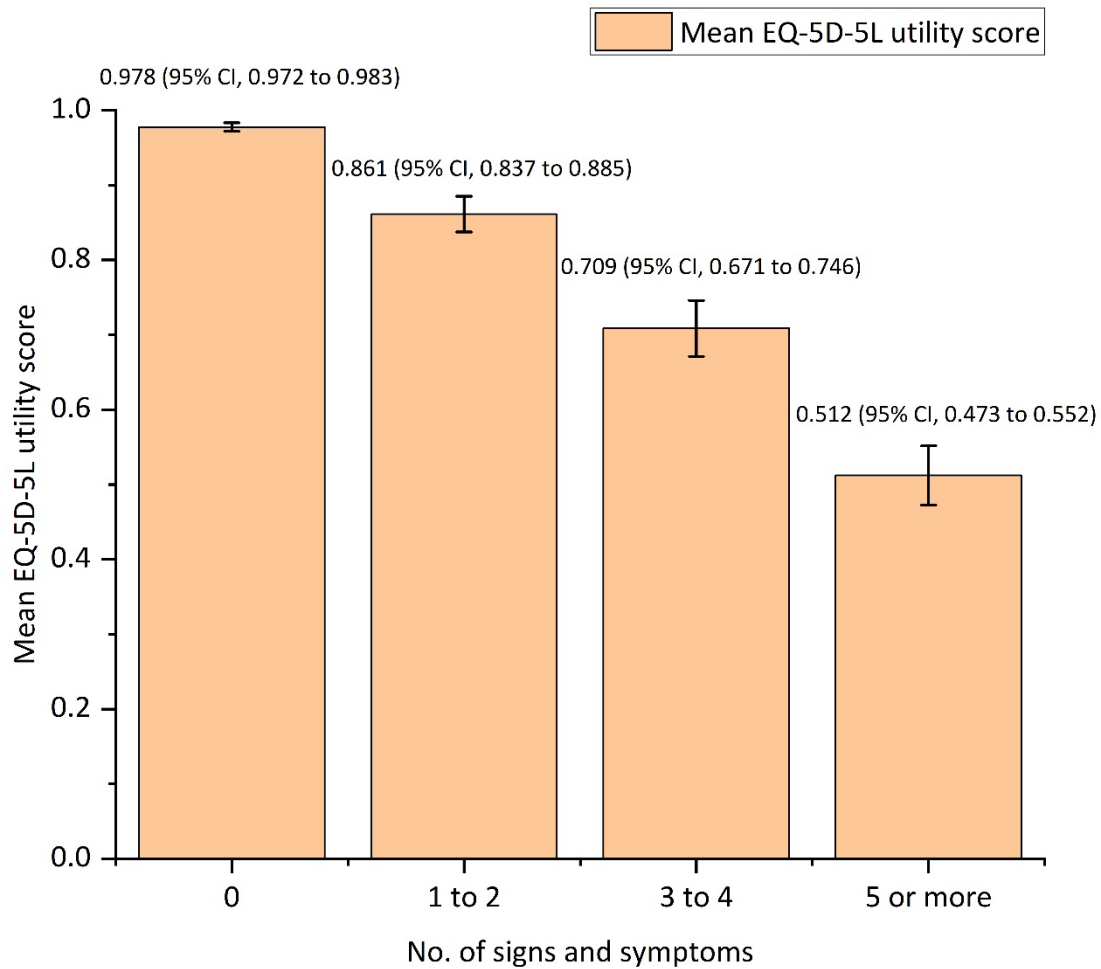


Figure S3. Mean EQ-5D-5L utility scores with 95% confidence intervals according to number of signs and symptoms among coronavirus disease 2019 (COVID-19) patients aged ≥ 18 years who were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at a clinic in Tokyo, Japan, between January 2022 and January 2023

Abbreviations: CI, confidence interval

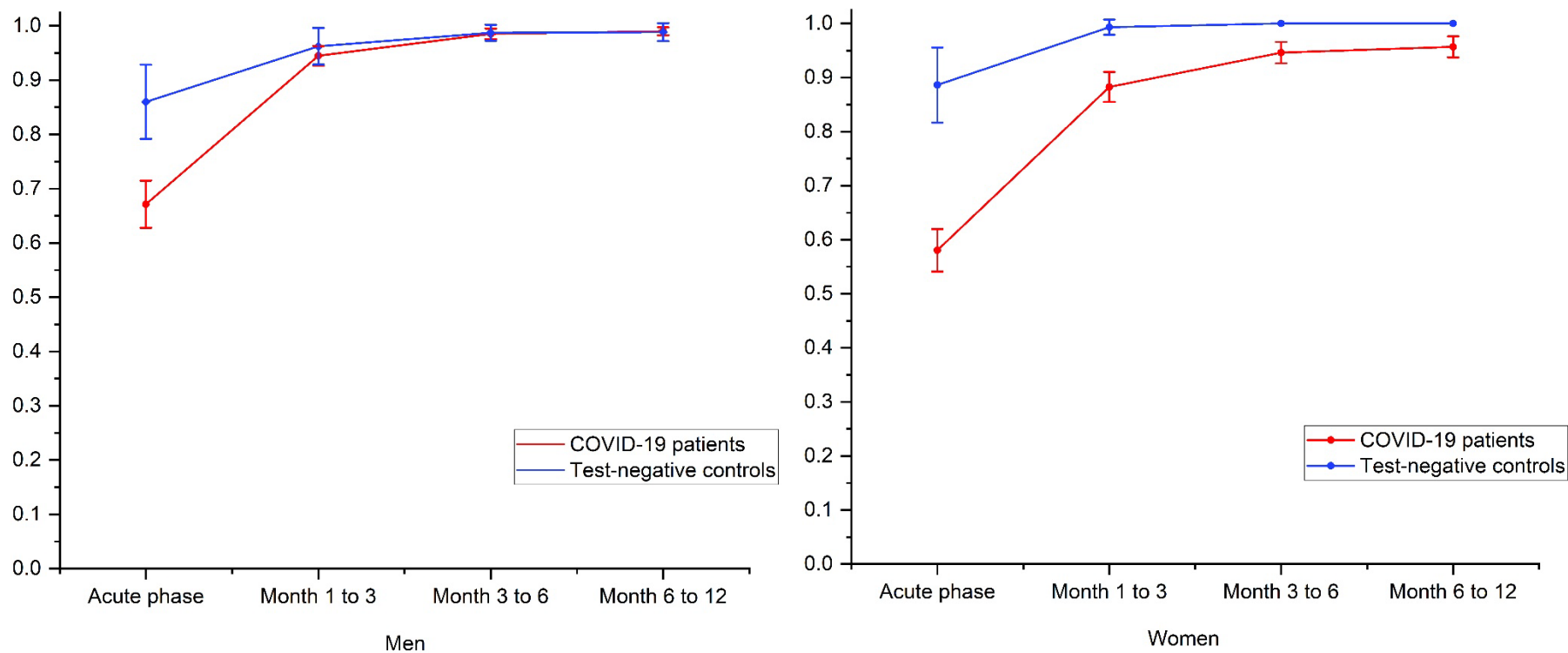


Figure S4. Mean EQ-5D-5L utility scores with 95% confidence intervals in the acute phase, month 1 to 3, month 3 to 6, and month 6 to 12 after testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at a clinic in Tokyo, Japan, between January 2022 and January 2023, among coronavirus disease 2019 (COVID-19) patients and test-negative controls, stratified by sex

Abbreviations: COVID-19, coronavirus disease 2019