Cross-Sectional Study

Prevalence, Risk Factors and Pain Subtypes of Post-COVID Pain in Nonhospitalized Older Adults: A Cross-Sectional Study

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Background: Post-COVID pain (PCP) is a condition that ensues from an infection of coronavirus disease 2019 (COVID-19). Some researchers have explored the prevalence of PCP and its characteristics in the individuals who experience it. However, most individuals involved in the previous studies were middle-aged, and those studies focused mainly on hospital patients and musculoskeletal PCP. Existing data on PCP and its subtypes among older adults and outpatients are scanty.

Objective: Our study aims to identify PCP's prevalence and associated risk factors and to compare the quality of life (QoL), sleep quality, and anxiety and depression levels in nonhospitalized elderly COVID-19 survivors with different PCP subtypes.

Study Design: A cross-sectional study.

Setting: The study was conducted from April 2023 to June 2023 after the first outbreak of the Omicron variant of SARS-CoV-2 in the Taikang Yanyuan Continuing Care Retirement Community (CCRC) in China.

Methods: Eligible participants were surveyed using the Numeric Rating Scale (NRS), Douleur Neuropathique-4 questionnaire (DN4), EuroQol 5D-5L questionnaire (EQ-5D-5L), Pittsburgh Sleep Quality Index (PSQI), Generalized Anxiety Disorder 7 (GAD-7) scale, and Patient Health Questionnaire-9 (PHQ-9) scale. COVID-19 symptoms and laboratory parameters were obtained through an electronic healthcare system. Descriptive analysis was performed based on the presence of PCP and PCP subtypes. Multivariable logistic regression analysis and multiple linear regression were used for risk-factor analysis and adjustment of confounding factors.

Results: A total of 668 individuals (female: 59.3%, median age: 84 years) who had been infected with COVID-19 for a median duration of 145 (126-168) days were enrolled in our study. PCP was observed in 9.4% (63/668) of elderly COVID-19 survivors. Number of COVID-19 symptoms (aOR 1.31, 95%CI 1.05-1.64, $P = 0.018$) and previous chronic pain (aOR 4.24, 95%CI 1.59-11.27, $P = 0.004$) were risk factors associated with PCP. Individuals with neuropathic PCP exhibited higher NRS scores (5 [5-6] vs. 3 [3-4], $P < 0.001$) and more use of analgesic drugs (70.0%, 7/10 vs. 20.8%, 11/53, $P = 0.005$) for pain management. Neuropathic PCP was associated with lower scores on the EQ-5D index (B = -0.210, 95% CI -0.369 to -0.051, $P = 0.011$) and EQ-VAS (B = -10.808, 95% CI -21.149 to -0.468, $P = 0.041$) and higher PHQ-9 scores (B = 3.154, 95% CI 0.674-5.634, $P = 0.014$).

Limitations: It is difficult to establish a strong causality between PCP and SARS-CoV-2 infection due to the study's cross-sectional nature. Selection bias could not be eliminated, since our study relied on volunteer participation. Due to neuropathic PCP's lower prevalence than nonneuropathic PCP, larger sample sizes and multicenter studies are crucial for a comprehensive understanding of the neuropathic PCP condition.

Conclusion: Our study found a PCP prevalence of 9.4% in nonhospitalized older adults who had survived COVID-19. Number of COVID-19 symptoms and history of previous chronic pain seemed

to be potential risk factors for PCP. Neuropathic PCP was associated with lower QoL and a more severe depression level.

Key words: Post-COVID pain, elderly, prevalence, risk factor, pain subtypes

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Since the advent of coronavirus disease 2019 (COVID-19), an increasing number of scholars have begun focusing on the enduring alterations in multiple biological systems that result from severe infections of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1,2). Post-COVID pain (PCP), a manifestation of the post-COVID-19 condition, is a persistent symptom that leads to a great burden on the individual's quality of life (QoL) and mental health. To date, multiple studies have explored PCP's prevalence and characteristics in the individuals it affects (3). Some of these studies indicate that approximately 15.1% to 45.1% of patients infected with SARS-CoV-2 have suffered from PCP (4,5), and a noteworthy correlation has emerged between laboratory parameters and PCP's persistence (1). Several additional studies have explored the effects of different strains of SARS-CoV-2 on patients experiencing PCP, and these findings have indicated a higher prevalence of PCP among individuals infected with the disease's original strain than in those infected with either the Alpha or Delta variants (5).

Previous studies have provided greatly valuable knowledge about PCP . However, there are still some issues that have not received further investigation. Most individuals involved in these studies are middle-aged hospital patients, leaving a gap in our understanding of older adults and outpatients infected with SARS-CoV-2. The elderly population has exhibited a higher risk of adverse clinical outcomes and infection fatality after COVID-19, primarily because of the age-related decline in immune function and homeostasis (6,7). Attempting to collect comprehensive data from outpatients poses challenges, resulting in a lack of extensive research on this population (8). In addition, most of the studies in this area focus on musculoskeletal PCP, and the data on different PCP subtypes and their effects on clinical outcomes remain scanty.

To address these gaps in knowledge, our study aims to explore PCP's prevalence and associated risk factors in nonhospitalized older adults with SARS-CoV-2. The study's other main goal is to evaluate the impacts of different PCP subtypes on QoL, sleep quality, and anxiety and depression levels.

Methods

Study Design and Patients

This project was a cross-sectional study conducted in the Taikang Yanyuan Continuing Care Retirement Community (CCRC) from April 2023 to June 2023, after the first wave of the Omicron variant of the COVID-19 pandemic (from December 2022 to January 2023) in China. Eligible individuals were recruited for our study through the CCRC's internal digital media. Approval for the study was granted by the Ethics Committee of Sanbo Brain Hospital, Capital Medical University (SBNK-YJ-2023-013-01), and prior to enrollment, informed consent was obtained from all patients or their legally authorized representatives.

Criteria for inclusion encompassed the following categories: (I) age of 65 years or older, (II) confirmed SARS-CoV-2 diagnosis through a real-time reverse transcription-polymerase chain reaction (RT-PCR) assay of nasopharyngeal/oral swab samples over 3 months before the study, and (III) no hospitalization due to a COVID-19 infection. Patients were excluded if they had the following diseases or statuses: (I) cognitive disability, (II) psychiatric disorder, (III) severe systemic diseases, including heart-pulmonary insufficiency and multi-organ dysfunction, (IV) an inability to complete the assessments.

Patient Selection and Assessment Procedure

All eligible individuals were scheduled for a structured interview during the routine home visits. A total of 8 family physicians and 4 pain physicians participated in data collection. During this interview, demographic data, COVID-19 diagnoses, vaccination statuses, and medical conditions were initially collected by family physicians, since they were more familiar with the conditions of the CCRC residents. Thereafter, the individuals were also investigated if there was any new-onset pain that persisted for over 3 months after the SARS-CoV-2 infection. This investigation was done by a pain physician, using a structured questionnaire about PCP (Suppl. File. 1) PCP was defined as the presence of new-onset pain symptoms lasting for over 3 months without any underlying medical conditions that could have caused them (3). If there was uncer-

tainty about the PCP diagnosis, a unanimous position would be achieved through a discussion between pain specialists and doctors with experience in examining post-COVID-19 conditions. PCP was considered only when the new-onset pain still existed at the time of our assessment. This rigorous criterion was applied to eliminate recall bias and guarantee the utmost reliability of our research, given that certain instances of PCP would resolve themselves eventually (8). After the presence of PCP was confirmed, its location and intensity, the nature of pain, and the use of analgesics were also documented. In addition, QoL, sleep quality, and anxiety and depression levels were evaluated through this interview simultaneously. It is important to note that to ensure interrater reliability, investigators underwent a comprehensive training session on questionnaire and scale completion, a unified recording method, and judgment criteria before the research began. Emphasis was placed on the diagnosis of PCP and the determination of pain intensity, frequency, and characteristics as well as other assessment scales. To maintain survey quality, the items and options on the questionnaires were verbalized by the investigators and completed based on the patients' responses. Upon the conclusion of the data collection, 2 graduate students entered the data concurrently. Any inconsistencies in the data were cross-checked and entered according to the original questionnaire, thus preserving their authenticity and accuracy.

Grouping

Eligible individuals were grouped into 2 categories: the post-COVID pain group (PCP group) and the non-post-COVID pain group (NPCP group), based on whether or not PCP was present during the assessment. Subgroup analysis was conducted in individuals with PCP according to the presence or absence of neuropathic components: neuropathic PCP and nonneuropathic PCP.

Outcome Measurement

A verbal numeric rating scale (NRS) was used to assess the intensity of the pain each patient experienced during the past week, ranging from 0 (absence of pain) to 10 (the most severe pain). The subtype and nature of pain were classified as neuropathic or nonneuropathic and evaluated through the Douleur Neuropathique-4 questionnaire (DN-4) (9). A DN-4 score of ≥ 4 indicated neuropathic pain. The DN-4 questionnaire has been proven to be highly accurate in identifying neuropathic PCP (2). The EuroQol 5D-5L questionnaire (EQ-5D-5L) was employed to evaluate the individual's health status, which encompassed a descriptive system of 5 dimensions—mobility, self-care, usual activities, pain and discomfort, and anxiety and depression—and a visual analog scale (VAS) was used for the self-reported QoL state (10). Each dimension in the description system was divided into 5 levels. The EQ-5D index was derived from the aforementioned five-dimensional levels and estimated value set in China (11), which represented an index value ranging from < 0 (a negative value meant worse than death) to one (perfect health). The EQ-5D VAS served as an instrument for subjective health status assessment, ranging from 0 (the worst health status) to 100 (the best health status). Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI), with higher scores indicating poorer sleep quality (12). The generalized anxiety disorder (GAD-7) scale and the Patient Health Questionnaire-9 (PHQ-9) scale were employed to screen for anxiety and depression, respectively, with higher scores indicating greater levels of anxiety and depression (13, 14). All the scales mentioned above were validated Chinese versions (15-19).

Data Collection

Information about post-COVID pain, QoL, sleep quality, and anxiety and depression levels were recorded during our face-to-face interviews. In addition to the above scales, computed tomography (CT) of the chest, COVID-19 symptoms, and laboratory parameters (hemoglobin, lymphocyte count, neutrophils count, platelet count, glucose, creatine, hs-CRP, ALT, AST, D-dimer, and PCT) during the first 7 days after SARS-CoV-2 infection were also collected through the Taikang electronic healthcare system. Whenever multiple laboratory results were available, the outcomes displaying the greatest deviation from the normal values were recorded for the case.

Statistical Analysis

Total sample size was not calculated, since we intended to include all eligible individuals who met the inclusion criteria and were willing to participate. Risk factor analysis requires that a sample size be 10 times the total number of risk factors. Based on previous studies (1,4), 5 to 6 possible risk factors of PCP were identified, and we estimated it was appropriate to include > 50 individuals in the PCP group. Depending upon their distribution, continuous data were presented as medians and interquartile ranges (IQRs)

or mean and SD. Categorical data were represented as frequency distributions. Difference analysis was conducted using the Mann-Whitney U test, Student's t-test, or the chi-square test, depending on the data type and distribution. Multivariable logistic regression was applied for the risk factor analysis using the stepwise procedure. Variables included age, gender, medical comorbidities, vaccination status, COVID-19 symptoms, and laboratory parameters selected by univariable logistic regression, with *P*-value < 0.1 as the independent variables and PCP as the dependent variable. Relevant outcomes were represented by the adjusted odds ratio (aOR) and 95% confidence interval (CI). Multiple linear regressions were performed to assess PCP's association with QoL, sleep quality, anxiety, and depression as well as to adjust the effects of confounders in the baseline on the above outcomes. Whenever missing values accounted for under 20% of the data, multiple imputation was performed to fill in the missing values, using the predictive mean matching method.

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

Results

A total of 813 patients, 668 of whom were eventually included, received preliminary screenings for our study. Sixty-three individuals were assigned to the PCP group, and 605 individuals were placed in the NPCP group (Fig. 1). Most of the individuals enrolled in our study were women (59.3%, 396/668), and the patients' median age was 84 (79-87) years. For all patients, the median duration between the onset of COVID-19 and the enrollment in the study was 145 (126-168) days. The PCP group, which consisted of a greater proportion of women (74.6%, 47/63 vs. 57.7%, 349/605, $P = 0.009$), exhibited a higher prevalence of PCP (90.5%, 57/63 vs. 60.0%, 363/605, $P < 0.001$) and a higher number of medical comorbidities (4 [3-5] vs. 3 [2-4], $P = 0.002$) than did the NPCP group. There was no significant differ-

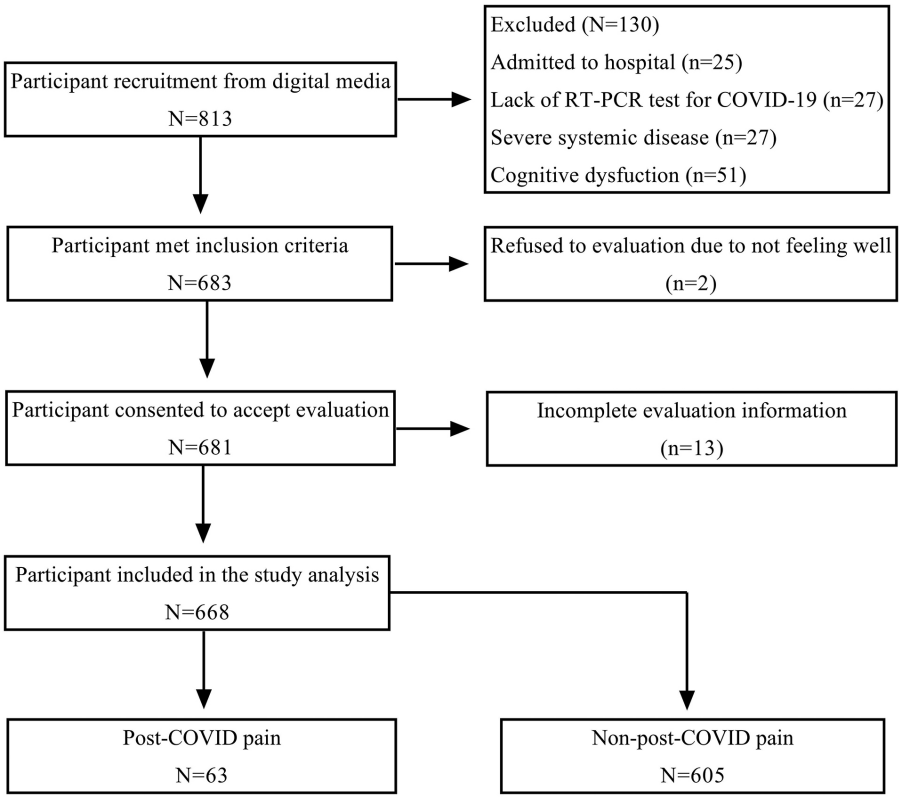

Fig. 1. *Flow chart of included patients.*

ence in vaccination status, other demographic data, or medical comorbidities between the 2 groups (Table 1).

COVID-19 Symptoms and Laboratory Parameters

Regarding COVID-19 symptoms, individuals in the PCP group reported higher incidences of myalgia (31.7%, 20/63 vs. 14.2%, 86/605, $P = 0.001$) and ageusia (19.0%, 12/63 vs. 8.1%, 49/605, $P = 0.004$) and heavier loads of onset symptoms (4 [3-4] vs. 3 [2-4], $P < 0.001$) during the first 7 days after their SARS-CoV-2 infections than did those in the NPCP group. Additionally, the 2 groups showed a similar rate of SARS-CoV-2-related pneumonia (54.3%, 25/46 vs. 54.9%, 150/273, $P = 0.940$). As for laboratory parameters, a total of 274 patients underwent laboratory examination during the first 7 days of their SARS-CoV-2 infections. Forty-two of the patients were in the PCP group, and 232 were in the NPCP group. The measurements of all of those parameters (hemoglobin, lymphocyte count, neutrophils count, platelet count, glucose, creatine, hs-CRP, ALT, AST, D-dimer, and PCT) showed no significant difference between the 2 groups (Table 2).

Risk Factors Associated with PCP

Univariable logistic regression analysis revealed that gender (OR 0.46, 95%CI 0.26-0.84, $P = 0.011$); previous chronic pain (OR 6.33, 95%CI 2.69-14.92, $P < 0.001$); number of medical comorbidities (OR 1.31, 95%CI 1.09-1.56, $P = 0.004$); symptoms of myalgia (OR 2.81, 95%CI 1.58-5.00, $P < 0.001$), anosmia (OR 2.17, 95%CI 0.86-5.46, $P = 0.100$), and ageusia (OR 2.67, 95%CI 1.34-5.34, $P = 0.006$); number of COVID-19 symptoms (OR 1.41, 95%CI 1.18-1.68, $P < 0.001$; and glucose levels (OR 0.86, 95%CI 0.71-1.03, $P = 0.099$) were potential candidate variables associated with PCP. Subsequently, the candidate variables were used for further analysis with multivariable logistic regression. No multicollinearity was observed among these variables. Multivariable logistic regression analysis showed that number of COVID-19 symptoms (aOR 1.31, 95%CI 1.05-1.64, $P = 0.018$) and previous chronic pain (aOR 4.24, 95%CI 1.59-11.27, $P = 0.004$) were independent risk factors associated with PCP (Table 3).

Prevalence, Characteristics, and Subtypes of PCP

PCP was observed in 9.4% (63/668) of nonhospitalized elderly COVID-19 survivors. The most reported new-onset pain location was the back (25.4%, 16/63), followed by lower limbs (20.6%, 13/63), knee (20.6%, 13/63), shoulders (11.8%, 8/68), hip (11.1%, 7/63), head and neck (9.5%, 6/63), and upper limbs (7.9%, 5/63). Widespread pain was reported least often (4.8%, 3/63). Most PCP (84.1%, 53/63) was nonneuropathic, and most of the individuals with PCP (87.3%, 55/63) had a frequency of > 15 days per month. The average NRS of PCP in the past week was 4 (3-5), and 28.6% (18/63) of PCP cases required analgesic drugs for pain management (Table 4). Compared to nonneuropathic PCP, older adults with neuropathic PCP exhibited higher NRS scores (5 [5-6] vs. 3 [3-4], $P < 0.001$) and more use of analgesic drugs (70.0%, 7/10 vs. 20.8%, 11/53, $P = 0.005$) for pain management. Pain frequency did not differ between the 2 groups. PCP that appeared in the lower limbs seemed likelier to be neuropathic (50.0%, 5/10 vs. 15.1%, 8/53, $P = 0.038$) (Table S1). Tingling (80.0%, 8/10) was the most frequent sensation associated with neuropathic PCP, and hypoesthesia to touch (90.0%, 9/10) or pinprick (80.0%, 8/10) was the most common symptom found through physical examination (Table S2).

Table 1. *Demographic data and medical comorbidities among elderly COVID-19 survivors.*

Variables	PCP (n = 63)	NPCP (n = 605)	*P* value
Age, median (IQR), years	85 (79-88)	84 (79-87)	0.411
Gender, female,* n (%)	47 (74.6)	349 (57.7)	0.009
Height, mean (SD), m	1.59 (0.09)	1.60 (0.09)	0.354
Weight, mean (SD), kg	62.2 (10.3)	61.9 (11.0)	0.792
Hypertension, n (%)	49 (77.8)	496 (82.0)	0.412
Diabetes, n (%)	29 (46.0)	256 (42.3)	0.570
Cardiovascular disease, n (%)	36 (57.1)	283 (46.8)	0.117
COPD, n (%)	9 (14.3)	62 (10.2)	0.315
Cerebrovascular disease, n (%)	16 (25.4)	123 (20.3)	0.346
Cancer, n (%)	8 (12.7)	75 (12.4)	0.945
Previous chronic pain,* n (%)	57 (90.5)	363 (60.0)	< 0.001
Other, n (%)	26 (41.3)	208 (34.4)	0.275
Number of medical comorbidities,* median (IQR)	4 (3-5)	3 (2-4)	0.002
Vaccination, n (%)	46/58 (79.3)	417/556 (73.7)	0.468

Data are expressed as n (%), mean (SD), or median (IQR). PCP = post-COVID pain. NPCP = non-post-COVID pain. COPD = chronic obstructive pulmonary disease.

* Represents a statistically significant difference, with $P < 0.05$.

Table 2. *COVID-19 symptoms and laboratory parameters in initial 7 days after the diagnosis of SARS-CoV-2.*

COVID-19 Symptoms	PCP (n = 63)	NPCP (n = 605)	*P* value
Fever, n (%)	52 (82.5)	434 (71.7)	0.067
Dyspnea, n (%)	7 (11.1)	40 (6.6)	0.184
Cough, n (%)	41 (65.1)	337 (55.7)	0.153
Myalgia,* n (%)	20 (31.7)	86 (14.2)	0.001
Diarrhea, n (%)	4 (6.3)	24 (4.0)	0.369
Anosmia, n (%)	6 (9.5)	28 (4.6)	0.092
Ageusia,* n (%)	12 (19.0)	49 (8.1)	0.004
Throat pain, n (%)	32 (50.8)	243 (40.2)	0.103
Vomiting, n (%)	4 (6.3)	16 (2.6)	0.101
Fatigue, n (%)	46 (73.0)	436 (72.1)	0.873
Number of COVID-19 symptoms,* median (IQR)	4 (3-4)	3 (2-4)	< 0.001
Laboratory Parameters	PCP (n = 42)	NPCP (n = 232)	
Hemoglobin (g/dL), mean (SD)	12.9 (1.2)	13.1 (1.4)	0.416
Lymphocyte (×109/L), median (IQR)	0.85 (0.65-1.27)	1.00 (0.65-1.38)	0.478
Neutrophils (×109/L), median (IQR)	3.22 (2.42-5.36)	3.26 (2.44-4.48)	0.435
Platelets (×109/L), median (IQR)	169 (123-207)	154 (121-198)	0.275
Glucose (mg/mL), median (IQR)	6.26 (5.26-7.81)	6.73 (5.87-8.48)	0.063
Creatine (μmol/L), median (IQR)	73.9 (61.7-91.5)	78.2 (65.2-96.9)	0.248
hs-CRP (mg/L), median (IQR)	7.44 (2.70-18.93)	8.45 (3.17-22.21)	0.678
ALT (U/L), median (IQR)	17.2 (12.8-25.4)	19.7 (15.4-27.3)	0.175
AST (U/L), median (IQR)	26.4 (21.0-31.9)	27.6 (21.8-36.2)	0.472
D-dimer (ng/mL), median (IQR)	0.47 (0.27-0.82)	0.43 (0.28-0.62)	0.400
PCT (ng/ml), median (IQR)	0.07 (0.05-0.09)	0.07 (0.05-0.09)	0.863

Data are expressed as n (%), mean (SD), or median (IQR). PCP = post-COVID pain. NPCP = non-post-COVID pain. COVID-19 = coronavirus disease of 2019. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
* Represents a statistically significant difference between the 2 groups, with $P < 0.05$.

Table 3. *Univariable and multivariable logistic regression analysis for post-COVID pain among elderly COVID-19 survivors.*

Variables	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	*P*	aOR (95% CI)	*P*
Gender	0.46 (0.26-0.84)	0.011		
Previous chronic pain*	6.33 (2.69-14.92)	< 0.001	4.24 (1.59-11.27)	0.004
Number of medical comorbidities	1.31 (1.09-1.56)	0.004		
Myalgia	2.81 (1.58-5.00)	< 0.001		
Anosmia	2.17 (0.86-5.46)	0.100		
Ageusia	2.67 (1.34-5.34)	0.006		
Number of COVID-19 symptoms at 0-7 days*	1.41 (1.18-1.68)	< 0.001	1.31 (1.05-1.64)	0.018
Glucose levels	0.86 (0.71-1.03)	0.099		

Hosmer-Lemeshow test: $P = 0.300$. OR = odds ratio. aOR = adjusted odds ratio. CI = confidence interval. COVID-19 = coronavirus disease of 2019.
* Represents a statistically significant difference, with $P < 0.05$.

Comparison of QoL, Sleep Quality, and Anxiety and Depression Levels Between Neuropathic and Nonneuropathic PCP Groups

Individuals with neuropathic PCP were older (85 [79-88] vs. 84 [79-87], $P = 0.045$) and exhibited a higher prevalence of myalgia (70.0%, 7/10 vs. 24.5%, 13/53, $P = 0.014$) and ageusia (50.0%, 5/10 vs. 13.2%, 7/53, $P = 0.023$) during the first 7 days after COVID-19 than elderly adults with nonneuropathic PCP (Table S3 and S4). A lower EQ-5D score (0.66 [0.47-0.81] vs. 0.82 [0.66-0.89], $P = 0.026$) was observed in individuals with neuropathic PCP. This discrepancy was correlated with an increased burden on the dimension of pain and discomfort (median level: 3 [2.75-3.25] vs. 2 [2-2], $P < 0.001$). However, there was no difference in EQ-VAS between the 2 groups (62.5 [55.0-78.5] vs. 78.0 [62.5-82.5], $P = 0.077$). After adjustments were made for age, gender, and medical comorbidities, multiple linear regression showed that neuropathic PCP was associated with a lower EQ-5D (B = -0.210, 95% CI -0.369 to -0.051, $P = 0.011$) and EQ-VAS score (B = -10.808, 95% CI -21.149 to -0.468, $P = 0.041$). In terms of sleep quality, there was no significant difference in the PSQI scores (8.5 [3.25-13.5] vs. 8.0 [4.0-10.5], $P = 0.631$) between the 2 groups, and multiple linear regression also showed that neuropathic PCP was not associated with PSQI score (B

= 2.217, 95% CI -0.648-5.083, *P* = 0.127). As for anxiety and depression levels, the 2 groups showed no significant difference in their GAD-7 or PHQ-9 scores (Table 5). Once more adjustments for age, gender, and medical comorbidities were made, multiple linear regressions showed that neuropathic PCP was associated with a higher PHQ-9 score (B = 3.154, 95% CI 0.674-5.634, *P* = 0.014), but no association was detected between neuropathic PCP and GAD-7 score (B = 1.883, 95% CI -0.190-3.957, *P* = 0.074).

Table 4. *Characteristics of PCP in elderly COVID-19 survivors.*

Variables	PCP (n = 63)
Location	
Head & neck, n (%)	4 (6.3)
Back, n (%)	16 (25.4)
Knee, n (%)	13 (10.0)
Hip, n (%)	7 (11.1)
Shoulder, n (%)	11 (17.5)
Upper limbs, n (%)	5 (7.9)
Lower limbs, n (%)	13 (20.6)
Widespread, n (%)	3 (4.8)
Nature of Pain	
Neuropathic, n (%)	10 (15.9)
Nonneuropathic, n (%)	53 (84.1)
Frequency	
> 15 days per month, n (%)	55 (87.3)
< 15 days per month, n (%)	8 (12.7)
Average NRS in the past week, median (IQR)	4 (3-5)
Number of patients requiring analgesics, n (%)	18 (28.6)

Data are expressed as n (%) or median (IQR). PCP = post-COVID pain.

Discussion

To the best of our knowledge, ours is the first study investigating PCP among elderly outpatients with a median age of 84 years after the COVID-19 outbreak in Asia. Previous studies, by contrast, focused on PCP in European populations of middle-aged, hospitalized patients. Our research revealed that 9.4% of nonhospitalized older adults suffered from PCP for a median duration of 145 days since their SARS-CoV-2 infections began. Patients' number of COVID-19 symptoms and history of PCP seemed to be risk factors for post-COVID PCP. Neuropathic PCP was likely associated with lower QoL scores and more severe depression levels than those of older adults with nonneuropathic PCP.

Whereas other studies reported a PCP prevalence of 15.1% to 45.1% (4,5), our study found this figure in older adults was only 9.4%, obviously lower than the prevalence among middle-aged and hospitalized COVID-19 survivors. This difference could be attributed to the attenuated virulence of the Omicron variant. Evidence suggests that individuals who contract the Omicron variant exhibit fewer long-COVID symptoms than do those who have been infected with other variants (20). In addition, the length of the follow-up period after a SARS-CoV-2 infection also influences the prevalence of PCP. A study revealed that the prevalence of post-COVID symptomatology increased after 60 days but decreased after 180 days (8,21). Our investigation was conducted after a median duration of 145 days subsequent to a COVID-19 infection. Consequently, our findings were limited to reflecting the prevalence of PCP exclusively within this time frame. Whether and for how long the PCP would resolve itself, improve, or even worsen remain unclear. These issues need our further investigation.

As for the risk factors associated with PCP, many studies have investigated the correlation between PCP and biological factors. Earlier evidence supported that some laboratory parameters and heavier loads of COVID-19 symptoms were associated with the development of PCP (4,22). However, there is still a controversy because of the weak association and even contrary outcomes between some prognostic laboratory parameters and long-term PCP in the published studies (3,23). Nonetheless, the presence of multiple comorbidities and a weakened immune system in elderly individuals may result in different changes in COVID-19 symptoms and laboratory parameters. Therefore, certain associated risk factors may not be relevant in cases involving older adults, and it is crucial to identify the risk factors in elderly individuals who are susceptible to the development of PCP. In our study, we observed that the number of COVID-19 symptoms and previous chronic pain emerged as potential risk factors associated with PCP, and no correlation between laboratory parameters and the condition was detected. This finding was consistent with Fernández-de-Las-Peñas's study (4), which also revealed that loads of COVID-19 symptoms and history of musculoskeletal pain were factors correlated with PCP one year after the infection. Some studies speculate that the overproduction of inflammatory mediators and prolonged proinflammatory responses caused by SARS-CoV-2 may induce hyperexcitability of the central nervous system through various pathways, thereby

Table 5. *Quality of life, sleep quality, and anxiety and depression levels in individuals with different PCP subtypes.*

	Neuropathic PCP (n = 10)	Nonneuropathic PCP (n = 53)	*P*
EQ-5D index,* median (IQR)	0.66 (0.47-0.81)	0.82 (0.66-0.89)	0.026
EQ-VAS, median (IQR)	62.5 (55.0-78.5)	78.0 (62.5-82.5)	0.077
Mobility, n (%)			
Level 1	6 (60.0)	29 (54.7)	0.983
Level 2	2 (20.0)	15 (28.3)	
Level 3	0 (0)	6 (11.3)	
Level 4	0 (0)	1 (1.9)	
Level 5	2 (20.0)	2 (3.8)	
Self-care, n (%)			
Level 1	6 (60.0)	36 (67.9)	0.535
Level 2	2 (20.0)	11 (20.8)	
Level 3	1 (10.0)	4 (7.5)	
Level 4	0 (0)	1 (1.9)	
Level 5	1 (10.0)	1 (1.9)	
Usual activity, n (%)			
Level 1	3 (30.0)	22 (41.5)	0.620
Level 2	4 (40.0)	16 (30.2)	
Level 3	2 (20.0)	9 (17.0)	
Level 4	0 (0)	4 (7.5)	
Level 5	1 (10.0)	2 (3.8)	
Pain/discomfort, n (%)			
Level 1	0 (0)	12 (22.6)	< 0.001
Level 2	2 (20.0)	31 (58.5)	
Level 3	6 (60.0)	10 (18.9)	
Level 4	2 (20.0)	0 (0)	
Level 5	0 (0)	0 (0)	
Anxiety/depression, n (%)			
Level 1	3 (30.0)	31 (58.5)	0.105
Level 2	4 (40.0)	13 (24.5)	
Level 3	2 (20.0)	7 (13.2)	
Level 4	1 (10.0)	1 (1.9)	
Level 5	0 (0)	1 (1.9)	
PSQI score, median (IQR)	8.5 (3.25-13.5)	8.0 (4.0-10.5)	0.631
GAD-7 score, median (IQR)	3 (1.5-3.75)	1 (0-3)	0.083
PHQ-9 score, median (IQR)	5.5 (1.5-9.5)	3 (1-4)	0.106

Data are expressed as n (%) or median (IQR). PCP = post-COVID pain. EQ5D = EuroQol Five Dimensions Questionnaire. EQ-VAS= EuroQol visual analog scale. PSQI= Pittsburgh sleep quality index. GAD-7= Generalized Anxiety Disorder-7. PHQ-9= Patient Health Questionnaire-9. Level 1= no problem, level 2 = slight problem, level 3 = moderate problem, level 4 = severe problem, level 5 = confined to bed or extreme problem.
* Represents a statistically significant difference between the 2 groups, with $P < 0.05$.

fostering the progression of persistent PCP (24-26). Heavy loads of COVID-19 symptoms have suggested the engagement of systems beyond the respiratory tract, encompassing the musculoskeletal and nervous systems, within the context of virus-induced inflammatory reactions. Prolonged inflammatory reactions within these musculoskeletal and nervous systems may increase susceptibility to PCP. Notably, individuals suf-

fering from chronic pain often contend with inflammation processes and peripheral and central sensitization (27-29). These sensitized afferent neural pathways may trigger new-onset pain under the condition of systematic inflammation storms associated with SARS-CoV-2 infection, thus increasing the risk of PCP.

Currently, many studies are focused on musculoskeletal PCP, and few data are available for neuropathic PCP, primarily because of the latter's lower incidence. However, previous researches have addressed only the prevalence, features, and correlated factors of neuropathic PCP (2,30), whereas neuropathic PCP's effects on QoL and mental health have not been further investigated. Moreover, the individuals included in previous studies were middle-aged patients admitted to hospitals. In contrast, our study, which involved 668 COVID-19 survivors, investigated nonhospitalized older adults, and our findings indicated that older adults with neuropathic PCP exhibited severer pain intensity, lower QoL scores, and greater depression levels than did elderly patients with nonneuropathic PCP. Neuropathic PCP was associated with abnormal function or neurological damage secondary to viral infection, like postherpetic neuralgia. Such effects could lead to abnormal transmission and perception of pain signals (31,32). In addition to the persistent pain sensation, other accompanying symptoms, such as numbness, burning sensations, and allodynia, were significant contributing factors to the impaired QoL and severe anxiety and depression. Similar findings were identified in other studies that compared neuropathic pain to other types of chronic pain (33-35). Nevertheless, there is, to date, a lack of strong evidence supporting any treatment for the management of neuropathic PCP or musculoskeletal PCP (36). Therefore, further research is needed to better understand PCP's underlying causes and guide clinical decision-making in cases involving this condition.

Limitations

However, limitations remain in our study. First, this study was cross-sectional, so it was difficult to establish a strong causality between PCP and SARS-CoV-2 infection. Second, the possibility of selection bias could not be eliminated, since our study adhered to the principle of voluntary participation rather than employing random sampling methods. Third, most elderly people living in the CCRC that served as the study's setting had better health awareness due to regular health guidance from family physicians, a factor that may not be allowed for extrapolation to other elderly populations. Fourth, risk factor analysis for neuropathic PCP was not conducted, due to the enrollment of only a few patients (n = 10) whose PCP was neuropathic. Larger sample sizes and multicenter studies are crucial for a comprehensive understanding of neuropathic PCP.

Conclusion

Our study found that among nonhospitalized older adults, 9.4% were suffering from PCP after a median duration of 145 days since their SARS-CoV-2 infections. Number of COVID-19 symptoms and history of previous chronic pain seemed to be potential risk factors associated with the onset of post-COVID pain. Compared to nonneuropathic PCP, neuropathic PCP would lead to a greater decline of QoL and a more severe depression level, which needs to attract more attention and spur the development of potential preventive actions and therapeutic methods.

Ethics Approval and Informed Consent

The study was approved by the Ethics Committee of Sanbo Brain Hospital, Capital Medical University (SBNK-YJ-2023-013-01). All patients provided written informed consent before participation.

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Author Contributions

CHW, YL, FW and BGW designed the study. Data collection was performed by CHW, MWY, YRL, HQW and LH. CHW and MWY contributed to the data analysis. CHW was the major contributor to the composition of the manuscript. BGW was the major contributor to the revision of the manuscript.

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Table S1. *Pain characteristics in different PCP subtypes among elderly COVID-19 survivors*

	Neuropathic PCP (n = 10)	**Nonneuropathic PCP (n = 53)**	***P***
Location			
Head & neck, n (%)	2 (20.0)	4 (7.5)	0.520
Back, n (%)	0 (0)	16 (30.2)	-
Knee, n (%)	1 (10.0)	12 (22.6)	0.631
Hip, n (%)	0 (0)	7 (13.2)	-
Shoulder, n (%)	1 (10.0)	10 (18.9)	0.823
Upper limbs, n (%)	1 (10.0)	4 (7.5)	1.000
Lower limbs,* n (%)	5 (50.0)	8 (15.1)	0.038
Widespread, n (%)	0 (0)	3 (5.7)	-
Average NRS in the past week,* median (IQR)	5 (5-6)	3 (3-4)	<0.001
Frequency of > 15 days per month, n (%)	9 (90.0)	46 (86.8)	1.000
Analgesic drugs,* n (%)	7 (70.0)	11 (20.8)	0.005

Data are expressed as n (%), mean (SD), or median (IQR). PCP = post-COVID pain. NPCP = non-post-COVID pain. COVID-19 = coronavirus disease 2019. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* Represents a statistically significant difference, with $P < 0.05$.

Table S2. *DN4 questionnaire descriptors*.

DN4 Questionnaire Descriptors	Neuropathic PCP (n = 10)
Burning	3 (30.0)
Painful cold	0 (0)
Electric shocks	4 (40.0)
Tingling	8 (80.0)
Pins and needles	4 (40.0)
Numbness	2 (20.0)
Hypoesthesia to touch	9 (90.0)
Hypoesthesia to pinprick	8 (80.0)
Pain caused or increased by brushing	3 (30.0)

Table S3. *Demographic data and medical comorbidities in individuals with different PCP subtypes*.

Variables	Neuropathic PCP (n = 10)	Nonneuropathic PCP (n = 53)	*P*
Age,* median (IQR), years	85 (79-88)	84 (79-87)	0.045
Gender, female, n (%)	7 (70.0)	40 (75.5)	1.000
Height, mean (SD), m	1.63 (0.07)	1.58 (0.08)	0.119
Weight, mean (SD), kg	65.0 (8.7)	61.7 (10.6)	0.358
Hypertension, n (%)	6 (60.0)	43 (81.1)	0.289
Diabetes, n (%)	4 (40.0)	25 (47.2)	0.943
Cardiovascular disease, n (%)	6 (60.0)	30 (56.6)	1.000
COPD, n (%)	1 (10.0)	8 (15.1)	1.000
Cerebrovascular disease, n (%)	1 (10.0)	15 (28.3)	0.410
Cancer, n (%)	1 (10.0)	7 (13.2)	1.000
Previous chronic pain, n (%)	10 (100.0)	47 (88.7)	0.595
Other,a n (%)	5 (50.0)	21 (39.6)	0.794
Number of medical comorbidities, median (IQR)	4 (3-5)	3 (2-4)	0.518
Vaccination, n (%)	9/10 (90.0)	37/49 (75.5)	0.556

Data are expressed as n (%), mean (SD) or median (IQR). PCP = post-COVID pain. NPCP = non-post-COVID pain. COPD = chronic obstructive pulmonary disease.
* Represents a statistically significant difference, with $P < 0.05$.
[a] Includes hyperlipidemia, chronic kidney disease, chronic gastritis, Parkinson's disease, and rheumatic disease.

Table S4. ***COVID-19 symptoms and laboratory parameters in individuals with different PCP subtypes.***

COVID-19 symptoms	Neuropathic PCP (n = 10)	Nonneuropathic PCP (n = 53)	*P*
Fever, n (%)	9 (90.0)	43 (81.1)	0.823
Dyspnea, n (%)	2 (20.0)	5 (9.4)	0.670
Cough, n (%)	6 (60.0)	35 (66.0)	0.995
Myalgia,* n (%)	7 (70.0)	13 (24.5)	0.014
Diarrhea, n (%)	0 (0)	4 (7.5)	-
Anosmia, n (%)	1 (10.0)	5 (9.4)	1.000
Ageusia,* n (%)	5 (50.0)	7 (13.2)	0.023
Throat pain, n (%)	5 (50.0)	27 (50.9)	1.000
Vomiting, n (%)	0 (0)	4 (7.5)	-
Fatigue, n (%)	9 (90.0)	37 (69.8)	0.873
Number of COVID-19 symptoms, median (IQR)	4 (3.75-5.25)	4 (2-4)	0.352
Laboratory Parameters	Neuropathic PCP (n = 6)	Nonneuropathic PCP (n = 36)	
Hemoglobin (g/dL), mean (SD)	12.8 (1.0)	12.9 (1.3)	0.867
Lymphocyte (×109/L), median (IQR)	0.90 (0.62-1.77)	0.84 (0.65-1.32)	0.886
Neutrophils (×109/L), median (IQR)	3.30 (3.05-6.23)	3.14 (2.31-4.76)	0.184
Platelets (×109/L), median (IQR)	240 (128-293)	164 (131-193)	0.196
Glucose (mg/mL), median (IQR)	6.20 (5.25-8.35)	6.44 (5.26-7.79)	0.943
Creatine (μmol/L), median (IQR)	78.0 (64.3-91.0)	72.5 (61.3-92.1)	0.719
hs-CRP (mg/L), median (IQR)	5.23 (0.52-22.60)	7.44 (3.37-19.37)	0.208
ALT (U/L), median (IQR)	15.1 (13.5-32.1)	17.5 (12.1-24.8)	0.815
AST (U/L), median (IQR)	24.0 (19.5-28.6)	26.7 (21.2-34.5)	0.359
D-dimer (ng/mL), median (IQR)	0.42 (0.25-0.75)	0.47 (0.27-0.83)	0.666
PCT (ng/ml), median (IQR)	0.06 (0.03-0.13)	0.07 (0.05-0.09)	0.426

Data are expressed as n (%), mean (SD) or median (IQR). PCP = post-COVID pain. NPCP = non-post-COVID pain. COVID-19 = coronavirus disease 2019. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

* Represents a statistically significant difference between the 2 groups, with $P < 0.05$.