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Pain Manifestations of COVID-19 and Their Association With Mortality: A Multicenter Prospective Observational Study

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Abstract

Objectives: To determine the prevalence and breakdown of pain symptoms among patients with coronavirus disease 2019 (COVID-19) infection admitted for nonpain symptoms and the association between the presence of pain and intensive care unit (ICU) admission and death.

Patients and Methods: In this multicenter prospective study, data on the intensity and type of pain were collected on 169 patients with active severe acute respiratory syndrome coronavirus 2 infection at 2 teaching hospitals in the United States and Korea and on 8 patients with acute pain at another large teaching hospital between February 1, 2020, and June 15, 2020.

Results: Sixty-five of 169 patients (38.5%) reported an active pain condition. Among the 73 patients with pain, the most common pain symptoms were headache (n=22; 30.1%), chest pain (n=17; 23.3%), spinal pain (n=18; 24.7%), myalgia (n=13; 17.8%), abdominal or pelvic pain (n=13; 17.8%), arthralgia (n=11; 15.1%), and generalized pain (n=9; 12.3%). Those reporting headache as their main symptom were less likely to require ICU admission (P=.003). Acetaminophen or nonsteroidal anti-inflammatory drugs were prescribed to 80.8% (n=59), opioids to 17.8% (n=13), adjuvants to 8.2% (n=6), and ketamine to 5.5% (n=4) of patients with pain. When age 65 years and older and sex were controlled for in multivariable analysis, the absence of pain was associated with ICU admission (odds ratio, 2.92; 95% CI, 1.42 to 6.28; P=.004) and death (odds ratio, 3.49; 95% CI, 1.40 to 9.76; P=.01).

Conclusion: Acute pain is common during active COVID-19 infection with the most common manifestations being headache, chest pain and spine pain. Individuals without pain were more likely to require intensive care and expire than those with pain. Reasons why pain may be associated with reduced mortality include that an intense systemic stimulus (eg, respiratory distress) might distract pain perception or that the catecholamine surge associated with severe respiratory distress might attenuate nociceptive signaling.

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The global pandemic has affected health systems, providers, and patients, cutting across all geographical, specialty, and socioeconomic boundaries. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus that causes coronavirus disease 2019 (COVID-19), can affect nearly every organ system, causing cardiovascular, gastrointestinal, musculoskeletal, respiratory, and neurologic symptoms.[1-5] Previous epidemics have also resulted in an increase in nociplastic pain (eg, fibromyalgia and irritable bowel syndrome), a new pain category in which central sensitization is believed to play a major role.[6] In addition to directly infiltrating pain-sensitive organ systems (eg, HIV neuropathy), other mechanisms by which pathogens such as COVID-19 may precipitate pain include deconditioning from quarantine, the well-known ability of viral illnesses to cause myalgias and headaches, through psychological stress as an inciting event (biopsychosocial model), and as a direct trigger for pain (eg, Epstein-Barr virus causing a postviral syndrome that includes pain, severe acute respiratory syndrome (coronavirus 1, SARS) causing postviral diffuse myalgias, and infection as a

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precursor for irritable bowel syndrome).[6-9] If acute pain was associated with viral load or virulence, pain might serve as a marker for more severe illness (eg, requirement for admission or mortality), potentially altering the decision tree for front-line health care providers such as emergency department physicians.

The field of pain medicine covers numerous specialties, such that postgraduate pain programs train residents from numerous specialties, and articles on pain medicine are published in specialty journals in every medical discipline. Among the more than 50,000 peer-reviewed articles that have been published since January 2020 on COVID-19 infection, only a handful have been devoted to how the disease affects pain, with nearly all focusing on logistical (eg, risk mitigation strategies and patient triage) and educational issues.[10-12] To date, there have been no major studies on pain manifestations caused by COVID-19 infection.

We hypothesized that pain might be a biomarker for virulence or viral load and be associated with poorer outcomes. The objectives of this study are to: (1) describe the major pain symptoms caused by active COVID-19 infections and how they are treated; and (2) determine whether pain symptoms are associated with overall outcome (eg, admission rates and mortality).

PATIENTS AND METHODS
Permission to conduct this study was granted by the institutional review boards of Johns Hopkins Medical Institutions, Seoul National University (SNU), and Westchester Medical Center (WMC). All patients were treated between February 1 and June 15, 2020. At WMC and SNU, all patients with COVID-19 diagnosed by polymerase chain reaction who were admitted with viral-related symptoms severe enough to warrant hospitalization (n=169) were surveilled regarding pain, including questions pertaining to the location of pain, baseline magnitude of pain on a numerical rating scale (NRS) of 0 to 10 before analgesic interventions, and prior pain conditions. In addition to pain symptoms and analgesic treatment, disposition was recorded. At Johns Hopkins,

8 patients who were referred for pain medicine services for either a primary (reason for admission) or secondary pain symptom were included, with data for diagnosis, location of pain, and pain scores on an NRS of 0 to 10 recorded prospectively.

Data included the following information: age, sex, primary pain diagnosis, presence of pre-existing concomitant pain conditions, baseline pain score, and opioid and nonopioid analgesic medications. A pain condition was defined as a pain score of 2 of 10 or greater at baseline or during the course of treatment as recorded by both NRS and verbal rating scales. Pain diagnoses were primarily based on history, limited physical examination, and other diagnostic test reports when available. Treatments were broken down into opioids, adjuvants (eg, antidepressants and anticonvulsants), ketamine, nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, muscle relaxants, and others.

Statistical Analyses
Statistical analyses were performed using R, version 3.6.3 (R Core Team). Continuous variables are reported as mean ± SD or median with interquartile range (IQR) depending on the result of a Shapiro-Wilk normality test. Categorical demographic and clinical data are reported using numbers of participants and percentage. Normally distributed continuous variables were compared using unpaired t test, and non-normally distributed continuous variables were compared using Mann-Whitney U test. Categorical variables were compared using χ^2 test or Fisher exact test. Multivariable logistic regression was used to estimate odds ratios (ORs) for death and intensive care unit (ICU) admission adjusted for age 65 years or older and sex because these variables have been shown to affect outcomes.[13] All P values presented are 2 tailed, with $P<.05$ considered to indicate statistical significance.

RESULTS

Baseline Demographic and Clinical Data
At SNU and WMC, a total of 169 patients were admitted with active COVID-19

infection during the 4.5-month period, with 3 excluded because they were intubated at the time of evaluation. Sixty-five (38.5%; 95% CI, 31.2% to 46.3%) reported an active pain condition (≥2/10 pain score), with 3 others reporting a pain score of 1 (40.2%; 95% CI, 32.3% to 48.1%). Patients with pain had a median age of 56.0 (IQR, 43.0-69.0) years, and 28 (of 65) (43.1%) were women. Sixteen of 65 (24.6%) patients with pain had a pre-existing pain condition, with 5 reporting an exacerbation of that pain condition and the remainder reporting new symptoms.

A total of 8 pain consults were performed on patients with active COVID-19 infection at Johns Hopkins. These patients had a median age of 32.5 (IQR, 26.0-56.0) years, and 4 were women. The youngest was 18 years old. Six of the 8 had a pre-existing pain condition, with 4 experiencing an exacerbation of this condition as their primary pain symptom. Among these patients, 2 required ICU admission and none died (Table 1).

Comparison of COVID-19 Patients With and Without Pain

Compared with patients with pain at WMC and SNU, the 101 patients without pain had a median age of 61.0 (IQR, 45.0-76.0) years (P=.19), with 31 (30.7%) being women (P=.19). The median length of hospital stay for patients with pain (16.0; IQR, 9.0-26.0 days) was not different from that of patients without pain (16.0; IQR, 9.0-28.0 days; P=.69). Fifty-one of the 65 (78.5%) patients with pain were discharged to home without requiring intensive care and 14 (21.5%) required ICU admission, while 40 (39.6%) patients without pain required ICU admission (P=.02). Seven of 65 (10.8%) patients with pain died, whereas 27 of 101 patients (26.7%) with no or minimal pain died (P=.02).

Clinical Pain Presentation

Among the 73 total patients with pain, the most common pain diagnoses were headache (n=22; 30.1%), chest pain (n=17; 23.3 %), spinal pain (n=18; 24.7%), myalgia (n=13; 17.8%), abdominal or pelvic pain (n=13; 17.8%), arthralgia (n=11; 15.1%), and generalized pain (n=9; 12.3%). Among 18 patients with spinal pain, 5 (27.8%) had radicular symptoms. The median baseline pain score was 5.0 (IQR, 3.0-6.0). Most patients reported new pain symptoms, with 22 (30.1%) reporting a pre-existing chronic pain condition but only 9 (12.3%) reporting that their primary pain symptom was an exacerbation of a pre-existing condition. Thirteen (17.8%) were prescribed opioids,

TABLE 1. Demographic and Non—Pain-Related Clinical Data Stratified by Pain Diagnosis				
Pain-Related Diagnosis/Symptom[a]	No. (%)	Age (y), median, (interquartile range)	Female Sex, no. (%)	Pre-existing Pain Condition[b]
Chest pain	17 (23.3%)	54.0 (38.0-61.0)	5 (29.4%)	1 (5.9%)
Spinal pain	18 (24.7%)	52.5 (43.0-67.0)	10 (55.6%)	5 (27.8%)
Radicular	5 (6.8%)	43.0 (37.0-61.0)	3 (60.0%)	2 (40.0%)
Nonradicular	13 (17.8%)	54.0 (46.0-71.0)	7 (53.8%)	3 (23.1%)
Headache	22 (30.1%)	53.5 (38.0-65.0)	7 (31.8%)	2 (9.1%)
Nonradicular neurologic symptom(s)	2 (2.7%)	56.0 (56.0-56.0)	1 (50.0%)	2 (100.0%)
Myalgia	13 (17.8%)	53.0 (44.0-71.0)	8 (61.5%)	2 (15.4%)
Sickle cell crisis	2 (2.7%)	26.0 (24.0-28.0)	0 (0.0%)	2 (100.0%)
Arthralgia	11 (15.1%)	52.0 (45.0-59.0)	5 (45.5%)	3 (27.3%)
Abdominal/pelvic pain	13 (17.8%)	65.0 (50.0-73.0)	6 (46.2%)	2 (15.4%)
Fibromyalgia or diffuse pain	9 (12.3%)	51.0 (47.0-55.0)	3 (33.3%)	3 (33.3%)

[a]Includes only individuals reporting 2 or more of 10 pain score.
[b]Denotes any pre-existing pain condition (n=22), with 9 (41.0%) reporting an exacerbation of that condition as their primary pain complaint.

including 6 who received oral morphine equivalent doses of 50 mg per day or greater; 6 (8.2%), adjuvants (4 of whom received 2 adjuvants); 59 (80.8%), NSAIDs (n=2) or acetaminophen (n=57); 2 (2.7%), muscle relaxants; 4 (5.5%), ketamine infusions, and 2 (2.7%) others (e.g. topical lidocaine). Ten (13.7%) patients with pain received no analgesics. Patients with sickle cell anemia (n=2) were more likely to receive opioids than those with other conditions (P=.03), whereas those with arthralgia were less likely to receive NSAIDs or acetaminophen (P=.01; Table 2; Figure).

We separately examined patients with the most common diagnosis, headache, which represents a continuum of conditions with multiple mechanisms. Four patients exhibited migraine headaches, 12 had tension-type headaches, 2 presented with cervicogenic headaches, and 4 others had indeterminate or mixed headache features. Only 1 of the 2 patients with a pre-existing pain condition had a headache history (pre-existing migraines in a patient who presented with a tension-type headache). One of the 4 patients who developed a migraine headache with COVID-19 infection continues to have persisting migraine headaches

8 months after other symptom resolution despite having no medical or family history.

Variables Associated With ICU Admission and Mortality

Among all patients, the absence of pain (OR, 2.92; 95% CI, 1.42 to 6.28; P=.004) was associated with ICU admission when age 65 years or older (OR, 2.67; 95% CI, 1.35 to 5.39; P=.005) and sex (OR, 2.24; 95% CI, 1.10 to 4.64; P=.03) were controlled for in multivariable analysis. Absence of pain (OR, 3.49; 95% CI, 1.40 to 9.76; P=.01) was also associated with death when age 65 years or older (OR, 5.46; 95% CI, 2.35 to 13.7; P<.001) and sex (OR, 1.61; 95% CI, 0.67 to 3.90; P=.28) were controlled for in multivariable analysis.

Among patients with COVID-19 infection and pain (n=73), age 65 years or older (OR, 5.73; 95% CI, 1.75 to 21.1; P=.005) was the only variable associated with ICU admission. Pain intensity as measured using NRS was not significantly associated with ICU admission or death. The presence of headache was associated with a lower likelihood of ICU admission than other pain conditions (0% vs 15/51 [29.4%]; P=.003). Age of 65 years or older was associated with a

TABLE 2. Pain-Related Diagnoses and Treatments[a]

Pain-Related Diagnosis/Symptom[b]	Opioids, no. (%)	P	NSAID/Acetaminophen, no. (%)	P	Adjuvants, no. (%)	P	Ketamine, no. (%)	P	Others,[c] no. (%)	P
Chest pain	4 (23.5%)	.48	16 (94.1%)	.16	0 (0.0%)	.33	1 (5.9%)	1.00	1 (5.9%)	>.99
Spinal pain	4 (22.2%)	.31	13 (72.2%)	.74	4 (22.2%)	.030	1 (5.6%)	>.99	1 (5.6%)	.43
Radicular	1 (20.0%)	>.99	3 (60.0%)	.24	2 (40.0%)	.051	1 (20.0%)	.25	0 (0.0%)	>.99
Nonradicular	3 (23.1%)	.69	10 (76.9%)	.70	2 (15.4%)	.29	0 (0.0%)	>.99	1 (7.7%)	.33
Headache	3 (13.6%)	.74	20 (90.9%)	.20	1 (4.5%)	.66	2 (9.1%)	.58	2 (9.1%)	.09
Nonradicular neurologic symptom(s)	0 (0.0%)	>.99	2 (100.0%)	>.99	1 (50.0%)	.16	0 (0.0%)	>.99	0 (0.0%)	>.99
Myalgia	1 (7.7%)	.68	9 (69.2%)	.45	1 (7.7%)	>.99	0 (0.0%)	>.99	1 (7.7%)	.56
Sickle cell crisis	2 (100%)	.03	1 (50.0%)	.38	0 (0.0%)	>.99	1 (50.0%)	.11	0 (0.0%)	>.99
Arthralgia	3 (27.3%)	.38	5 (45.5%)	.008	0 (0.0%)	>.99	2 (18.2%)	.11	1 (9.1%)	.49
Abdominal/pelvic pain	4 (30.8%)	.23	9 (69.2%)	.26	1 (7.7%)	>.99	0 (0.0%)	>.99	1 (7.7%)	.33
Fibromyalgia or diffuse pain	3 (33.3%)	.17	9 (100.0%)	.19	0 (0.0%)	>.99	0 (0.0%)	>.99	0 (0.0%)	>.99

[a]NSAID = nonsteroidal anti-inflammatory drug.
[b]Includes only individuals reporting pain score of 2 or greater of 10.
[c]Others includes topical analgesics and muscle relaxants.

greater likelihood of death (OR, 5.75; 95% CI, 1.14 to 42.6; *P*=.046; Table 3).

DISCUSSION

In this study, we found that a substantial proportion of patients admitted for respiratory distress and other viral-related symptoms experienced significant pain, presenting with a wide variety of chronic pain symptoms. The most common pain symptoms involved generalized constitutional symptoms such as myalgias, arthralgias, and headaches, which are common in acute viral illnesses and may persist in a small subset of patients. Mechanisms by which viral illnesses may induce muscle pain include cytokine activation and stimulation of adrenergic receptors present in smooth and skeletal muscle fibers.[14] The pathophysiology of viral-induced arthralgias is similarly complex and may result from direct invasion of the joint, immune complex formation, and immune modulation causing chronic inflammation.[15] Pleuritic chest pain may result from direct infection of the lungs and the ensuing inflammatory response. Headaches may result from numerous causes, including myofascial pathology, psychological stress, and vascular pathology (eg, temporal arteritis, microbleeds, thromboembolic disease, vasospasm, and dilation), all of which are common with COVID-19 infection.[16-18]

The prevalence of pain in our study was 38.5% (65 of 169) among patients admitted with COVID-19 infection to WMC and SNU, which is significantly higher than other studies that have examined clinical symptoms in COVID-19 infection. In a retrospective study performed in 99 patients admitted to a Wuhan, China, hospital with active disease, 11% reported myalgias; 8%, headache; 2%, chest pain; and 3%, gastrointestinal symptoms, though the proportion with abdominal pain was not noted.[19] A similar study from a different hospital in Wuhan performed in 138 patients found that 35% reported myalgias; 7%, headache; and 2%, abdominal pain.[20] However, research conducted in other viral illnesses report much higher rates of pain, with more than 50% of patients with the common cold and flu experiencing myalgias and headaches, and disabling arthralgias and
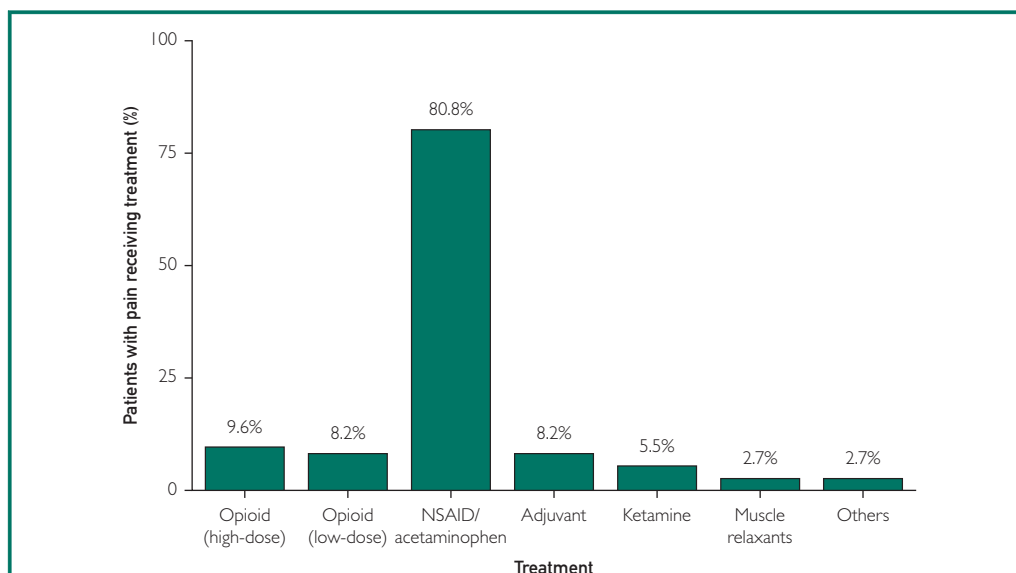

FIGURE. Pain treatments received by patients with coronavirus disease 2019 (COVID-19) infection with acute pain. High-dose opioids refers to 50 or greater oral morphine milligram equivalents per day; low-dose, to less than 50 mg/d. Others include topical creams, abortive headache therapies, etc. Adjuvant, anticonvulsant and antidepressant use for pain relief; NSAID = nonsteroidal anti-inflammatory drug.

TABLE 3. Clinical Data for Pain-Related Diagnoses

Pain-Related Diagnosis/Symptom	Baseline Pain Scores, median (interquartile range)[a]	Intensive Care Unit Admission[b,c]	P[d]	Died	P[d]
Chest pain	5.0 (3.0-6.0)	3 (17.6%)	>.99	2 (11.8%)	.66
Spinal pain	4.5 (4.0-6.0)	4 (22.2%)	>.99	1 (5.6%)	.67
Radicular	5.0 (4.0-6.0)	0 (0%)	.58	0 (0.0%)	>.99
Nonradicular	4.0 (3.0-6.0)	4 (30.8%)	.45	1 (7.7%)	>.99
Headache	4.0 (4.0-5.0)	0 (0%)	.003	0 (0.0%)	.09
Nonradicular neurologic symptom(s)	5.5 (3.0-8.0)	0 (0%)	>.99	0 (0.0%)	>.99
Myalgia	4.0 (3.0-6.0)	2 (15.4%)	>.99	1 (7.7%)	>.99
Sickle cell crisis	7.0 (4.0-10.0)	0 (0%)	>.99	0 (0.0%)	>.99
Arthralgia	5.0 (3.5-6.2)	3 (27.3%)	.69	0 (0.0%)	.59
Abdominal/pelvic pain	4.0 (3.0-6.0)	5 (38.5%)	.12	3 (23.1%)	.10
Fibromyalgia or diffuse pain	5.0 (4.0-6.0)	2 (22.2%)	>.99	1 (11.1%)	>.99

[a]Includes only individuals reporting pain score of 2 or greater of 10.
[b]Includes any patient who required intensive care treatment.
[c]Based on number of people with the pain diagnosis.
[d]Compared with other pain conditions.

myalgias being reported in upward of 90% of individuals with Chikungunya viral infection.[21,22] In addition to differences in virulence, organ infectivity, and ability to stimulate the inflammatory cascade, another reason for the discrepancy in pain incidence is the method of surveillance, with higher rates reported with greater surveillance frequency and questions directed toward specific symptoms.[23,24]

Thirty percent of patients (22 of 73) had a history of a pre-existing pain condition, 41% (n=9/22) of whom experienced a recurrence, which is common with acute life-threatening infectious diseases, including COVID-19 infection.[6,25] Mechanisms by which viral infections may exacerbate pain include directly increasing pain sensitivity through metabolic pathways and by physical and psychological stressors, including anxiety and depression, sleep deprivation, activation of the sympathetic nervous system, and deconditioning (ie, biopsychosocial model).[26,27]

We hypothesized that individuals with significant pain would be more likely to experience adverse outcomes including ICU admission and death, but when controlling for age and sex, the opposite was true. It was thought that pain might be a marker for either virulence or viral burden, both of which might lead to a higher rate of chronic pain. In previous studies that correlated viral load with acute pain symptoms, some (eg, acute herpes zoster) have found a direct relationship between viral burden and pain,[28] whereas others examining the relationship in Chikungunya and HIV infections have failed to demonstrate an association.[29,30] The observation that an absence of pain was associated with a poorer prognosis could be explained because pain assumed a lower priority for those with life-threatening symptoms, whereas those with less severe respiratory symptoms focused more on somatic symptoms. Reasons why pain could have been associated with better outcomes include that an intense systemic stimulus (eg, respiratory distress or anxiety) might inhibit pain signals (similar to conditioned pain modulation) or that the catecholamine surge associated with severe respiratory distress might attenuate nociceptive signaling.[31] This phenomenon whereby more severe injury is associated with lesser degrees of pain has previously been described for traumatic brain injury (ie, greater burden is associated with less pain).[32]

Two patients (2.7%) were treated with NSAIDs; 78.1% (n=57), with acetaminophen; 6.8% (n=6), with adjuvants; 17.8% (n=13), with opioids; and 5.5% (n=4), with intravenous ketamine. A substantial proportion of patients, 96% (45 of 47) at WMC (the two who did not received no analgesics), received acetaminophen, which has less analgesic and antipyretic efficacy than NSAIDs.[33,34] In mid-March 2020, non—peer-reviewed anecdotal reports emerged linking NSAIDs to exacerbation of COVID-19 illness, which led to warnings against their use by the World Health Organization and some national health agencies, a position that has since been refuted.[35,36] No patients at SNU received opioids, which have well-known respiratory depressant effects and may inhibit one's ability to cough. Adjuvants such as antidepressants (6.8%; 5 of 73) and anticonvulsants (6.8%; 5 of 73) were administered to only a small number of people because few people had nonradicular neuropathic pain and adjuvants have scant evidence in radiculopathy. Antidepressants, gabapentinoids, and muscle relaxants all act centrally to depress the nervous system and may increase the likelihood of opioid-related complications, including respiratory depression.[37,38] Ketamine is a powerful nonopioid analgesic that maintains minute ventilation at therapeutic doses but may precipitate arrhythmias, angina, and cardiac depression in catecholamine-depleted ICU patients.[39]

However, despite these risks, which can be minimized or eliminated in a controlled hospital setting, the risks of undertreating pain may be more consequential. Poorly treated acute pain has been shown in observational studies to increase the risk for persistent postinjury pain and has long-term psychological consequences, including higher rates of anxiety and depression.[40]

Several limitations of our study should be acknowledged. First, as the virus evolves and because all centers were major teaching hospitals with sufficient resources and expertise, our results may not be generalizable to different times and settings. Second, the relatively small sample size calculated from 2 sites may raise questions regarding the reproducibility of our results, as evidenced by the wide CIs for pain prevalence. Finally, because few patients were admitted primarily for pain, diagnoses may have lacked precision (eg, causes of abdominal and neuropathic pain, and precision on headache types).

The results of our study may have implications beyond the immediate course of illness. Postinfectious chronic pain syndromes have been reported for a whole host of pathogens, including the coronavirus that causes severe acute respiratory syndrome (SARS).[7,41,42] Although there are scant data on the prognostic value of acute pain during an active infection for the development of chronic pain, there is evidence that the severity of pain during acute herpes zoster infection significantly increases the risk for postherpetic neuralgia, which is consistent with the overarching literature suggesting that severe acute pain predisposes patients to chronic pain after injury.[43,44]

CONCLUSION

In summary, we found that pain during active COVID-19 infection was common, occurring in 38.5% (65 of 169) of infected individuals, with the most frequent symptoms being headache, chest pain, spine pain, myalgias, and pelvic/abdominal pain. Individuals without pain were more likely to be admitted to an ICU and die than those with pain. More research in the form of larger multicenter studies are needed to provide better precision for pain prevalence rates and determine the optimal means to treat it.

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