Korean J Pain 2022;35(4):458-467
https://doi.org/10.3344/kjp.2022.35.4.458
pISSN 2005-9159 eISSN 2093-0569

KJP

Clinical Research Article

Check for updates

Associations of unspecified pain, idiopathic pain and COVID-19 in South Korea: a nationwide cohort study

Namwoo Kim[1,2,*], Jeewuan Kim[3,*], Bo Ram Yang[4], and Bong-Jin Hahm[1,5]

[1]*Department of Neuropsychiatry, Seoul National University Hospital, Seoul, Korea*
[2]*Department of Clinical Medical Sciences, Seoul National University College of Medicine, Seoul, Korea*
[3]*Department of Statistics and Data Science, Yonsei University, Seoul, Korea*
[4]*College of Pharmacy, Chungnam National University, Daejeon, Korea*
[5]*Department of Psychiatry and Behavioral Sciences, Seoul National University College of Medicine, Seoul, Korea*

Received May 4, 2022
Revised June 18, 2022
Accepted June 30, 2022

Handling Editor: Francis S. Nahm

Correspondence
Bong-Jin Hahm
Department of Neuropsychiatry, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-2458
Fax: +82-2-743-2838
E-mail: hahmbj@gmail.com

*These authors contributed equally to this work.

Background: Few studies have investigated unspecified or idiopathic pain associated with COIVD-19. This study aimed to provide the incidence rates of unspecified pain and idiopathic pain in patients with COVID-19 for 90 days after COVID-19 diagnosis.
Methods: A propensity score matched cohort was used, including all patients with COVID-19 in South Korea, and analyzed their electronic medical records. The control group consisted of those who had not had tests for COVID-19 at all. Unspecified pain diagnoses consisted of diagnoses related to pain included in the ICD-10 Chapter XVIII. Idiopathic pain disorders included fibromyalgia, temporomandibular joint disorders, headaches, chronic prostatitis, complex regional pain syndrome, atypical facial pain, irritable bowel syndrome, and interstitial cystitis.
Results: After matching, the number of participants in each group was 7,911. For most unspecified pain, the incidences were higher in the COVID-19 group (11.7%; 95% confidence interval [CI], 11.0–12.5) than in the control group (6.5%; 95% CI, 6.0–7.1). For idiopathic pain, only the headaches had a significantly higher incidence in the COVID-19 group (6.6%; 95% CI, 6.1–7.2) than in the control group (3.7%; 95% CI, 3.3–4.1). However, using a different control group that included only patients who visited a hospital at least once for any reasons, the incidences of most unspecified and idiopathic pain were higher in the control group than in the COVID-19 group.
Conclusions: Patients with COVID-19 might be at a higher risk of experiencing unspecified pain in the acute phase or after recovery compared with individuals who had not had tests for COVID-19.

Key Words: COVID-19; Electronic Health Records; Epidemiologic Studies; Headache; Insurance Claim Review; Pain; Post-Acute COVID-19 Syndrome; Post-Infectious Disorders; Propensity Score.

INTRODUCTION

Although coronavirus disease 2019 (COVID-19) vaccines have been developed, many people continue to contract COVID-19 due to the emergence of variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
© The Korean Pain Society, 2022

Author contributions: Namwoo Kim: Study conception; Jeewuan Kim: Formal analysis; Bo Ram Yang: Writing/manuscript preparation; Bong-Jin Hahm: Supervision.

[1]. People with COVID-19 may experience several medical problems in addition to respiratory symptoms in the acute phase [2,3]. According to a meta-analysis, more than 80% of survivors experienced at least one symptom after recovery from the primary illness, and more than 50 different post-recovery symptoms have been reported, the most common of which were fatigue, headache, difficulty concentrating, and hair loss [4].

In comparison with other symptoms experienced in the acute phase and after recovery from COVID-19, pain has been less intensively researched. Myalgia, arthralgia, and chest pain have been reported as common types of pain in patients with COVID-19, in addition to headaches [5–7]. If pain occurs due to COVID-19 sequelae after the acute phase has passed, it may appear with non-specific characteristics. It is also possible that, in such cases, pain might be diagnosed as unspecified pain because its cause is unclear. However, few studies have investigated non-specific, unspecified pain in the context of COVID-19, and COVID-19-related pain research has mainly focused on chronic pain and its management [8–11]. Studies including a control group are even rarer [6,12,13]. Moreover, few studies have explored the associations between COVID-19 and various idiopathic pain disorders with unknown causes, such as fibromyalgia, chronic prostatitis, chronic cystitis, temporomandibular joint disorders, and complex regional pain syndrome. Therefore, a large-scale study with a control group on the incidence of unspecified pain and idiopathic pain in COVID-19 patients is needed.

As an indirect indicator for investigating the onset or worsening of pain in individuals who contracted COVID-19, prescription records of analgesics, including opioid medications, can be used [14]. However, most opioid-related research on COVID-19 to date has focused on individuals with opioid use disorders [15].

The aim of this study was to examine the incidence rates and relative risks of unspecified pain diagnoses, idiopathic pain disorders, and prescriptions of opioid medications in patients with COVID-19 through a large-scale study of the electronic medical records of a nationwide cohort including all patients with COVID-19 in South Korea.

MATERIALS AND METHODS

1. Study design and participants

All patients with COVID-19 in South Korea are included in the government-created COVID-19 nationwide cohort. We used the electronic medical records of this cohort through the claims database of the Health Insurance Review and Assessment Service of Korea (HIRA), which includes data on sociodemographic characteristics, International Classification of Diseases (ICD) codes, prescriptions, and medical procedures. Detailed information on the HIRA has been described in other studies [16,17].

The participants of this study were people who were diagnosed with COVID-19 during the first four months of the pandemic (from February 1 to May 31, 2020) when COVID-19 cases surged rapidly in South Korea. SARS-CoV-2 infection was diagnosed by real-time reverse-transcription polymerase chain reaction (RT-PCR) assays. The control group included in the government-created cohort consisted of those who did not receive RT-PCR testing at all. They were matched by age and sex to the COVID-19 group. All COVID-19 tests and treatments were provided free of charge by the government.

All personal information was unidentifiable and the requirement for written informed consent was waived by the ethics committee. This study protocol was exempted from review by the Institutional Review Board of Seoul National University Hospital and the Seoul National University College of Medicine (IRB number: E-2106-051-1225).

2. Variables of interest

To find people with symptoms of unspecified pain, we used the following diagnoses from ICD-10 Chapter XVIII ('Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified [(R00-R99]'): pain in the throat and chest (ICD-10 code R07); abdominal and pelvic pain (R10); pain associated with micturition (R30); and pain, not elsewhere classified (R52) [18]. These correspond to every code that includes the word "pain" among the diagnoses belonging to R00-R99.

The diagnostic codes considered as idiopathic pain disorders were as follows: fibromyalgia (M797); temporomandibular joint disorders (K076); headaches (G43, G44, R51); chronic prostatitis (N411); complex regional pain syndrome (G564, G578, G5880, G5881, M89); atypical facial pain (G501); irritable bowel syndrome (K58); and interstitial cystitis (N301) [19].

In the region where the initial COVID-19 outbreak in South Korea occurred, governmental measures to prevent the spread of COVID-19 were stricter than in other regions. To take this into account, 'region of residence' was included as a variable as follows: the Daegu and Gyeongbuk area (Daegu/Gyeongbuk), where a major outbreak occurred in the early period of the pandemic; the capital area including Seoul (capital); and all other areas (others). Economic status was divided into five levels: the Medical aid group, containing individuals who are unable to pay for national health insurance coverage, and four categories of national health insurance subscribers divided according to their

income.

The following underlying diseases were identified based on individuals' electronic medical records from the past 5 years: mood disorders, hypertension, diabetes, nicotine dependence, alcohol dependence, chronic lower respiratory diseases, heart disease, chronic kidney disease, malignant neoplasms, and stroke (the corresponding ICD codes are described in the **Supplementary Table 1**). It has been widely reported that COVID-19 infection occurs more frequently in environments where people live in groups, such as nursing homes, assisted living homes, and group homes [20]. Because this may cause selection bias, 'admission to skilled nursing facilities' was included as a variable.

3. Outcomes

The primary outcome was whether the incidence rates of unspecified pain diagnoses and idiopathic pain disorders differed between the COVID-19 group and the control group during the acute phase of the illness and a certain period after recovery. To investigate this outcome, the COVID-19 group and the control group were 1:1 matched, and incidence rates and hazard ratios (HRs) of the unspecified pain diagnoses and idiopathic pain disorders were measured for 90 days from the date of COVID-19 diagnosis.

Since the use of analgesics implies the presence of pain, prescriptions for opioid medications were examined. The secondary outcome was whether there were differences in incidence rates and HRs of prescriptions of opioid medications for 90 days from the date of COVID-19 diagnosis between the COVID-19 and control group. Because patients with malignant neoplasms are frequently prescribed opioid medications, those who were not diagnosed with malignant neoplasms were analyzed separately. Additionally, since antidepressants and anticonvulsants may be used for pain control, we investigated whether there was a difference in the proportion of people who were prescribed antidepressants or anticonvulsants between the COVID-19 and control groups. Additional details on opioid medications, antidepressants, and anticonvulsants are provided in **Supplementary Table 1**.

As a subgroup analysis of people who did not have a pain diagnosis before contracting COVID-19, the analysis was repeated with the exclusion of those who had any pain diagnoses (the unspecified pain diagnoses and the idiopathic pain disorders described above) during the past year (from January 1, 2019 to January 31, 2020). The comparison of the COVID-19 and the control group was imbalanced because the COVID-19 group had an illness (COVID-19), but the control group did not. To address this problem through various analytical lenses, new control groups were created with the following five conditions: control groups with participants (1) who had visited a hospital at least once for any reasons; (2) who had been hospitalized at least once for any reasons; (3) who were diagnosed with an upper respiratory tract infection; (4) who were diagnosed with fracture of a large bone; or (5) who were diagnosed with depressive disorders. The ICD-10 codes corresponding to the conditions applied to the new control groups are listed in **Supplementary Table 1**.

4. Statistical analysis

To compare the COVID-19 group and the control group, a 1:1 matched cohort was created by adjusting baseline characteristics through propensity score matching. The propensity score was calculated through logistic regression and the greedy nearest neighbor algorithm. The covariates used for propensity score matching were age, sex, region of residence, economic status, underlying diseases, and admission to skilled nursing facilities. The date of the diagnosis of COVID-19 was defined as the index date. Since the control group did not have an index date, the index date of each patient with COVID-19 was given to the matched control participant after 1:1 matching. The newly created five control groups were also matched 1:1 with the COVID-19 patients to create five new cohorts.

Adequate matching was confirmed for each covariate by a standardized mean difference (SMD) less than 0.1. The incidence rates of unspecified and idiopathic pain diagnoses from the index date to 90 days were calculated through Kaplan–Meier estimation. Comparisons between the COVID-19 group and the control group were performed using the log-rank test. The Cox proportional hazard model was used to calculate HRs. Statistical significance was set at two-sided $P < 0.05$. Adjusted HRs were calculated after adjusting for covariates including age, sex, region of residence, economic status, underlying diseases, and admission to skilled nursing facilities. Statistical analyses were performed in SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC).

RESULTS

As a result of 1:1 propensity score matching between the COVID-19 group and the control group, the entire cohort (not considering whether individuals had a history of the pain diagnoses) included 7,911 participants in each group (**Table 1**). Before matching, the COVID-19 and the control groups included 8,070 and 116,628 participants, respectively. The baseline characteristics of the cohort before matching are provided in **Supplementary Table 2**. The cohort without a history of the pain diagnoses included 1,504

Table 1. Propensity score matched baseline characteristics

Characteristics	Entire cohort			Cohort without a history of the pain diagnoses		
	COVID-19	Control group	SMD	COVID-19	Control group	SMD
Total						
Before matching	8,070	116,628	–	1,557	24,321	–
After matching	7,911 (100)	7,911 (100)	–	1,504 (100)	1,504 (100)	–
Age (yr)						
0–19	346 (4.4)	349 (4.4)	0.002	99 (6.6)	102 (6.8)	0.008
20–39	2,835 (35.8)	2,851 (36.0)	0.004	710 (47.2)	722 (48.0)	0.016
40–59	2,554 (32.3)	2,574 (32.5)	0.005	444 (29.5)	437 (29.1)	0.010
60–69	1,176 (14.9)	1,161 (14.7)	0.005	153 (10.2)	142 (9.4)	0.025
70–79	604 (7.6)	581 (7.3)	0.011	50 (3.3)	52 (3.5)	0.007
≥ 80	396 (5.0)	395 (5.0)	0.001	48 (3.2)	49 (3.3)	0.004
Sex						
Female	4,760 (60.2)	4,779 (60.4)	0.005	729 (48.5)	733 (48.7)	0.005
Male	3,151 (39.8)	3,132 (39.6)	0.005	775 (51.5)	771 (51.3)	0.005
Region of residence						
Capital	971 (12.3)	982 (12.4)	0.004	270 (18.0)	278 (18.5)	0.014
Daegu/Gyeongbuk	6,097 (77.1)	6,097 (77.1)	0.000	1,043 (69.3)	1,042 (69.3)	0.001
Others	843 (10.7)	832 (10.5)	0.005	191 (12.7)	184 (12.2)	0.014
Economic status						
Medical aid	637 (8.1)	622 (7.9)	0.007	100 (6.6)	84 (5.6)	0.044
0–25%	1,814 (22.9)	1,787 (22.6)	0.008	353 (23.5)	335 (22.3)	0.028
26–50%	1,489 (18.8)	1,497 (18.9)	0.003	278 (18.5)	302 (20.1)	0.040
51–75%	1,668 (21.1)	1,660 (21.0)	0.002	323 (21.5)	333 (22.1)	0.016
76–100%	2,289 (28.9)	2,315 (29.3)	0.007	445 (29.6)	435 (28.9)	0.015
Underlying diseases						
Mood disorders	1,316 (16.6)	1,310 (16.6)	0.002	135 (9.0)	131 (8.7)	0.009
Hypertension	1,846 (23.3)	1,844 (23.3)	0.001	203 (13.5)	184 (12.2)	0.038
Diabetes	1,411 (17.8)	1409 (17.8)	0.001	139 (9.2)	133 (8.8)	0.014
Obesity	19 (0.2)	22 (0.3)	0.007	3 (0.2)	0 (0.0)	0.063
Nicotine dependence	2 (0.0)	3 (0.0)	0.007	0 (0.0)	0 (0.0)	–
Alcohol dependence	116 (1.5)	97 (1.2)	0.021	25 (1.7)	24 (1.6)	0.005
Chronic lower respiratory diseases	3,847 (48.6)	3,860 (48.8)	0.003	429 (28.5)	435 (28.9)	0.009
Heart diseases	817 (10.3)	799 (10.1)	0.008	55 (3.7)	55 (3.7)	0.000
Chronic kidney diseases	99 (1.3)	80 (1.0)	0.023	13 (0.9)	9 (0.6)	0.031
Malignant neoplasms	477 (6.0)	467 (5.9)	0.005	42 (2.8)	37 (2.5)	0.021
Stroke	303 (3.8)	261 (3.3)	0.029	14 (0.9)	9 (0.6)	0.038
Admission to skilled nursing facilities	301 (3.8)	291 (3.7)	0.007	53 (3.5)	50 (3.3)	0.011

Values are presented as number (%).
SMD: standardized mean difference.

participants in each group. The SMDs were less than 0.1 in all cases, indicating that the matching was done properly.

The incidence rates and HRs for the outcomes are presented in **Tables 2** and **3**. For the unspecified pain diagnoses, the COVID-19 group had higher incidence rates and HRs than the control group for pain in the throat and chest, abdominal and pelvic pain, and pain not elsewhere classified, regardless of whether being diagnosed with the pain disorders in the past year; however, this trend was not found for pain associated with micturition. The most common diagnosis was pain in the throat and chest: 6.0% (95% confidence interval, 5.5–6.6) in the COVID-19 group, whereas this was 1.6% (1.4–1.9) in the control group. The HR for pain in the throat and chest was 3.74 (3.07–4.55) in the entire cohort and 11.63 (4.64–29.1) in the cohort without a history of the pain diagnoses.

In the entire cohort, headaches were the only idiopathic pain disorder that showed a significantly higher incidence rate in the COVID-19 group (6.6%, 6.1–7.2) than in the control group (3.7%, 3.3–4.1) and the corresponding HR was 1.80 (1.55–2.08). Diagnoses of fibromyalgia, temporomandibular joint disorders, and atypical facial pain did not occur at any time during 90 days from the index date. In the cohort without a history of pain diagnoses, in addition to headaches, the incidence rate of irritable bowel syndrome was higher in the COVID-19 group (1.2%, 0.70–1.8) than in the control group (0.40%, 0.17–0.84), and the corresponding HR was 2.88 (1.13–7.39).

The incidence rate of prescriptions of opioid medication in the entire cohort was higher in the COVID-19 group (12.8%, 12.1–13.6) than in the control group (10.7%, 10.0–11.4), and the corresponding HR was 1.23 (1.12–1.35). This

Table 2. Incidence rates of the unspecified pain diagnoses, idiopathic pain disorders, and prescription of opioid medications

Variable	Entire cohort			Cohort without a history of the pain diagnoses		
	COVID-19 (n = 7,911)	Control (n = 7,911)	*P* value	COVID-19 (n = 1,504)	Control (n = 1,504)	*P* value
Unspecified pain (any one of the following)	862 (11.7%, 11.0–12.5)	499 (6.5%, 6.0–7.1)	< 0.001	99 (7.2%, 5.9–8.7)	19 (1.3%, 0.8–2.0)	< 0.001
Pain in throat and chest	449 (6.0%, 5.5–6.6)	129 (1.6%, 1.4–1.9)	< 0.001	53 (3.9%, 2.9–5.0)	5 (0.33%, 0.13–0.75)	< 0.001
Abdominal and pelvic pain	321 (4.3%, 3.9–4.8)	278 (3.6%, 3.2–4.0)	0.020	32 (2.3%, 1.6–3.2)	9 (0.60%, 0.30–1.1)	< 0.001
Pain associated with micturition	20 (0.25%, 0.16–0.39)	20 (0.25%, 0.16–0.39)	0.858	3 (0.20%, 0.06–0.61)	1 (0.07%, 0.01–0.37)	0.281
Pain, not elsewhere classified	150 (2.0%. 1.7–2.4)	113 (1.4%, 1.2–1.7)	0.005	15 (1.1%, 0.6–1.8)	4 (0.27%, 0.09–0.66)	0.006
Idiopathic pain disorders (any one of the following)	744 (10.1%, 9.4–10.8)	519 (6.7%, 6.2–7.3)	< 0.001	74 (5.4%, 4.3–6.7)	17 (1.1%, 0.7–1.8)	< 0.001
Fibromyalgia	0	0	–	0	0	–
Temporomandibular joint disorders	0	0	–	0	0	–
Headaches	491 (6.6%, 6.1–7.2)	289 (3.7%, 3.3–4.1)	< 0.001	57 (4.1%, 3.2–5.3)	9 (0.60%, 0.3–1.1)	< 0.001
Chronic prostatitis	25 (0.34%, 0.22–0.49)	20 (0.25%, 0.16–0.39)	0.347	1 (0.07%, 0.01–0.40)	2 (0.13%, 0.03–0.46)	0.622
CRPS	7 (0.09%, 0.04–0.19)	9 (0.11%, 0.06–0.21)	0.701	1 (0.07%, 0.01–0.40)	0	0.301
Atypical facial pain	0	0		0	0	-
Irritable bowel syndrome	254 (3.4%, 3.0–3.9)	231 (3.0%, 2.6–3.4)	0.108	16 (1.2%, 0.70–1.8)	6 (0.40%, 0.17–0.84)	0.019
Interstitial cystitis	2 (0.03%, 0.01–0.10)	3 (0.04%, 0.01–0.11)	0.702	0	0	-
Opioid	950 (12.8%, 12.1–13.6)	821 (10.7%, 10.0–11.4)	< 0.001	98 (7.1%, 5.8–8.5)	48 (3.2%, 2.4–4.2)	< 0.001
Opioid without malignant neoplasm	878 (11.8%, 11.1–12.6)	763 (9.9%, 9.2–10.5)	< 0.001	95 (6.9%, 5.6–8.3)	45 (3.0%, 2.2–4.0)	< 0.001

Values are presented as number (%, 95% confidence interval).
CRPS: complex regional pain syndrome.

pattern was similar even upon the exclusion of patients with malignant neoplasms and in the cohort without a history of pain diagnoses.

The incidence rates and HRs for prescriptions of antidepressants were not significantly different between the two groups, whether they were prescribed by a psychiatrist or not (**Supplementary Tables 3**, **4**). The incidence rate of prescriptions of anticonvulsants was higher in the COVID-19 group than in the control group.

The results of HRs from the five new, matched cohorts are presented in **Tables 4** (the entire cohort) and **5** (the cohort without a history of the pain diagnoses). The baseline characteristics of the five matched cohorts and corresponding incidence rates are provided in **Supplementary Tables 5–12**. In the case of the entire cohort, HRs for the unspecified pain diagnoses and the idiopathic pain disorders were less than 1 in all five matched cohorts (control group as reference) except for pain in throat and chest. That is, all five control groups were more likely to experience most of the unspecified pain and all of the idiopathic pain disorders than the COVID-19 group. Prescriptions of opioid medications also showed similar results.

The overall results were similar in the cohort without a history of the pain diagnoses. In the cohort matched to the control group that visited a hospital at least once for any reasons, the HR of prescription of opioid medications was greater than 1 in the COVID-19 group, however, for unspecified pain and idiopathic pain disorders, the HRs were mostly less than 1. In the other four control matched cohorts, the HRs of most outcomes were less than 1 or not significant.

DISCUSSION

This study conducted a large-scale analysis of electronic medical records using a nationwide cohort that included all patients with COVID-19 in South Korea. We examined whether there were differences in the incidence rates of unspecified pain diagnoses, idiopathic pain disorders, and prescriptions of opioid medications between patients with COVID-19 and those who had not had RT-PCR testing for COVID-19. We found that the risk of unspecified pain and the likelihood of being prescribed opioid medications were higher in the COVID-19 group. Among idiopathic pain disorders, only the incidence of headaches was higher in the COVID-19 group, and there were no significant differences in other idiopathic pain disorders. A similar pattern was also observed in the cohort without a history of the pain diagnoses.

Since SARS-CoV-2 infection occurs primarily in the respiratory tract, symptoms of respiratory tract infection

Table 3. HRs of the unspecified pain diagnoses, idiopathic pain disorders, and prescription of opioid medications

Variable	Entire cohort (n = 7,911)		Cohort without a history of the pain diagnoses (n = 1,504)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Unspecified pain (any one of the following)	1.83 (1.64–2.04)	< 0.001	5.81 (3.55–9.50)	< 0.001
Pain in throat and chest	3.74 (3.07–4.55)	< 0.001	11.63 (4.64–29.1)	< 0.001
Abdominal and pelvic pain	1.19 (1.01–1.40)	0.004	3.84 (1.83–8.06)	< 0.001
Pain associated with micturition	1.04 (0.56–1.94)	0.887	2.30 (0.21–24.6)	0.491
Pain, not elsewhere classified	1.39 (1.09–1.78)	0.008	3.85 (1.26–11.7)	0.018
Idiopathic pain disorders (any one of the following)	1.50 (1.34–1.68)	< 0.001	4.80 (2.83–8.15)	< 0.001
Fibromyalgia	–	–	–	–
Temporomandibular joint disorders	–	–	–	–
Headaches	1.80 (1.55–2.08)	< 0.001	6.96 (3.44–14.1)	< 0.001
Chronic prostatitis	1.34 (0.74–2.42)	0.332	0.67 (0.06–8.04)	0.750
CRPS	0.80 (0.30–2.16)	0.659	–	–
Atypical facial pain	–	–	–	–
Irritable bowel syndrome	1.14 (0.95–1.36)	0.157	2.88 (1.13–7.39)	0.027
Interstitial cystitis	0.69 (0.11–4.12)	0.682	–	–
Opioid	1.23 (1.12–1.35)	< 0.001	2.26 (1.59–3.21)	< 0.001
Opioid without malignant neoplasm	1.22 (1.11–1.35)	< 0.001	2.40 (1.67–3.45)	< 0.001

Control group as reference.

HR: hazard ratio, CI: confidence interval, CRPS: complex regional pain syndrome.

are the most common in COVID-19 patients, but nonspecific symptoms also have been frequently reported as a primary presentation, including pain such as myalgia, stomachache, or headache [2]. In addition, a higher risk for neurological disorders has also been found in COVID-19 survivors in a large-scale, long-term observational study [21]. Since disorders related to nerves, nerve roots, or plexuses, Guillain–Barré syndrome, and stroke, which were included in the study outcomes, can all be accompanied by neuropathic pain, COVID-19 might cause various types of pain.

Fatigue that occurs after the acute phase of various viral infections has been reported and studied [22]. This is called post-viral fatigue syndrome, or myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). To help clinicians and researchers better understand this phenomenon, the World Health Organization newly created an ICD code 'post-COVID-19 condition' in January 2021 [23]. The diagnostic criteria for ME/CFS include exacerbation of pain, and one of the hypotheses about the cause or exacerbation of the pain relates to inflammation [24]. Research has shown that low levels of inflammation are maintained even after recovery from a viral infection, and this inflammation can increase pain sensitivity, causing pain that was not previously felt or exacerbating existing pain [25,26]. Through this mechanism, COVID-19 survivors can experience new or worsening pain as well as chronic fatigue.

COVID-19 has also been associated with the development, exacerbation, and recurrence of chronic pain. A previous report described cases wherein patients who had experienced chronic pain in the past, but had stably improved, were diagnosed with COVID-19 upon visiting a hospital for treatment of recurrent chronic pain [27]. Although it is unclear whether worsening of chronic pain makes patients more susceptible to COVID-19, or whether the pain worsens after contracting COVID-19, COVID-19 infection should be suspected if pain worsens.

This study investigated whether patients with COVID-19 were more likely to experience unspecified pain or idiopathic pain through comparisons with different control groups derived to include individuals with various health conditions. The results of the subgroup analyses were reversed: the new control groups had higher risks of experiencing most of the unspecified pain and idiopathic pain conditions than the COVID-19 group.

The strengths of this study include its analysis of a nationwide cohort of all patients with COVID-19 in South Korea, its use of propensity score matching, and the subanalyses of different control groups with various health conditions. No previous study has analyzed the prevalence of pain using ICD codes, which is both a strength and a limitation of this study. This method has the advantage of enabling the inclusion of a large number of participants for the investigation of the incidence of pain, but at the same time, a limitation is that the nature of pain cannot be clearly identified based on ICD codes alone. Interviewing patients with COVID-19 and identifying pain through physical examinations, rather than using electronic medical records, would be suitable for describing and diagnosing the characteristics of pain in detail and accurately. However, this method is difficult to carry out with a large number of subjects, and it is also difficult to recruit a con-

Table 4. HRs for the outcomes in the entire cohort (not considering whether individuals had a history of the pain diagnoses)

Variable	Visiting a hospital at least once (n = 7,905)		Hospitalized at least once (n = 4,294)		Upper respiratory infection (n = 7,525)		Fracture of a large bone (n = 1,210)		Depressive disorders (n = 2,080)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Unspecified pain (any one of the following)	0.84 (0.76–0.93)	< 0.001	0.64 (0.58–0.72)	< 0.001	0.76 (0.69–0.84)	< 0.001	0.47 (0.38–0.58)	< 0.001	0.79 (0.67–0.94)	0.006
Pain in throat and chest	2.06 (1.72–2.46)	< 0.001	1.07 (0.90–1.28)	0.423	1.56 (1.34–1.83)	< 0.001	1.19 (0.83–1.70)	0.360	1.41 (1.07–1.86)	0.015
Abdominal and pelvic pain	0.48 (0.41–0.56)	< 0.001	0.43 (0.36–0.50)	< 0.001	0.52 (0.45–0.61)	< 0.001	0.26 (0.19–0.35)	< 0.001	0.54 (0.42–0.68)	< 0.001
Pain associated with micturition	0.32 (0.19–0.55)	< 0.001	0.42 (0.23–0.79)	0.007	0.42 (0.24–0.72)	0.002	0.59 (0.19–1.84)	0.359	1.01 (0.41–2.50)	0.982
Pain, not elsewhere classified	0.70 (0.56–0.87)	0.002	0.69 (0.54–0.89)	0.004	0.48 (0.39–0.60)	< 0.001	0.49 (0.29–0.81)	0.006	0.74 (0.51–1.08)	0.121
Idiopathic pain disorders (any one of the following)	0.68 (0.61–0.75)	< 0.001	0.76 (0.67–0.86)	< 0.001	0.58 (0.53–0.64)	< 0.001	0.55 (0.44–0.70)	< 0.001	0.46 (0.39–0.55)	< 0.001
Headaches	0.85 (0.75–0.97)	0.013	0.86 (0.73–1.00)	0.050	0.61 (0.54–0.69)	< 0.001	0.82 (0.60–1.12)	0.201	0.47 (0.39–0.57)	< 0.001
Chronic prostatitis	0.29 (0.18–0.47)	< 0.001	0.67 (0.34–1.31)	0.244	0.45(0.27–0.73)	0.001	0.15 (0.06–0.42)	< 0.001	0.20 (0.06–0.60)	0.004
CRPS	0.57 (0.21–1.56)	0.274	0.35 (0.11–1.14)	0.082	0.88 (0.28–2.74)	0.820	0.22 (0.02–2.30)	0.202	0.68 (0.15–3.11)	0.623
Irritable bowel syndrome	0.50 (0.42–0.59)	< 0.001	0.63 (0.51–0.77)	< 0.001	0.51 (0.44–0.61)	< 0.001	0.41 (0.29–0.60)	0.198	0.51 (0.39–0.66)	< 0.001
Interstitial cystitis	0.37 (0.06–2.43)	0.320	0.18 (0.02–1.61)	0.125	0.56 (0.09–3.47)	0.536	–	–	–	–
Opioid	1.03 (0.94–1.12)	0.576	0.39 (0.36–0.43)	< 0.001	0.39 (0.36–0.43)	< 0.001	0.41 (0.35–0.49)	< 0.001	0.82 (0.71–0.94)	0.003
Opioid without malignant neoplasm	1.01 (0.92–1.11)	0.794	0.41 (0.37–0.45)	< 0.001	0.38 (0.35–0.41)	< 0.001	0.40 (0.34–0.48)	< 0.001	0.81 (0.70–0.93)	0.004

Fibromyalgia, temporomandibular joint disorders, and atypical facial pain were omitted from the table because there was no occurrence.
HR: hazard ratio, CI: confidence interval, CRPS: complex regional pain syndrome.

Table 5. HRs for the outcomes in the cohort without a history of the pain diagnoses

Variable	Visiting a hospital at least once (n = 1,503)		Hospitalized at least once (n = 470)		Upper respiratory infection (n = 907)		Fracture of a large bone (n = 95)		Depressive disorders (n = 182)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Unspecified pain (any one of the following)	0.68 (0.51–0.91)	0.010	0.52 (0.33–0.81)	0.004	0.76 (0.52–1.10)	0.142	0.06 (0.01–0.49)	0.009	1.76 (0.75–4.11)	0.192
Pain in throat and chest	1.29 (0.80–2.07)	0.290	1.19 (0.60–2.37)	0.615	1.31 (0.75–2.30)	0.354	0.13 (0.01–1.25)	0.078	2.99 (0.76–11.8)	0.121
Abdominal and pelvic pain	0.38 (0.24–0.61)	< 0.001	0.24 (0.11–0.53)	0.003	0.55 (0.30–1.01)	0.053	–	–	1.06 (0.26–4.34)	0.940
Pain associated with micturition	0.41 (0.08–1.99)	0.271	0.45 (0.02–10.20)	0.615	0.17 (0.02–1.82)	0.143	–	–	–	–
Pain, not elsewhere classified	0.42 (0.20–0.86)	0.018	0.16 (0.04–0.73)	0.018	0.36 (0.15–0.87)	0.023	–	–	0.75 (0.09–6.29)	0.794
Idiopathic pain disorders (any one of the following)	0.62 (0.45–0.87)	0.005	1.19 (0.68–2.10)	0.541	0.70 (0.47–1.04)	0.081	0.14 (0.04–0.54)	0.004	0.59 (0.25–1.37)	0.215
Headaches	1.18 (0.75–1.85)	0.472	2.08 (1.01–4.30)	0.047	0.80 (0.49–1.32)	0.382	0.15 (0.01–2.44)	0.181	0.62 (0.25–1.53)	0.304
Chronic prostatitis	0.05 (0.01–0.42)	0.005	–	–	2.02 (0.05–80.7)	0.705	–	–	–	–
CRPS	0.45 (0.02–10.08)	0.610	–	–	–	–	–	–	–	–
Irritable bowel syndrome	0.29 (0.16–0.53)	< 0.001	0.46 (0.15–1.43)	0.178	0.53 (0.26–1.10)	0.088	0.02 (0.00–0.65)	0.026	–	–
Opioid	1.36 (1.01–1.85)	0.045	0.31 (0.21–0.44)	< 0.001	0.26 (0.19–0.37)	< 0.001	0.31 (0.15–0.66)	0.002	1.06 (0.57–1.98)	0.852
Opioid without malignant neoplasm	1.40 (1.03–1.91)	0.034	0.33 (0.23–0.48)	< 0.001	0.25 (0.18–0.36)	< 0.001	0.30 (0.14–0.64)	0.002	1.10 (0.58–2.10)	0.763

Fibromyalgia, temporomandibular joint disorders, and atypical facial pain were omitted from the table because there was no occurrence.
HR: hazard ratio, CI: confidence interval, CRPS: complex regional pain syndrome.

https://doi.org/10.3344/kjp.2022.35.4.458

trol group with the same pain diagnosis procedures [6].

The second limitation is that the diagnosis of unspecified pain itself is unclear. According to the ICD-10, the Chapter XVIII codes ('Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified [R00-R99]') can be used for pain that is unspecific, has no clear diagnosis, does not have an identifiable cause, cannot be classified into a specific category, or is transient, as well as if the test result has not been received yet [28]. Nevertheless, if the pain is actually a sequela of COVID-19, it might be difficult to determine the cause of the pain, and a doctor would be likely to make a diagnosis of unspecified pain. Thus, with the diagnoses used in this study, it is possible to find some, but potentially not all, people with pain due to COVID-19 sequelae. In addition, since a uniform definition of idiopathic pain disorder does not currently exist, the types of pain disorders included in idiopathic pain disorder in this study are based on the judgment of the authors. Therefore, depending on the definition of idiopathic pain disorder, there may be differences in results between studies, which is a limitation of the study.

Third, the incidences of idiopathic pain disorders other than headaches was very low, and no subjects had fibromyalgia, temporomandibular joint disorders, or atypical facial pain. For example, we speculated that the incidence of temporomandibular joint disorders might be higher in the COVID-19 group because psychological stress is known to be a risk factor, but there were no incident cases [29]. Therefore, there is a need for a study that includes more COVID-19 patients with long-term follow-up.

Finally, it was not possible to exclude the possibility that physical pain could be caused by psychological pain. It has been found that many patients with COVID-19 experience psychological illnesses such as depression and anxiety during the acute phase and even after recovery [21]. Psychological stress appears to predispose a person to post-viral fatigue syndrome [30], and among patients with COVID-19, those with more severe depression felt more fatigue [31]. Since depression is a factor that aggravates pain, these psychological factors may have acted as a confounder in the occurrence of pain, but the present study could not adjust for this possible confounder.

To our knowledge, this is the first study with a large cohort to investigate the incidence of unspecified pain and idiopathic pain in patients with COVID-19 during an observation period of 90 days after COVID-19 diagnosis. Patients with COVID-19 were found to be at a higher risk of experiencing unspecified pain than those who had not had RT-PCR testing for COVID-19. However, the risk was lower compared to those who visited a hospital for any reasons. Since it has been shown that there are also many patients with COVID-19 who take opioid medications, a careful differential diagnosis will be particularly important for people who suffer from pain, and on this basis, opioid medications should be used with an appropriate diagnosis. In summary, patients with COVID-19 might be at a higher risk of experiencing unspecified pain in the acute phase or after recovery compared with individuals who had not had tests for COVID-19. However, the risk may differ depending on the control group. It is necessary to study the risk of unspecified or idiopathic pain due to COVID-19 through a more accurate diagnosis and control group setting.

DATA AVAILABILITY

The datasets supporting the findings of this study are not publicly available due to personal information protective policy and technical limitations.

ACKNOWLEDGMENTS

We would like to thank all staff members of the National Health Insurance Sharing Service.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), and Ministry of Health & Welfare, Republic of Korea (grant number: HI21C0198).

ORCID

Namwoo Kim, https://orcid.org/0000-0002-1684-5417
Jeewuan Kim, https://orcid.org/0000-0002-2945-3893
Bo Ram Yang, https://orcid.org/0000-0002-8771-8829
Bong-Jin Hahm, https://orcid.org/0000-0002-2366-3275

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.3344/kjp.2022.35.4.458.

REFERENCES

1. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (delta) variant. N Engl J Med 2021; 385: 585-94.
2. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry 2020; 7: 611-27.
3. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol 2020; 19: 767-83.
4. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Sci Rep 2021; 11: 16144.
5. Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain 2020; 143: 3104-20.
6. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021; 397: 220-32.
7. Köseoğlu Toksoy C, DemirbaşH, Bozkurt E, Acar H, Türk Börü Ü. Headache related to mask use of healthcare workers in COVID-19 pandemic. Korean J Pain 2021; 34: 241-5.
8. Clauw DJ, Häuser W, Cohen SP, Fitzcharles MA. Considering the potential for an increase in chronic pain after the COVID-19 pandemic. Pain 2020; 161: 1694-7.
9. Chaturvedi SK. Health anxiety, health-related life events, and somatization during COVID-19 pandemic can increase chronic pain. Pain 2020; 161: 2652.
10. Karos K, McParland JL, Bunzli S, Devan H, Hirsh A, Kapos FP, et al. The social threats of COVID-19 for people with chronic pain. Pain 2020; 161: 2229-35.
11. Drożdżal S, Rosik J, Lechowicz K, Machaj F, Szostak B, Majewski P, et al. COVID-19: pain management in patients with SARS-CoV-2 infection-molecular mechanisms, challenges, and perspectives. Brain Sci 2020; 10: 465.
12. Xiong Q, Xu M, Li J, Liu Y, Zhang J, Xu Y, et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. Clin Microbiol Infect 2021; 27: 89-95.
13. CarfìA, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. JAMA 2020; 324: 603-5.
14. Mun CJ, Campbell CM, McGill LS, Aaron RV. The early impact of COVID-19 on chronic pain: a cross-sectional investigation of a large online sample of individuals with chronic pain in the United States, April to May, 2020. Pain Med 2021; 22: 470-80.
15. Nunes EV, Levin FR, Reilly MP, El-Bassel N. Medication treatment for opioid use disorder in the age of COVID-19: can new regulations modify the opioid cascade? J Subst Abuse Treat 2021; 122: 108196.
16. Kim N, Cho SJ, Kim H, Kim SH, Lee HJ, Park CHK, et al. Epidemiology of pharmaceutically treated depression and treatment resistant depression in South Korea. PLoS One 2019; 14: e0221552.
17. Kim L, Kim JA, Kim S. A guide for the utilization of Health Insurance Review and Assessment Service National Patient Samples. Epidemiol Health 2014; 36: e2014008.
18. World Health Organization. ICD-10: international statistical classification of diseases and related health problems: tenth revision. 2nd ed. Geneva, World Health Organization. 2004.
19. Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders--pathways of vulnerability. Pain 2006; 123: 226-30.
20. McMichael TM, Currie DW, Clark S, Pogosjans S, Kay M, Schwartz NG, et al. Epidemiology of Covid-19 in a long-term care facility in King County, Washington. N Engl J Med 2020; 382: 2005-11.
21. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry 2021; 8: 416-27.
22. Komaroff AL, Bateman L. Will COVID-19 lead to myalgic encephalomyelitis/chronic fatigue syndrome? Front Med (Lausanne) 2021; 7: 606824.
23. Vollbracht C, Kraft K. Feasibility of vitamin C in the treatment of post viral fatigue with focus on long COVID, based on a systematic review of IV vitamin C on fatigue. Nutrients 2021; 13: 1154.
24. Shorey S, Chan V. Lessons from past epidemics and pandemics and a way forward for pregnant women, midwives and nurses during COVID-19 and beyond: a meta-synthesis. Midwifery 2020; 90: 102821.
25. Mueller C, Lin JC, Sheriff S, Maudsley AA, Younger JW. Evidence of widespread metabolite abnormalities in Myalgic encephalomyelitis/chronic fatigue syndrome: assessment with whole-brain magnetic resonance spectroscopy. Brain Imaging Behav 2020; 14: 562-72.
26. Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. Nat Rev Dis Primers 2017; 3: 17002.
27. Alizadeh R, Aghsaeifard Z. Does COVID19 activates previous chronic pain? A case series. Ann Med Surg (Lond) 2021; 61: 169-71.
28. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, American Psychiatric Publishing. 2013.
29. Poveda Roda R, Bagan JV, Díaz Fernández JM, Hernández

Bazán S, Jiménez Soriano Y. Review of temporomandibular joint pathology. Part I: classification, epidemiology and risk factors. Med Oral Patol Oral Cir Bucal 2007; 12: E292-8.
30. Afari N, Buchwald D. Chronic fatigue syndrome: a review. Am J Psychiatry 2003; 160: 221-36.
31. Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS One 2020; 15: e0240784.