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Master's Thesis of Hi Sun Soh

**Long COVID and Health-Related
Quality of Life of Mild Cases in
Korea: 3-Months Follow-up of a
Single Community Treatment Center**

**코로나 경증 환자의 후유증과 건강 관련 삶의 질:
단일 생활치료센터의 3 개월 추적 관찰**

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**Long COVID and Health-Related
Quality of Life of Mild Cases in
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Single Community Treatment Center**

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Abstract

Keyword: COVID-19; Long COVID; COVID-19 complications; persistent symptoms; health-related quality of life; HRQoL

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Background: SARS-CoV-2 (COVID-19) survivors mount as the pandemic continues. To date, studies on persistent symptoms and their effect on health-related quality of life (HRQoL) in mild COVID-19 cases have been limited.

Methods: A prospective online survey was conducted in COVID-19 patients who were admitted to Seongnam Community Treatment Center, an isolation

center in South Korea, from November 23rd 2021 to January 2nd 2022.

Patients above the age of 19 with no or mild symptoms were included in the study. Total of 147 patients returned to the follow-up survey 3 months after discharge. Baseline demographics, clinical characteristics, symptoms, and EuroQol-5 dimensions-5 levels (EQ-5D-5L) measures were investigated.

Results: The median (interquartile range [IQR]) interval period between the initial and follow-up survey was 96.0 (93.0-98.0) days. The median (IQR) age of participants was 51.0 (43.0-61.0). During isolation, 131 (89.1%) patients manifested symptoms. On follow-up, 82 (55.8%) participants remained symptomatic. Common symptoms were constitutional (fatigue, myalgia), neurological (memory impairment, hyposmia, hypogeusia, dizziness), and neuropsychiatric (anxiety) symptoms. Symptomatic survivors reported lower HRQoL compared to asymptomatic survivors. No factors other than long COVID were identified to be relevant to diminished HRQoL. Constitutional,

cardiopulmonary, neurological, and neuropsychiatric symptoms were significantly associated with low HRQoL.

Conclusion: 55.8% of mild COVID-19 survivors remained symptomatic.

Constitutional, cardiopulmonary, neurological, and neuropsychiatric symptoms at follow-up were significantly associated with low HRQoL.

Observations of long-term symptoms of COVID-19 with decline in HRQoL and integrated research in COVID-19 survivors are warranted.

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Chapter 1. Introduction

Since the outbreak of SARS-CoV-2 (COVID-19) in Hubei Province, China, in December 2019,¹ there have been more than 510 million cases, six million deaths worldwide. Seventeen million cases and 23 thousand deaths in South Korea have been ascribed to COVID-19.²

With mounting cases of COVID-19, the Community Treatment Center (CTC) was deployed in South Korea for mild cases during the acute COVID-19 phase. Admission criteria at the time of entry were: patients (1) who are alert (2) who are asymptomatic or mildly symptomatic to the level where symptoms were relieved by oral medications; (3) whose body temperature measures up to 37.5 degrees Celsius without taking antipyretics or up to 38.0 degrees Celsius by taking antipyretics; (4) who have no or well-controlled underlying diseases; (5) who do not require oxygen

treatment. If symptoms aggravated and required medical care, the patient was transferred to a hospital.

The ongoing pandemic commonly manifests constitutional, cardiopulmonary, neurological, and gastrointestinal symptoms during the acute phase.^{3, 4} Still, COVID-19 can produce prolonged debilitating sequelae, namely the "Long COVID."⁵ In a nationwide study on the US Veterans, an association was found between the severity of COVID-19 and long COVID.⁶ One systematic review pointed out that although COVID-19-associated symptoms were more distinct in patients with severe illness, individuals with mild and moderate severity also reported various symptoms after the acute phase.⁷ Also, in a study on home-isolated young patients, 61% reported residual symptoms at six months, irrespective of the disease severity during the acute phase.⁸

Published data have concentrated on hospitalized patients. Hence, the impact of clinical sequelae on non-hospitalized patients with mild

severity remains elusive. A case-fatality ratio of 0.13% in South Korea⁹ and increasing number of COVID-19 survivors highlight the necessity of investigation into long COVID and its impact on survivors' health in mild cases. This study aimed to determine persistent symptoms in asymptomatic and mildly symptomatic patients and their impact on health-related quality of life (HRQoL) using the EuroQol-5 dimensions-5 levels (EQ-5D-5L) measure.

Chapter 2. Methods

2.1. Study design and data collection

This prospective online survey study was conducted on COVID-19 patients admitted to Seongnam CTC, located in Gyeonggi province, South Korea, from November 23rd, 2021 to January 2nd, 2022. All cases were reverse transcription-polymerase chain reaction (RT-PCR)-confirmed. No antiviral therapy was administered. On admission day, patients above the age of 19 were invited to participate in the study, and those who agreed, filled in an online survey via cellular phone. The questionnaires on the survey consisted of date of birth, height, weight, smoking status, underlying medical conditions, present symptoms, and EQ-5D-5L measures. Electronic medical records were reviewed to update baseline symptoms and underlying medical conditions. Three months after discharge, patients were re-invited to fill out an online survey, which consisted of persistent symptoms and EQ-5D-5L questionnaires. For those who did not return to the 2nd survey, 2 additional text messages were sent for notification. Those who did not return to the survey following 3 notification messages were

excluded from the study.

Electronic informed consent was obtained, and the study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital. (IRB No.: 2110-065-1261)

We used the EuroQol Group's EQ-5D-5L questionnaire,¹⁰ a generally valid and responsive instrument¹¹ in assessing HRQoL, and Korean standard value set to assess HRQoL that is specified to the Korean population.¹² The EQ-5D-5L includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels of response options (no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems) to denote all possible health states. One level from each dimension is put together to make a combination numbers, ranging from 11111 (complete health state) to 55555 (poor health state). Based on this 5-digit combination of numbers, an index value, preference-based on the general population of a country, is provided,

ranging from -0.066 (worst HRQoL) to 1.000 (best HRQoL) in South Korea, with a score less than zero representing a health state worse than death.¹²

2.2. Definitions

Long COVID in this study were defined as any remaining or newly identified symptoms present at the time of follow-up that can only be explained by COVID-19 infection. Messenger ribonucleic acid (mRNA) and viral vector vaccines were available in South Korea during the study period. Complete vaccination was defined as inoculated with a booster shot or past 14 days from the 2nd dose of vaccination. Any other cases of vaccination were regarded as incomplete. The follow-up period was counted from the day of discharge from the CTC until the day when follow-up online survey was submitted.

For analysis, index values corresponding to the lower quartile were classified as low EQ-5D-5L index values. Symptoms were categorized by organ-systems for logistic regression analysis. Constitutional symptoms included fatigue, chilling sense, febrile sense, hyperhidrosis, anhidrosis, and myalgia. Cardiopulmonary symptoms included sore throat, globus sensation, sputum, rhinorrhea, nasal congestion, dyspnea, and chest discomfort or pain. Neurological symptoms included headache, dizziness, hyposmia, hypogeusia, memory impairment, extremity numbness, brain fog, and eye soreness. Gastrointestinal symptoms included dyspepsia, nausea or vomiting, and diarrhea or constipation. Neuropsychiatric symptoms included anxiety and insomnia. Dermatologic/musculoskeletal symptoms included rash, arthralgia, hair loss, and skin desquamation.

Participants with metabolic disease was defined as those with hypertension (HTN), dyslipidemia (DL), or diabetes mellitus (DM).

2.3. Statistical analysis

We conducted a descriptive analysis on baseline characteristics. Continuous variables are presented as median (interquartile range, IQR) or mean (standard deviation, SD) values, and categorical values are presented as numbers (percentage, %). Categorical variables were analyzed using the Chi-square test or Fisher's exact test, and non-categorical variables were analyzed using the t-test. Logistic regression analysis was used to examine the factors associated with Long COVID and decreased HRQoL at follow-up. Two-sided P values <0.05 were considered statistically significant. All analyses were performed using Stata Version 16.1 (StataCorp, College Station, TX, USA).

Chapter 3. Results

3.1. Demographics and characteristics

Table 1 shows the incidence of demographic characteristics, smoking status, and underlying medical conditions, vaccination status, length of stay at CTC, days to follow-up, and the presence of long COVID of the participants. 79 (53.7%) were male and 68 (46.3%) were female. The median (IQR) BMI was 23.9 (21.3-26.6). 85 (57.8%) were never smokers, 42 (28.6%) were ex-smokers, and 20 (13.6%) were current smokers. Sixty-seven participants (45.6%) did not have any underlying diseases. HTN was the most common comorbidity (41 [27.9%]) followed by DL (24 [16.3 %]), DM (16 [10.9%]) and cancer of any type (11 [7.5%]). Incidences of other medical conditions are demonstrated in Table 1. A hundred and fourteen patients (77.6%) had completed their COVID-19 vaccination and 33 (22.4%) had incomplete or uncertain vaccination history. The median (IQR) length of stay

in the CTC and the interval period (IQR) between the initial and follow-up survey were 8.0 (7.0–9.0) and 96.0 (93.0–98.0) days, respectively. Eighty-two participants (55.8%) had residual symptoms of COVID-19 (Table 1). Of the 147 participants, there were more females who reported low HRQoL and more males who reported above low HRQoL at follow-up ($P=0.005$). No difference in age, BMI, smoking status, underlying medical condition of metabolic disease, chronic liver disease, hypothyroidism or hyperthyroidism, and mood disorder, vaccination status, length of stay at CTC, and follow-up period between asymptomatic and symptomatic participants were identified ($P=0.644, 0.990, 0.148, 0.110, 0.336, 0.712, 0.513, 0.650, 0.862, \text{ and } 0.401$ respectively). While more participants who presented low HRQoL had long COVID, there were more participants with above low HRQoL without long COVID ($P<0.001$).

Table 1. Clinical characteristics of 147 participants at follow-up

Characteristics	Total (N=147)	Low HRQoL (N=40)	Above low HRQoL (N=107)	<i>P</i> value
Median Age (IQR), years	51.0 (43.0-61.0)	53.0 (46.5-61.5)	51.0 (43.0-62.0)	0.644
Sex				0.005
Male	79 (53.7%)	14 (35.0%)	65 (60.8%)	
Female	68 (46.3%)	26 (65.0%)	42 (39.2%)	
BMI, kg/m²	23.9 (21.3-26.6)	24.2 (21.8-26.2)	23.8 (21.4-26.0)	0.990
Smoking status				0.148
Never smoker	85 (57.8%)	28 (70.0%)	57 (53.3%)	
Ex-smoker	42 (28.6%)	7 (17.5%)	35 (32.7%)	
Current smoker	20 (13.6%)	5 (12.5%)	15 (14.0%)	
Underlying medical conditions				
None	65 (44.2%)	16 (40.0%)	49 (45.8%)	
Metabolic disease ^a	58 (39.5%)	20 (50.0%)	38 (35.5%)	0.110
Hypertension	41 (27.9%)	13 (32.5%)	28 (26.2%)	
Dyslipidemia	24 (16.3%)	10 (25.0%)	14 (13.1%)	

Diabetes mellitus	16 (10.9%)	5 (12.5%)	11 (10.3%)	
History of cancer	11 (7.5%)	6 (15.0%)	5 (4.7%)	0.034
Chronic liver disease	8 (5.4%)	1 (2.5%)	7 (6.5%)	0.336
Hypothyroidism or hyperthyroidism	5 (3.4%)	1 (2.5%)	4 (3.7%)	0.712
Mood disorder	5 (3.4%)	2 (5.0%)	3 (2.8%)	0.513
Other	14 (9.5%)	4 (10.0%)	10 (9.4%)	
Vaccination status				0.650
Complete	114 (77.6%)	30 (75.0%)	84 (78.5%)	
Incomplete or uncertain	33 (22.4%)	10 (25.0%)	23 (21.5%)	
Length of CTC stay (IQR), days	8.0 (7.0-9.0)	8.0 (7.0-9.0)	8.0 (7.0-9.0)	0.862
Follow-up period (IQR), days	96.0 (93.0-98.0)	95.0 (93.5-97.5)	96.0 (93.0-98.0)	0.401
Long COVID^b				<0.001
Absent	65 (44.2%)	1 (2.5%)	64 (59.8%)	
Present	82 (55.8%)	39 (97.5%)	43 (40.2%)	

HRQoL, Health-Related Quality of Life; IQR, interquartile range; BMI, body mass index; CTC, Community Treatment Center.

^a Hypertension, dyslipidemia, and diabetes mellitus.

^b Defined by any remaining or newly identified symptoms related to COVID-19 that were present at the time of

follow-up.

3.2. Characteristics of clinical sequelae and HRQoL assessment

At baseline, 131 of 147 patients (89.1%) had 1 or more symptoms. Upper respiratory symptoms (cough [61.2%], sputum [55.8%], rhinorrhea [51.0%], and sore throat [34.7%]) and neurological symptoms (headache [22.5%], hyposmia [21.1%], and hypogeusia [20.4%]) were pervasive. Eighty-two (55.8%) participants were symptomatic at follow-up. The most common persistent symptoms were fatigue (48 [32.7%]), memory impairment (22 [15.0%]), hyposmia (21 [14.3%]), anxiety (14 [9.5%]), myalgia (11 [7.5%]), hypogeusia (10 [6.8%]), and dizziness (10 [6.8%]) (Table 2).

At baseline and follow-up, the number of patients reporting no, slight, moderate problems on mobility dimension changed from 141 (95.9%) to 137 (93.2%), 5 (3.4%) to 9 (6.1%), 1 (0.7%) to 1 (0.7%), respectively. No

participant reported severe nor unable to/extreme problems on either point.

On the self-care dimension, the number of patients reporting no and slight problems was 145 (98.6%) and 5 (1.4%), respectively. There was no change incidence-wise. No participant reported moderate, severe, or unable to/extreme problems at baseline and follow-up. The number of patients suffering from no, slight, and moderate problems on usual activities dimension changed from 129 (87.8%) to 125 (85.0%), 17 (11.6%) to 21 (14.3%), and 1 (0.7%) to 1 (0.7%), respectively. No participant reported severe nor unable to/extreme problems on either point. The number of patients reporting no, slight, moderate, and severe problems on pain/discomfort dimension was 80 (54.4%) versus (vs.) 112 (76.2%), 60 (40.8%) vs. 30 (20.4%), 5 (3.4%) vs. 5 (3.4%), 2 (1.4%) vs. 0 (0.0%), respectively. No participant reported unable to/extreme problems at neither baseline nor follow-up. The number of patients reporting no, slight, moderate, and severe problems on anxiety/depression dimension was 98

(66.7%) vs. 109 (74.1%), 45 (30.6%) vs. 34 (23.1%), 2 (1.4%) vs. 3 (2.0%), 2 (1.4%) vs. 1 (0.7%), respectively. No participant reported being unable to/extreme problems on either point.

The 5-digit combination of EQ-5D-5L results were converted into index values, 0.661 being the smallest and 1.000 being the largest. The 25th percentile index value was 0.862.

Table 2. Comparison of symptoms at baseline and follow-up

	Baseline	Follow-up
Presence of symptoms		
Absent	16 (10.9%)	65 (44.2%)
Present	131 (89.1%)	82 (55.8%)
Symptoms		
Fatigue	27 (18.4%)	48 (32.7%)
Memory impairment	1 (0.7%)	22 (15.0%)
Hyposmia	31 (21.1%)	21 (14.3%)
Anxiety	20 (13.6%)	14 (9.5%)
Myalgia	22 (15.0%)	11 (7.5%)
Hypogeusia	30 (20.4%)	10 (6.8%)
Dizziness	16 (10.9%)	10 (6.8%)
Sputum	82 (55.8%)	9 (6.1%)
Cough	90 (61.2%)	8 (5.4%)
Rhinorrhea	75 (51.0%)	8 (5.4%)
Insomnia	24 (16.3%)	8 (5.4%)
Headache	33 (22.5%)	6 (4.1%)
Chest discomfort or pain	13 (8.8%)	5 (3.4%)
Dyspepsia	13 (8.8%)	5 (3.4%)
Sore throat	51 (34.7%)	4 (2.7%)
Hyperhidrosis	5 (3.4%)	4 (2.7%)
Dyspnea	4 (2.7%)	3 (2.0%)
Diarrhea or constipation	22 (15.0%)	2 (1.4%)
Skin rash	1 (0.7%)	2 (1.4%)
Lower extremity numbness	0 (0.0%)	2 (1.4%)
Nausea or vomiting	10 (6.8%)	1 (0.7%)

Chilling sense	6 (4.1%)	1 (0.7%)
Arthralgia	1 (0.7%)	1 (0.7%)
Anhidrosis	0 (0.0%)	1 (0.7%)
Nasal congestion	21 (14.3%)	0 (0.0%)
Febrile sense	13 (8.8%)	0 (0.0%)
Globus sensation	2 (1.4%)	0 (0.0%)
Other	0 (0.0%)	5 (3.4%) ^a

^a 2 hair loss, 1 brain fog, 1 eye soreness, 1 skin desquamation of finger.

3.3. Factors associated with low HRQoL

After observing the change of symptoms and EQ-5D-5L distribution at baseline and follow-up, factors associated with low HRQoL were investigated. Female sex (OR 2.87 [1.35-6.13], $P=0.006$), history of cancer (OR 3.60 [1.03-12.55], $P=0.044$), and long COVID (OR 58.05 [7.68-438.64], $P<0.001$) were associated with low HRQoL on univariate analysis. Increasing age and having metabolic diseases were not a relevant factor (Table 3). On multivariate analysis, long COVID was the only relevant factor for low HRQoL (OR 51.24 [6.65-394.80], $P<0.001$).

Next, symptoms associated with low HRQoL were investigated according to organ-systems. On univariate logistic regression, constitutional, cardiopulmonary, neurological, gastrointestinal, and neuropsychiatric symptoms at follow-up were associated with low HRQoL (OR 7.81 [3.44-

17.73], $P < 0.001$, OR 12.93 [4.82-34.65], $P < 0.001$, OR 7.59 [3.39-16.99], $P < 0.001$, OR 9.26 [1.79-48.07], $P = 0.008$, and OR 19.03 [5.85-61.89], $P < 0.001$, respectively). When adjusted for age, sex, metabolic disease, and history of cancer, constitutional, cardiopulmonary, neurological, and neuropsychiatric symptoms at follow-up were associated with low HRQoL (OR 6.15 [2.50-15.17], $P < 0.001$, OR 15.80 [5.34-46.70], $P < 0.001$, OR 7.03 [3.00-16.46], $P < 0.001$ and OR 15.00 [4.38-51.33], $P < 0.001$, respectively) (Table 4).

Table 3. Odds ratio of factors associated with low HRQoL

	Crude OR (95% CI)	<i>P</i> value	Adjusted^a OR (95% CI)	<i>P</i> value
Age	1.01 (0.98-1.04)	0.641	1.01 (0.97-1.05)	0.724
Female sex	2.87 (1.35-6.13)	0.006	1.93 (0.77-4.81)	0.159
Metabolic disease^b	1.82 (0.87-3.79)	0.112	1.95 (0.75-5.12)	0.172
History of cancer	3.60 (1.03-12.55)	0.044	1.34 (0.32-5.52)	0.687
Long COVID	58.05 (7.68-438.54)	<0.001	51.24 (6.65-394.80)	<0.001

HRQoL, Health-Related Quality of Life; OR, Odds ratio; CI, Confidence interval.

^a Adjusted for age, sex, metabolic disease, history of cancer, and long COVID.

^b Hypertension, dyslipidemia, and diabetes mellitus.

Table 4. Odds ratio of symptoms by organ-systems associated with low HRQoL

	Prevalence (N)	Crude OR (95% CI)	<i>P</i> value	Adjusted ^a OR (95% CI)	<i>P</i> value
Constitutional^b			<0.001		<0.001
Absent	91	1 (Reference)		1 (Reference)	
Present	56	7.81 (3.44-17.73)		6.15 (2.50-15.17)	
Cardiopulmonary^c			<0.001		<0.001
Absent	121	1 (Reference)		1 (Reference)	
Present	26	12.93 (4.82-34.65)		15.80 (5.34-46.70)	
Neurological^d			<0.001		<0.001
Absent	97	1 (Reference)		1 (Reference)	

Present	50	7.59 (3.39-16.99)		7.03 (3.00-16.46)	
Gastrointestinal^e			0.008		0.060
Absent	139	1 (Reference)		1 (Reference)	
Present	8	9.26 (1.79-48.07)		5.30 (0.93-30.24)	
Neuropsychiatric^f			<0.001		<0.001
Absent	126	1 (Reference)		1 (Reference)	
Present	21	19.03 (5.85-61.89)		15.00 (4.38-51.33)	
Dermatologic/muskuloskeletal^g			0.350		0.354
Absent	140	1 (Reference)		1 (Reference)	
Present	7	2.09 (0.45-9.77)		2.21 (0.41-11.74)	

HRQoL, Health-Related Quality of Life; OR, Odds ratio; CI, Confidence interval.

^a Adjusted for age, sex, metabolic disease, and history of cancer.

^b Constitutional symptoms include fatigue, chilling sense, febrile sense, hyperhidrosis, anhidrosis, and myalgia.

^c Cardiopulmonary symptoms include sore throat, globus sensation, sputum, rhinorrhea, nasal congestion, dyspnea, and chest discomfort or pain.

^d Neurological symptoms include headache, dizziness, hyposmia, hypogeusia, memory impairment, extremity numbness, brain fog, and eye soreness.

^e Gastrointestinal symptoms include dyspepsia, nausea or vomiting, and diarrhea or constipation.

^f Neuropsychiatric symptoms include anxiety and insomnia.

^g Dermatologic/musculoskeletal symptoms include rash, arthralgia, hair loss, and skin desquamation.

Chapter 4. Discussion

Based on the data collected from CTC, South Korea, 55.8% of mild COVID-19 survivors reported of long COVID; the most common residual symptoms were fatigue (32.7%), memory impairment (15.0%), hyposmia (14.3%), anxiety (9.5%), myalgia (7.5%), hypogeusia (6.8%), dizziness (6.8%). Similar to the findings of Ding et al.¹³ our study revealed that at follow-up, cardiopulmonary symptoms such as chest discomfort or pain, dyspnea, cough were minimal and constitutional, neurological and neuropsychiatric symptoms were pervasive in isolated patients.

On EQ-5D-5L, 25.9% had anxiety/depression, 23.8% had pain/discomfort, 15.0% had problems with usual activities, 6.8% had problems with mobility, and only 1.4% had self-care problems at follow-up. We expected neuropsychiatric symptoms to improve after discharge as

participants left the CTC, an unfamiliar environment, and returned to their residences but the mean EQ-5D-5L index value remained the lowest of all symptoms from that of baseline, which indicates that neuropsychiatric symptoms continued to affect HRQoL after recovery. This continuity can be explained by job losses, wage losses, uncertainty about the future, and the fear associated with the pandemic itself, such as losing a family member or a friend.¹⁴

Sudre et al.¹⁵ reported that old age, female sex, disease severity, and BMI were attributes and predictors of long COVID. Our study also revealed similar results in that female sex was associated with decreased HRQoL at follow-up on univariate analysis. However, on multivariate analysis, female sex was not a relevant factor for low HRQoL. Also, unlike the results from studies in the U.S. proving the association between vaccination with mRNA, viral vector vaccines and less COVID-19 hospitalization^{16,17}, vaccination status showed no statistical significance to long COVID. This may be

attributable to the difference in disease severity between the study participants. Patients who needed hospitalization or oxygen supply or had uncontrolled underlying diseases were excluded from our study, thereby neutralizing the effect of age, sex, BMI, and vaccination status on patients with minimal disease burden.

While a prior study concluded that COVID-19 severity is linked to a worse HRQoL,¹⁸ other studies have shown the association of mild COVID-19 survivors and decreased HRQoL, similar to our findings. Research has established that survivors with sequelae of COVID-19 are likely to report having a decreased HRQoL.^{19,20} 63 (44.1%) of 143 discharged patients reported worsened quality of life in a study conducted in Italy.²¹ Another study reported that functional impairment of non-hospitalized patients (n=96) was similar to that of hospitalized patients' (n=22) at 3–4 months post-COVID-19 diagnosis.²² Lower scores for both physical and mental component summary on a group of standardized instruments evaluating

neurocognitive function, psychiatric morbidity and quality of life were found in mild-to-severe COVID-19 survivors with neurocognitive impairment (n=179).²³ Given that innumerable persons worldwide are infected with COVID-19 or have recovered from the acute phase, it is necessary to assess the implication of long COVID on HRQoL.

Although EQ-5D-5L covers various domains of daily life and reflects generic health status, there is a shortfall in symptom-specific measurement and dimensions that are not included, such as sleep, concentration or vitality. As majority of survivors suffer from long COVID,²⁴ assessment based on 5-dimensions of life instrument alone may be insufficient to comprehensively analyze HRQoL of COVID-19 survivors. Based on the findings that post-COVID-19 symptom burdens are heterogeneous, including fatigue, anosmia, dyspnea, cough, chest pain, arthralgia, sleep disturbances, and worse mental health,^{25,26} symptom-specific questionnaires or a new preference-based HRQoL instrument must be considered together

for evaluation.

There are several limitations in this study. First, collected data on follow-up symptoms were not based on objective evaluation as our online survey was reported directly from participants. Second, as common symptoms of long COVID, such as pain, discomfort, anxiety, and depression, were a part of EQ-5D-5L dimension, the association between long COVID and low HRQoL has been exaggerated for analysis. Other measures for evaluation of HRQoL should also be considered. Third, the sample size in this study was considered not large enough. Future research might extend the explanations of the effect of lingering symptoms and low HRQoL with a larger study sample, providing improved validity and reliability. Forth, our study focused on the presence of symptoms, and the severity of symptoms has been overlooked. The correlation of symptom severity and degree of change in HRQoL requires further investigation. Self-selection bias is possible, as patients electing to participate in online follow-up surveys may

have more persistent symptoms than the average survivor. The generalizability of results is limited, given that this is a single-institution study.

Despite the limitations, to our acknowledgement, this is the first study conducted in South Korea to report on the clinical sequelae and their impact on HRQoL of asymptomatic or mildly symptomatic COVID-19 patients. Our results stress the need for further investigation into the long-term complications of COVID-19 cases and its health-related effects as long-term symptoms diminish HRQoL in COVID-19 survivors and as the current pandemic is begetting survivors relentlessly.

Chapter 5. Conclusion

Based on a single CTC sample data, 55.8% of mild COVID-19 survivors had long COVID. At follow-up, symptomatic survivors reported decreased HRQoL compared to asymptomatic survivors. Female sex and history of cancer were associated with diminished HRQoL on univariate analysis but not on multivariate analysis. The presence of constitutional, cardiopulmonary, neurological, and neuropsychiatric symptoms had significantly higher odds of low HRQoL than without. Observation of long-term symptoms of COVID-19 with diminished HRQoL and integrated research in COVID-19 survivors are warranted.

Bibliography

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020;20(5):533-4.
2. Our World in Data. <https://ourworldindata.org/explorers/coronavirus-data-explorer>. Accessed 5th May, 2022.
3. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020;323(11):1061-9.
4. Xie Y, Bowe B, Maddukuri G, Al-Aly Z. Comparative evaluation of clinical manifestations and risk of death in patients admitted to hospital with covid-19 and seasonal influenza: cohort study. *BMJ* 2020;371:m4677.
5. Mehandru S, Merad M. Pathological sequelae of long-haul COVID. *Nat Immunol* 2022;23:194-202.

6. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* 2021;594(7862):259-64.
7. Salamanna F, Veronesi F, Martini L, Landini MP, Fini M. Post-COVID-19 Syndrome: The Persistent Symptoms at the Post-viral Stage of the Disease. A Systematic Review of the Current Data. *Front Med (Lausanne)* 2021;8:653516.
8. Blomberg B, Mohn KG, Brokstad KA, *al. e.* Long COVID in a prospective cohort of home-isolated patients. *Nat Med* 2021;27:1607-13.
9. Coronavirus COVID-19 (2019-nCoV).
<https://coronavirus.jhu.edu/map.html>. Accessed 2nd May, 2022.
10. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36.
11. Finch AP, Brazier JE, Mukuria C. What is the evidence for the performance of generic preference-based measures? A systematic overview of reviews. *Eur J Health Econ* 2018;19(4):557-70.

12. Kim S-H, Ahn J, Ock M, Shin S, Park J, Luo N, et al. The EQ-5D-5L valuation study in Korea. *Quality of Life Research* 2016;25(7):1845-52.
13. Ding H, Yin S, Cheng Y, Cai Y, Huang W, Deng W. Neurologic manifestations of nonhospitalized patients with COVID-19 in Wuhan, China. *MedComm (2020)* 2020.
14. Cénat JM, Blais-Rochette C, Kokou-Kpolou CK, Noorishad PG, Mukunzi JN, McIntee SE, et al. Prevalence of symptoms of depression, anxiety, insomnia, posttraumatic stress disorder, and psychological distress among populations affected by the COVID-19 pandemic: A systematic review and meta-analysis. *Psychiatry Res* 2021;295:113599.
15. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. *Nat Med* 2021;27(4):626-31.
16. Tenforde MW, Self WH, Adams K, Gaglani M, Ginde AA, McNeal T, et al. Association Between mRNA Vaccination and COVID-19 Hospitalization and Disease Severity. *JAMA* 2021;326(20):2043-54.

17. Self WH, Tenforde MW, Rhoads JP, Gaglani M, Ginde AA, Douin DJ, et al. Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions - United States, March-August 2021. *MMWR Morb Mortal Wkly Rep* 2021;70(38):1337-43.
18. Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect* 2020;81(6):e4-e6.
19. Arab-Zozani M, Hashemi F, Safari H, Yousefi M, Ameri H. Health-Related Quality of Life and its Associated Factors in COVID-19 Patients. *Osong Public Health Res Perspect* 2020;11(5):296-302.
20. Moreno-Pérez O, Merino E, Leon-Ramirez JM, Andres M, Ramos JM, Arenas-Jiménez J, et al. Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. *J Infect* 2021;82(3):378-83.

21. Carfi A, Bernabei R, Landi F, Group ftGAC-P-ACS. Persistent Symptoms in Patients After Acute COVID-19. *JAMA* 2020;324(6):603-5.
22. Jacobson KB, Rao M, Bonilla H, Subramanian A, Hack I, Madrigal M, et al. Patients With Uncomplicated Coronavirus Disease 2019 (COVID-19) Have Long-Term Persistent Symptoms and Functional Impairment Similar to Patients with Severe COVID-19: A Cautionary Tale During a Global Pandemic. *Clin Infect Dis* 2021;73(3):e826-e9.
23. Méndez R, Balanzá-Martínez V, Luperdi SC, Estrada I, Latorre A, González-Jiménez P, et al. Short-term neuropsychiatric outcomes and quality of life in COVID-19 survivors. *J Intern Med* 2021;290(3):621-31.
24. Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Florencio LL, Cuadrado ML, Plaza-Manzano G, et al. Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. *Eur J Intern Med* 2021;92:55-70.

25. Goërtz YMJ, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FVC, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? *ERJ Open Res* 2020;6(4).
26. Malik P, Patel K, Pinto C, Jaiswal R, Tirupathi R, Pillai S, et al. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. *J Med Virol* 2022;94(1):253-62.

Abstract in Korean

서론: 성남 생활치료센터에 입소한 경증 COVID-19 환자들을 대상으로 3개월 후 추적관찰을 통해 COVID-19으로 인해 지속되는 증상과 그로 인한 건강 관련 삶의 질의 저하 유무에 대해 알아보고자 하였다.

방법: 2021년 11월 23일부터 2022년 1월 2일까지 성남 생활치료센터에 입소한 19세 이상의 COVID-19 환자들을 대상으로 온라인 설문조사를 시행하였다. 총 147명의 참여자가 입소 당시 그리고 3개월 후 추적 조사에 임하였다. 기본 인구 통계, 임상적 특성, 증상 및 EuroQol-5D-5L을 조사하였다.

결과: 55.8%의 환자가 long COVID를 호소하였으며 피로, 기억력 감퇴, 후각 저하, 불안, 근육통, 미각 저하, 어지럼증이 가장 많았다. Long COVID가 있는 경우, 없는 경우보다 낮은 건강 관련 삶의 질의 점수와 연관이 있는 것으로 나타났다. Long COVID의 증상 중에서는 전신, 심혈관 및 호흡기계, 신경계, 그리고 신경정신과적 증상이 낮은 건강 관련 삶의 질 점수와 연관되

었다.

결론: 경증 COVID-19 환자들의 55.8%에서 long COVID가 있는 것으로 나타났다. long COVID가 있는 경우, 없는 경우보다 건강 관련 삶의 질이 낮았다.

주요어: 코로나19, 코로나19 후유증, 코로나 후 증상, 건강 관련 삶의 질.