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ORIGINAL RESEARCH

Exacerbation of Pre-Existing Chronic Pain in Older Adults After SARS-CoV-2 Infection: A Single-Center, Cross-Sectional, Observational Study

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Purpose: To identify the prevalence of exacerbation of pre-existing chronic pain after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and investigate the impact of exacerbated previous chronic pain on quality of life, sleep quality, anxiety and depression levels and risk factors associated with exacerbated chronic pain among elderly coronavirus disease of 2019 (COVID-19) survivors.

Patients and Methods: In this cross-sectional study, elderly COVID-19 survivors with chronic pain residing in Continuing Care Retirement Community (CCRC) were recruited from April 2023 to June 2023. Eligible individuals were divided into exacerbation and non-exacerbation groups based on the patient-reported worsening symptoms of previous chronic pain after SARS-CoV-2 infection. Baseline information, COVID-19 symptoms, laboratory parameters, characteristics of exacerbated chronic pain, quality of life, anxiety and depression levels were systematically collected.

Results: Ninety-five (95/441, 21.5%) older adults suffered from exacerbated chronic pain with a median numerical rating scale (NRS) score of 6 (4–7) on a median duration of 4.9 (4.3–5.6) months after SARS-CoV-2 infection. More participants were not vaccinated against COVID-19 (46.5%, 40/86 vs 26.1%, 86/330, $P < 0.001$) in exacerbation group. Exacerbation group exhibited poor quality of life (EQ5D index: 0.734 [0.536–0.862] vs 0.837 [0.716–0.942], $P < 0.001$), more severe anxiety (GAD-7: 2 [0–5] vs 0 [0–3], $P < 0.001$) and depression (PHQ-9: 4 [2–7] vs 2.5 [0–5], $P < 0.001$) than non-exacerbation group. Risk factors significantly associated with exacerbation of pre-existing chronic pain were neuropathic pain (aOR 4.81, 95% CI 1.73–13.32, $P = 0.003$), lymphocyte count (aOR 0.31, 95% CI 0.12–0.78, $P = 0.013$) and D-dimer levels (aOR 6.46, 95% CI 1.92–21.74, $P = 0.003$).

Conclusion: Our study observed a prevalence of 21.5% exacerbation of pre-existing chronic pain after SARS-CoV-2 infection, with a consequence of poor quality of life, more severe anxiety and depression. Previous chronic neuropathic pain, lower lymphocyte count and higher D-dimer levels were risk factors associated with the development of exacerbated previous chronic pain.

Keywords: post-COVID-19, older adults, chronic pain, exacerbated symptoms

Introduction

After the coronavirus disease of 2019 (COVID-19) pandemic, attention has shifted towards the enduring alterations within multiple biological systems triggered by the infection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] The distinctive manifestation of post-COVID-19 condition (PCC) was post-COVID pain and exacerbated symptoms of previous chronic pain.[3] Several observational studies have investigated the new-onset musculoskeletal pain symptoms and risk factors correlated with post-COVID pain among COVID-19 survivors.[4,5] Approximately

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15.1% to 45.1% of COVID-19 survivors suffered from post-COVID pain,[6,7] and a correlation was found between prognostic serological biomarkers (eg, lymphocyte count, D-dimer levels, C-reactive protein concentration and glucose levels) and long-term post-COVID pain.[1,4] Conversely, only two studies have highlighted the exacerbation of pre-existing pain among middle-aged and hospitalized patients after SARS-CoV-2 infection, indicating a prevalence of 25.1% and 66.6%, respectively.[2,6]

As the virulence and transmission of SARS-CoV-2 continue to evolve,[8] an increasing number of people are facing the problem of SARS-CoV-2 infection. Among them, the elderly are more susceptible to COVID-19 due to waning immune functions and are prone to the development of chronic pain because of troubles caused by degenerative osteoarticular diseases.[9] However, less is known regarding the prevalence and compositions of exacerbated previous chronic pain, particularly among elderly COVID-19 survivors. Additionally, scanty data exist on the risk factors of exacerbated chronic pain and whether the exacerbated chronic pain would have impacts on quality of life, sleep quality and anxiety/depression levels in the elderly population.

In light of these gaps, the aims of our study were 1) to identify the prevalence of exacerbated previous chronic pain among elderly COVID-19 survivors; 2) to investigate the impact of exacerbated previous chronic pain on quality of life, sleep quality, anxiety and depression levels in elderly COVID-19 survivors; 3) to investigate risk factors associated with the development of exacerbation of previous chronic pain.

Materials and Methods

Study Design and Participants

It was a cross-sectional study conducted in Taikang Yanyuan Continuing Care Retirement Community (CCRC) in China, where 2105 older adults lived and their family physicians provided regular health care for them. Residents in the CCRC who recovered from COVID-19 (Omicron strain, infection date was between December 2022 and January 2023) from April 2023 to June 2023 were recruited through internal digital media. The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Sanbo Brain Hospital, Capital Medical University (SBNK-YJ -2023-013-01). Informed consent was obtained from all participants or their legally authorized representatives before enrollment.

Participants met the following criteria to be included: (I) age ≥65 years. (II) diagnosis of SARS-CoV-2 infection by real-time reverse transcription-polymerase chain reaction (RT-PCR) assay of nasopharyngeal/oral swab samples more than 3 months before the study inclusion. (III) participants had a history of chronic pain before SARS-CoV-2 infection. Chronic pain is defined according to the International Association for the Study of Pain (IASP) as persistent or recurrent pain lasting longer than 3 months.[10] Participants were excluded if they had the following diseases or status: (I) cognitive dysfunction, (II) mental illness, (III) severe systematic diseases (eg, severe cardiopulmonary disease, multi-organ dysfunction), and (IV) unable to complete the assessment due to various reasons.

Assessment Procedure

All eligible individuals were scheduled for a face-to-face interview, and an investigation was conducted based on a structured questionnaire mainly focusing on the exacerbation of previous chronic pain by pain physicians. Participants were asked for whether the pre-existing chronic pain was exacerbated and persisted at the time of assessment. Exacerbation of chronic pain was defined as the patient-reported worsening symptoms of previous chronic pain after SARS-CoV-2 infection (ie, increase of intensity, increase of frequency, or extension of distribution) that remained unresolved during the assessment.[6] In order to distinguish the extension of pain distribution and post-COVID pain, it was important to note that post-COVID pain was new-onset pain without underlying medical conditions to be explained and was clearly different from previous pain conditions (eg, affecting a distinct location or exhibiting varying pain characteristics), while the extension of pain distribution was considered when it was in line with innervation range of previous pain conditions or was associated with the medical history of chronic pain. If there was uncertainty about whether pre-existing chronic pain was exacerbated, a unanimous position would be achieved through a discussion between pain specialists and doctors with experience of PCC. If worsening symptoms of previous chronic pain were

observed, comprehensive data encompassing the location of exacerbated pain, manifestation of exacerbated symptoms, average pain intensity in the past week, nature of pain, and analgesic medication use would be documented. In cases where exacerbation was not observed, only average pain intensity in the past week, nature of pain, and analgesic medication use were recorded. Besides, quality of life, sleep quality, anxiety and depression levels were also evaluated through this interview simultaneously.

Grouping

Eligible participants were categorized into exacerbation group and non-exacerbation group determined by the presence of exacerbation of previous chronic pain during the assessment.

Scales and Definition

Pain intensity was assessed by the verbal numeric rating scale (NRS) ranging from 0 (absence of pain) to 10 (the utmost severity of pain). The nature of pain was evaluated through the Douleur Neuropathique-4 questionnaire (DN-4), consisting of 9 questions.[11] A DN-4 score ≥4 indicated neuropathic pain. The EuroQol 5D-5L questionnaire (EQ-5D-5L) was employed for evaluating an individual's health state, which involves 5 levels in 5 dimensions (ie, mobility, self-care, usual activities, pain and discomfort, anxiety and depression).[12] EQ-5D visual analogue scale (VAS) was an instrument for the evaluation of self-reported health status, ranging from 0 (the worst health status) to 100 (the best health status). EQ-5D index was an index value anchored at 0 for death and 1 for perfect health and was calculated according to the estimated value set in China.[13] Sleep quality was evaluated by the Pittsburgh Sleep Quality Index (PSQI).[14] Higher scores of PSQI indicate poorer sleep quality. The generalized anxiety disorder (GAD-7) scale and patient health questionnaire-9 (PHQ-9) scale were used for the screening of anxiety and depression, respectively.[15,16] Higher scores indicate a more severe state of anxiety and depression.

Data Collection

Clinical data including age, sex, height, weight, medical comorbidities, onset symptoms of COVID-19 within the first 7 days, and hospitalization were collected through the Taikang healthcare electronic system. If available, chest computed tomography (CT) and laboratory parameters (ie, hemoglobin, lymphocyte count, neutrophil count, platelet count, glucose, creatine, hs-CRP, ALT, AST, D-dimer and PCT) from the first 7 days after SARS-CoV-2 infection were systematically retrieved from this system as well.

Statistical Analysis

Normality of quantitative variables was analyzed through Kolmogorov–Smirnov test. Continuous data were presented as medians and interquartile ranges (IQRs) or mean and standard deviation (SD), contingent upon their distribution. Categorical data were represented as frequency distributions. Difference analysis was conducted using the Mann–Whitney *U*-test, Student's *t*-test, or chi-square test, depending on the data type and distribution. Multivariable logistic regression was applied for the risk factor analysis using the enter procedure, with variables including age, sex, medical comorbidities, nature of pain, COVID-19 symptoms and laboratory parameters selected by univariable logistic regression with P value <0.2 as independent variables, and exacerbation of previous chronic pain as dependent variable. Relevant outcomes were represented by adjusted odds ratio (aOR) and 95% confidence interval (CI). Multiple linear regressions were performed to adjust the effect of confounders in baseline on EQ-5D index, EQ-VAS, PSQI, GAD-7 and PHQ-9 scores, and the outcomes were represented by regression coefficient (B) and 95% CI. In cases where missing values accounted for less than 20% of the data, multiple imputation was performed to fill in the missing values using the predictive mean matching method.

All analyses were performed in SPSS (version 23.0, IBM, NY, USA). Statistical significance was set at a value of $P < 0.05$.

Results

A total of 813 participants underwent preliminary screening for inclusion and 441 of them were eventually investigated and included in our study, with 95 participants in exacerbation group and 346 participants in non-exacerbation group. Among them, 43 participants in exacerbation group and 148 participants in non-exacerbation group underwent laboratory tests during the first 7 days after SARS-CoV-2 infection (Figure 1).

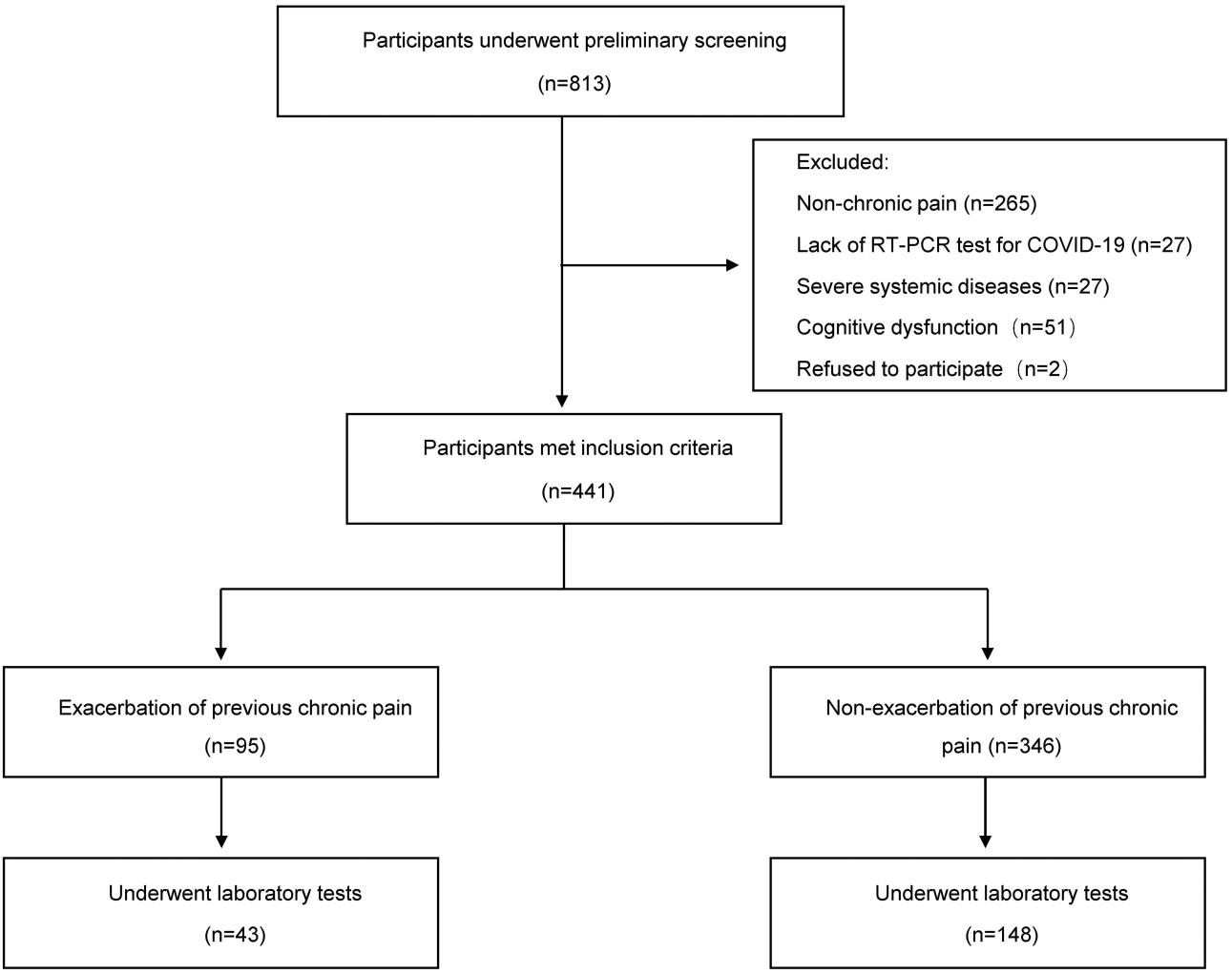

Figure 1 Flow chart of participants inclusion.

Demographic Data and Medical Comorbidities

Exacerbation group exhibited a higher prevalence of COPD (21.1%, 20/95 vs 10.1%, 35/346, P = 0.004) and cancer (20.0%, 19/95 vs 11.3%, 39/346, P = 0.026) when compared to the non-exacerbation group. No significant differences in demographic data and other medical comorbidities were observed between the two groups (Table 1).

Prevalence and Compositions of Exacerbated Chronic Pain

Ninety-five individuals (95/441, 21.5%) reported exacerbated chronic pain with a median NRS score of 6 (4–7) on a median duration of 4.9 (4.3–5.6) months after SARS-CoV-2 infection. Among older adults with chronic head and neck pain, 31.5% (11/35) reported a worsening of their pain symptoms. In individuals with chronic thoracic pain, 21.3% (5/16) reported an exacerbation in their pain symptoms. Within the older adults with chronic back pain, the prevalence of exacerbated chronic pain stood at a rate of 18.5% (48/259). In individuals with chronic pain in upper and lower limbs, the prevalence of exacerbation was 26.7% (20/75) and 26.5% (30/113), respectively. Moreover, we observed a prevalence of 22.6% (53/235) in elderly with exacerbated chronic joint pain, and the prevalence was 23.1% (3/13) in older adults with exacerbation of chronic widespread pain. The main complaint of exacerbation was the increase of intensity (62/95, 65.3%), followed by the increase of frequency (39/95, 41.1%) and extension of pain distribution (17/95, 17.9%). In individuals with neuropathic pain, 41.2% (21/51) of individuals reported exacerbated symptoms of neuropathic pain. Conversely, in individuals with non-neuropathic pain, only 19.0% (74/390) reported a worsening of their pain symptoms (Table 2).

Table 1 Demographic Data and Medical Comorbidities in Elderly COVOD-19 Survivors

Variables	Exacerbation (N=95)	Non-Exacerbation (N=346)	P
Age, years, median (IQR)	84 (80–87)	85 (80–87)	0.396
Sex, female, n (%)	67 (70.5)	225 (65.0)	0.316
Height, cm, median (IQR)	156 (152–165)	159 (153–165)	0.562
Weight, kg, mean (SD)	61.9 (10.4)	61.0 (10.9)	0.449
Medical comorbidities			
Hypertension, n (%)	77 (81.1)	286 (82.7)	0.716
Diabetes, n (%)	42 (44.2)	158 (45.7)	0.801
Cardiovascular disease, n (%)	49 (51.6)	189 (54.6)	0.598
COPD*, n (%)	20 (21.1)	35 (10.1)	0.004
Cerebrovascular disease, n (%)	20 (21.1)	81 (23.4)	0.628
Cancer*, n (%)	19 (20.0)	39 (11.3)	0.026
Other[a], n (%)	40 (42.1)	148 (42.8)	0.907
Number of medical comorbidities, median (IQR)	3 (2–4)	3 (2–4)	0.389

Notes: * Represents a statistically significant difference with P < 0.05. [a]Includes hyperlipidemia, chronic kidney disease, chronic gastritis, Parkinson's disease, and rheumatic disease.
Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SD, standard deviation.

Table 2 Exacerbation of Pre-Existing Chronic Pain in Elderly COVID-19 Survivors

Variables	COVID-19 Survivors (N = 441)
Exacerbated previous chronic pain, n (%)	95 (21.5)
Location of exacerbated chronic pain	
Head & neck, n (%)	11/35 (31.4)
Thorax, n (%)	5/16 (21.3)
Back, n (%)	48/259 (18.5)
Upper limbs, n (%)	20/75 (26.7)
Lower limbs, n (%)	30/113 (26.5)
Joints (knee, hip, hands and feet), n (%)	53/235 (22.6)
Widespread, n (%)	3/13 (23.1)
Manifestation of exacerbated pain symptoms	
Increase of intensity, n (%)	62 (65.3)
Increase of frequency, n (%)	39 (41.1)
Extension of distribution, n (%)	17 (17.9)

(*Continued*)

Table 2 (Continued).

Variables	COVID-19 Survivors (N = 441)
Nature of pain	
Neuropathic pain, n (%)	21/51 (41.2)
Non-neuropathic pain, n (%)	74/390 (19.0)
Average pain intensity in the past week, median (IQR)	6 (4–7)
Duration of COVID-19 to assessment, months, median (IQR)	4.9 (4.3–5.6)

Abbreviations: COVID-19, coronavirus disease of 2019; IQR, interquartile range.

Vaccination Status

A total of 416 (94.3%) records about COVID-19 vaccination were retrieved, 86 of which were in exacerbation group and 330 of which were in non-exacerbation group. More participants were not vaccinated against COVID-19 (46.5%, 40/86 vs 26.1%, 86/330, P < 0.001) and fewer individuals were vaccinated for more than 3 doses (37.2%, 32/86 vs 52.7%, 174/330, P = 0.010) in exacerbation group when compared with individuals in non-exacerbation group. There was no significant difference in the proportion of vaccinations administered with 1 and 2 doses between the two groups. In addition, the types of vaccines were not significantly different between the two groups (Table 3).

COVID-19 Symptoms and Laboratory Parameters

Regarding COVID-19 symptoms, participants in the exacerbation group exhibited a higher prevalence of dyspnea (14.7%, 14/95 vs 6.9%, 24/346, P < 0.001) and myalgia (32.6%, 31/95 vs 15.9%, 55/346, P < 0.001), along with a higher onset symptom load (3.26 ± 1.42 vs 2.93 ± 1.54, P = 0.043) during the initial 7 days post-infection in comparison to the non-exacerbation group. Moreover, lymphocyte count was significantly lower (0.83 [0.56–1.16] vs 0.99 [0.71–1.42], P = 0.034), while D-dimer levels were significantly higher (0.48 [0.30–0.92] vs 0.41 [0.27–0.57], P = 0.047) in participants of the exacerbation group (Table 4).

Pain, Quality of Life, Sleep Quality, Anxiety and Depression Levels

Participants in exacerbation group exhibited higher NRS scores (6 [4–7] vs 4 [3–5], P < 0.001), a greater prevalence of neuropathic pain (22.1%, 21/95 vs 8.7%, 30/346, P < 0.001), and more use of pain medication (46.3%, 44/95 vs 29.2%, 101/346, P = 0.002) in contrast to the non-exacerbation group. However, there was no significant difference in the use of NSAIDs (52.7%, 23/44 vs 65.3%, 66/101, P = 0.137), antiepileptic drugs (11.4%, 5/44 vs 9.9%, 10/101, P = 1.000), Chinese medicine

Table 3 Vaccination Status in Elderly COVID-19 Survivors

	Exacerbation (N=86)	Non-Exacerbation (N=330)	P
Vaccination			
No vaccination, n (%)	40 (46.5)	86 (26.1)	<0.001
1 dose, n (%)	2 (2.3)	10 (3.0)	1.000
2 doses, n (%)	12 (14.0)	60 (18.2)	0.356
≥3 doses, n (%)	32 (37.2)	174 (52.7)	0.010
Type of vaccines			
CoronaVac, Sinovac, n (%)	38 (82.6)	201 (82.4)	0.699
Covilo, Sinopharm, n (%)	5 (10.9)	33 (13.5)	
Convidecia, CanSinoBIO,n (%)	3 (6.5)	10 (4.1)	

Table 4 COVID-19 Symptoms and Laboratory Parameters Between Participants with or without Exacerbation of Pre-Existing Chronic Pain

Variables	Exacerbation (N=95)	Non-Exacerbation (N=346)	P
COVID-19 symptoms on initial 7 days			
Fever, n (%)	69 (72.6)	254 (73.4)	0.879
Dyspnea*, n (%)	14 (14.7)	24 (6.9)	<0.001
Cough, n (%)	56 (58.9)	195 (56.4)	0.652
Myalgia*, n (%)	31 (32.6)	55 (15.9)	<0.001
Diarrhea, n (%)	6 (6.3)	16 (4.6)	0.502
Anosmia, n (%)	9 (9.5)	20 (5.8)	0.198
Ageusia, n (%)	11 (11.6)	36 (10.4)	0.742
Throat pain, n (%)	41 (43.2)	149 (43.1)	0.987
Vomiting, n (%)	4 (4.2)	12 (3.5)	0.732
Fatigue, n (%)	69 (72.6)	253 (73.1)	0.924
Number of COVID-19 symptoms at 0–7 days*, mean (SD)	3.26 (1.42)	2.93 (1.54)	0.043
Abnormal chest CT, n (%)	37/59 (62.7)	103/184 (56.0)	0.362
Hospitalization, n (%)	7 (7.4)	14 (4.0)	0.178
Laboratory tests	N=43	N=148	
Hemoglobin (g/dL), mean (SD)	12.9 (1.39)	13.0 (1.36)	0.515
Lymphocyte* ($\times 10^9$/L), median (IQR)	0.83 (0.56–1.16)	0.99 (0.71–1.42)	0.034
Neutrophils ($\times 10^9$/L), median (IQR)	3.23 (2.48–4.59)	3.07 (2.34–4.67)	0.576
Platelets ($\times 10^9$/L), median (IQR)	149 (105–189)	156 (123–197)	0.421
Glucose (mg/mL), median (IQR)	6.58 (5.51–8.15)	6.62 (5.79–7.98)	0.444
Creatine (μmol/L), median (IQR)	77.1 (63.3–91.1)	75.3 (63.8–94.2)	0.903
hs-CRP (mg/L), median (IQR)	8.61 (1.79–19.6)	8.16 (2.88–21.5)	0.767
ALT (U/L), median (IQR)	17.9 (14.2–27.1)	19.1 (13.7–27.3)	0.855
AST (U/L), median (IQR)	27.8 (21.0–45.4)	26.9 (21.8–34.3)	0.259
D-dimer* (ng/mL), median (IQR)	0.48 (0.30–0.92)	0.41 (0.27–0.57)	0.047
PCT (ng/mL), median (IQR)	0.07 (0.05–0.09)	0.06 (0.05–0.09)	0.892

Note: *Represents a statistically significant difference with $P < 0.05$.
Abbreviations: COVID-19, coronavirus disease of 2019; CT, computed tomography; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PCT, procalcitonin; IQR, interquartile range; SD, standard deviation.

plaster (52.7%, 23/44 vs 62.4%, 63/101, P = 0.255), and tramadol (6.8%, 3/44 vs 12.9%, 13/101, P = 0.435) between the two groups (Table S1). Lower EQ-5D index (0.734 [0.536–0.862] vs 0.837 [0.716–0.942], P < 0.001) and lower EQ-VAS (70 [60–80] vs 75 [65–80], P = 0.001) were observed in exacerbation group than that in non-exacerbation group. This discrepancy was correlated to an increased burden on the subsequent dimensions of quality of life: mobility (2 [1–3] vs 1 [1–2], P = 0.017), usual activity (2 [1–3] vs 2 [1–2], P = 0.013), pain/discomfort (3 [2–3] vs 2 [2–2.5], P < 0.001) and anxiety/depression (2 [1–3] vs 1 [1–2], P < 0.001). After adjusting for age, sex, medical history of COPD and cancer, multiple linear regression showed the

exacerbation of previous chronic pain was negatively associated with EQ-5D index (B=−0.112, 95% CI: −0.172 to −0.053, P < 0.001) and EQ-VAS (B=−3.792, 95% CI: −6.679 to −0.804, P = 0.013). Similarly, GAD-7 and PHQ-9 scores also indicated more severe levels of anxiety (2 [0–5] vs 0 [0–3], P < 0.001) and depression (4 [2–7] vs 2.5 [0–5], P < 0.001) in the exacerbation group. After adjusting for age, sex, medical history of COPD and cancer, and antiepileptic drugs, multiple linear regression showed the exacerbation of previous chronic pain was positively associated with GAD-7 (B = 1.122, 95% CI: 0.431–1.813, P = 0.002) and PHQ-9 scores (B = 1.531, 95% CI: 0.698–2.364, P < 0.001). However, significant differences were not observed in PSQI (8 [4–12] vs 7 [4–11], P = 0.265) between the two groups, and no association was detected between exacerbation of chronic pain and PSQI scores (B = 0.475, 95CI: −0.535–1.485, P = 0.356) after the adjustment of age, sex, and medical history of COPD and cancer (Table 5).

Risk Factors of Exacerbated Pre-Existing Chronic Pain

Univariable logistic regression analysis revealed that COPD (OR 2.37, 95% CI 1.29–4.33, P = 0.005), cancer (OR 1.96, 95% CI 1.07–3.59, P = 0.028), vaccination status (OR 0.73, 95% CI 0.61–0.87, P < 0.001), symptoms of dyspnea (OR 2.31, 95% CI 1.14–4.68, P = 0.019) and myalgia (OR 2.56, 95% CI 1.52–4.29, P < 0.001), numbers of COVID-19 symptoms (OR 1.15, 95% CI 0.99–1.34, P = 0.060), neuropathic pain (OR 2.98, 95% CI 1.62–5.15, P < 0.001), lymphocyte count (OR 0.42, 95% CI 0.20–0.89, P = 0.024), and D-dimer levels (OR 5.13, 95% CI 1.77–14.83, P = 0.003) were potential candidate variables associated with exacerbation of pre-existing chronic pain. Subsequently, the candidate variables were used for further analysis with multivariable logistic regression, and there was no multi-collinearity observed among these variables. Multivariable logistic regression analysis revealed that neuropathic pain (aOR 4.81, 95% CI 1.73–13.32, P = 0.003), lymphocyte count (aOR 0.31, 95% CI 0.12–0.78, P = 0.013) and D-dimer levels (aOR 6.46, 95% CI 1.92–21.74, P = 0.003) were independent risk factors associated with exacerbation of pre-existing chronic pain (Table 6).

Table 5 Pain, Quality of Life, Sleep Quality, Anxiety and Depression Levels Between Participants with or without Exacerbation of Pre-Existing Chronic Pain

Variables	Exacerbation (N=95)	Non-Exacerbation (N=346)	P
Average pain intensity in the past week*, median (IQR)	6 (4–7)	4 (3–5)	<0.001
Neuropathic pain*, n (%)	21 (22.1)	30 (8.7)	<0.001
Pain medication*, n (%)	44 (46.3)	101 (29.2)	0.002
EQ5D index*, median (IQR)	0.734 (0.536–0.862)	0.837 (0.716–0.942)	<0.001
Mobility*, median (IQR)	2 (1–3)	1 (1–2)	0.017
Self-care, median (IQR)	1 (1–2)	1 (1–2)	0.128
Usual activity*, median (IQR)	2 (1–3)	2 (1–2)	0.013
Pain/discomfort*, median (IQR)	3 (2–3)	2 (2–2.5)	<0.001
Anxiety/depression*, median (IQR)	2 (1–3)	1 (1–2)	<0.001
EQ-VAS*, median (IQR)	70 (60–80)	75 (65–80)	0.001
PSQI, median (IQR)	8 (4–12)	7 (4–11)	0.265
GAD-7*, median (IQR)	2 (0–5)	0 (0–3)	<0.001
PHQ-9*, median (IQR)	4 (2–7)	2.5 (0–5)	<0.001

Note: *Represents a statistically significant difference with P < 0.05.
Abbreviations: EQ5D, EuroQol Five Dimensions Questionnaire; EQ-VAS, EuroQol visual analogue scale; PSQI, Pittsburgh Sleep Quality Index; GAD-7, Generalized Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9; IQR, interquartile range.

Table 6 Univariable and Multivariable Logistic Regression Analysis for Exacerbation of Pre-Existing Chronic Pain Among Elderly COVID-19 Survivors

Variables	Univariable		Multivariable	
	OR (95% CI)	P	aOR (95% CI)	P
Age	0.97 (0.94–1.01)	0.249	–	–
Sex	0.77 (0.47–1.27)	0.316	–	–
COPD	2.37 (1.29–4.33)	0.005	1.82 (0.64–5.14)	0.262
Cancer	1.96 (1.07–3.59)	0.028	2.52 (0.84–7.50)	0.098
Numbers of comorbidities	1.06 (0.89–1.26)	0.507	–	–
Vaccination	0.73 (0.61–0.87)	<0.001	0.94 (0.68–1.29)	0.694
Dyspnea	2.31 (1.14–4.68)	0.019	0.50 (0.11–2.22)	0.363
Myalgia	2.56 (1.52–4.29)	<0.001	2.82 (0.76–6.90)	0.144
Numbers of COVID-19 symptoms at 0–7 days	1.15 (0.99–1.34)	0.060	1.03 (0.76–1.40)	0.854
Neuropathic pain*	2.98 (1.62–5.15)	<0.001	4.81 (1.73–13.32)	0.003
Lymphocyte ($\times 10^9$/L) *	0.42 (0.20–0.89)	0.024	0.31 (0.12–0.78)	0.013
D-dimer (ng/mL) *	5.13 (1.77–14.83)	0.003	6.46 (1.92–21.74)	0.003

Notes: Hosmer–Lemeshow test: P=0.79. * Represents a statistically significant difference with P < 0.05.
Abbreviations: OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease of 2019.

Discussion

In the present study, we observed 21.5% of elderly COVID-19 survivors suffered from exacerbation of chronic pain after a median duration of 4.9 months since SARS-CoV-2 infection. Notably, exacerbation of chronic pain correlated with a poor quality of life, more severe anxiety, and depression in contrast to individuals without such exacerbation. Moreover, previous chronic neuropathic pain, lower lymphocyte count, and higher D-dimer levels were identified as potential predictors for the exacerbation of chronic pain.

Exacerbated Pre-Existing Chronic Pain in Elderly Post-Infection

The elderly population, in theory, would face a higher risk of post-infectious exacerbation of chronic pain due to decreased physical fitness, more comorbidities, and age-related alterations in the immune system.[17] These factors could magnify the virus's impact on immune responses and inflammation regulation, subsequently increasing the likelihood of post-COVID pain or the exacerbation of chronic pain. However, in our study, the prevalence of exacerbated pre-existing chronic pain was 21.5%, below the documented rates of 25.1% and 66.6% in existing literature.[2,6] This divergence could be attributed to the attenuated virulence of the Omicron variant since evidence suggested that people infected with Omicron variant exhibited fewer long-COVID symptoms.[18] Furthermore, an additional factor contributing to the variance in the prevalence pertained to the varying follow-up periods, because a fluctuating characteristic of post-COVID symptomatology was found with an increased prevalence after 60 days and a decrease after 180 days.[5] In our study, exacerbation of previous chronic pain was considered only when individuals reported the presence of exacerbated chronic pain after SARS-CoV-2 infection and the symptoms still existed during our assessment. It is important to acknowledge that our findings might not account for instances where exacerbated pain symptoms persisted for several months yet resolved before the assessment, which might lead to an underestimation of the prevalence of exacerbated pre-existing chronic pain but reduce the potential for recall bias. Besides, our study reported the exacerbation of chronic pain based on different pain types, regions and manifestation, which was not specifically described in other studies.[2,6]

A pivotal information gleaned from our study was that the exacerbation of chronic pain was associated with a decreased quality of life, more severe anxiety and depression among the elderly population. However, whether and for how long this exacerbated chronic pain would be self-resolved, improved, or even worsened remains unclear. Therefore, a longer-term cohort study with multiple follow-ups is needed to bring us further insight into these issues.

Risk Factors and Potential Mechanisms

There was limited research exploring the association between serological biomarkers during the acute phase of COVID-19 and the exacerbation of chronic pain in the elderly. Our findings indicated that previous chronic neuropathic pain, lower lymphocyte count, and elevated D-dimer levels may be indicative of the exacerbation of previous chronic pain among elderly COVID-19 survivors. This finding aligned with Bakilan et al's study,[1] which also identified similar changes in D-dimer and lymphocyte counts in patients whose pain symptoms were initiated or exacerbated by COVID-19. Lower lymphocytes reflected prolonged viral activity and incomplete infection resolution,[19] which resulted in prolonged proinflammatory responses. Elevated D-dimer levels were also a consequence of cytokine storms (IL-1, IL-6, etc.).[20,21] These inflammatory cytokines would lead to hyper-excitability of the central nervous system via different pathways. Given that the development of chronic pain was associated with inflammation and peripheral and central sensitization, the damage of musculoskeletal and nervous systems and overproduction of inflammatory mediators caused by SARS-CoV-2 infection were possible explanations for the exacerbation of previous chronic pain.[5,22–24] Autoantibody or autoimmune processes, triggered by SARS-CoV-2 through molecular mimicry or sustained modification of immune responses by viral antigen,[25,26] might contribute to persistent symptoms of exacerbated chronic pain, along with other manifestations related to long-COVID. Besides, evidence suggested that previous neuropathic pain, such as postherpetic neuralgia and trigeminal neuralgia, was exacerbated after SARS-CoV-2 infection.[27] This might be due to the invasion of SARS-CoV-2 in peripheral or central nervous systems and the virus-induced second damage to nerves would result in exacerbation of previous chronic neuropathic pain. Moreover, headache was the most prevalent symptom of COVID-19 according to a review,[28] and our study found the prevalence of exacerbated head and neck pain was 31.5%. To date, several studies have found a relationship between the atypical onset of exacerbated migraine headaches and COVID-19 infection in patients with a prolonged history of migraine.[28,29] Evidence suggested that headache onset was also a common adverse event after COVID-19 vaccination.[30] Reasons might contribute to systemic inflammatory response or nasal inflammation,[28,31] but the mechanism of which was still unclear.

Strength and Limitation

There are some strengths in our study. First, to the best of our knowledge, it is the first study investigating the prevalence of exacerbated previous chronic pain and its impact on quality of life, sleep quality, anxiety and depression levels as well as risk factors associated with exacerbation of pre-existing chronic pain, especially in the elderly COVID-19 survivors. However, most of the studies mainly focused on new-onset post-COVID pain and the target population was middle-aged and hospitalized patients. Second, our face-to-face interview could provide individuals with physical examinations to obtain more accurate information, which could reduce potential bias compared to those studies with telephone interviews. Third, exacerbated symptoms of previous chronic pain after being infected with Omicron variant have not been addressed in other studies.

Nevertheless, our findings have potential limitations. First, it is difficult to establish the strong causality between exacerbation of chronic pain and SARS-CoV-2 infection because of the design of cross-sectional study. Second, the potential for selection bias could not be excluded given that our study followed the principle of voluntary participation rather than random sampling. Third, elderly individuals residing in this CCRC might have better health awareness because they accepted regular health guidance from their family physicians, which may not be allowed for extrapolation to other elderly groups.

Conclusion

Our study observed 21.5% of elderly COVID-19 survivors experienced exacerbation of pre-existing chronic pain, with a consequence of poor quality of life, more severe anxiety and depression on a median duration of 4.9 months after

SARS-CoV-2 infection. Our findings identify the risk factors including previous chronic neuropathic pain, lower lymphocyte count and higher D-dimer levels for the exacerbation of previous chronic pain in elderly COVID-19 survivors. However, there is still lack of strong evidence lending support to the efficacy of any specific treatment for exacerbated previous chronic pain after SARS-CoV-2 infection to date. Therefore, further research is urgently needed to address this gap in knowledge.

Ethics Approval and Consent to Participate

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Sanbo Brain Hospital, Capital Medical University (SBNK-YJ-2023-013-01). Informed consent was obtained from all participants or their legally authorized representatives before enrollment.

Consent for Publication

The authors confirm that all the contents in this article can be published.

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Disclosure

The authors report no conflicts of interest in this work.

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