

# Pain Symptoms in Patients with Coronavirus Disease (COVID-19): A Literature Review

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**Purpose:** On 11 March, 2020, the coronavirus disease (COVID-19) outbreak was declared as a global pandemic by the World Health Organization. It brought substantial physical and psychological burden on individuals and financial loss across countries. Patients with COVID-19 may exhibit various symptoms, such as fever, cough, dyspnea, muscle pain, sore throat, headache, chest pain, and abdominal pain, at 2–14 days after exposure to the novel coronavirus (severe acute respiratory syndrome [SARS]-CoV-2). Pain symptoms present important challenge to clinicians' diagnosis when treating COVID-19 patients with mild symptoms. Considering the increasing number of confirmed COVID-19 cases, the pain symptoms should be systematically summarized.

**Results:** The virus can invade different tissues of the body and cause different pain manifestations. SARS-CoV-2 primarily invades the respiratory system, and patients develop sore throat, fever, cough, and other pneumonia-associated symptoms. Moreover, it infects the nervous system (eg, headache, dizziness, and confusion), digestive system (eg, abdominal pain, diarrhea), and cardiovascular system (eg, chest pain, palmus, and cardiac injury). The incidence rate is 1.7–33.9% for headache, 0.7–47.1% for sore throat, 1.5–61.0% for myalgia/arthritis, 1.6–17.7% for chest pain, and 1.9–14.5% for abdominal pain. In comparison with chest and abdominal pain, COVID-19 patients are more likely to develop headache, sore throat, and myalgia/arthritis.

**Conclusion:** Different pain reflects the damage of different body systems. Therefore, the summary of pain symptoms for COVID-19 patients can help doctors improve the accuracy and efficiency of diagnosis when treating COVID-19 patients with atypical or mild symptoms and adopt more targeted treatment methods.

**Keywords:** pain, COVID-19, SARS-CoV-2, symptom

## Introduction

On 11 March 2020, the coronavirus disease (COVID-19) outbreak was declared as a global pandemic by the World Health Organization.<sup>1</sup> The WHO reported that the total number of confirmed COVID-19 cases has increased sharply to 79,231,893 (1,754,574 deaths, 2.21% fatality ratio) in 219 countries/territories/areas as of December 29, 2020.<sup>2</sup> The fatality ratio in France, Italy, and United Kingdom reached 2.48% (62,197 deaths, 2,507,532 confirmed cases), 3.52% (71,620 deaths, 2,038,759 confirmed cases), and 3.12% (70,405 deaths, 2,256,009 confirmed cases), respectively.<sup>2</sup> The spread of COVID-19 is becoming unstoppable across the world,<sup>3,4</sup> and the global pandemic brought substantial physical and psychological burden on individuals and financial loss across countries.<sup>5–7</sup>

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Patients with COVID-19 exhibit various symptoms, such as fever, cough, dyspnea, muscle pain, headache, sore throat, chest pain, and abdominal pain, at 2–14 days after exposure to the novel coronavirus (severe acute respiratory syndrome [SARS]-CoV-2).<sup>8–17</sup> Huang et al<sup>10</sup> first reported the clinical symptoms at the onset of illness in patients with COVID-19, in which fever was the most common symptom (98%), followed by cough (76%), dyspnea (55%), muscle pain or fatigue (44%), sputum production (28%), headache (8%), haemoptysis (5%), and diarrhoea (3%). Guan et al<sup>9</sup> found that the common pain symptoms include myalgia or arthralgia (14.9%), sore throat (13.9%), and headache (13.6%). Apart from respiratory symptoms, pain symptoms, such as headache, sore throat, myalgia or arthralgia, chest pain, and abdominal pain are common in patients with COVID-19. Similarly, patients with SARS also reported pain symptoms.<sup>18–21</sup> such as myalgia (49.3–60.9%), headache (35.4–55.8%), sore throat (12.5–23.2%), chest pain (10.4%), and abdominal pain (3.5%).

Due to the high incidence of pain, it can be used as a symptom identified in the course of COVID-19, reminding people with pain to be vigilant and help doctors diagnose as soon as possible. In addition, it also presents important challenge to clinicians' diagnosis when treating patients with COVID-19 having mild symptoms. Considering the increasing number of confirmed COVID-19 cases, the pain symptoms of COVID-19 should be systematically summarized. At present, no reviews of pain symptoms for these patients with COVID-19 have been done. This review aimed to elaborate the pain symptoms of patients with COVID-19 based on published data.

## Headache

Headache refers to the pain in the head or upper neck.<sup>22</sup> Globally, the prevalence of general population is 47% and the lifetime prevalence is 66%.<sup>23</sup> For individuals, this condition can cause suffering, reduced quality of life, and disability.<sup>24</sup> Headache is also a very common clinical symptom, and the infection with the COVID-19 is not an exception. In a recent retrospective case study, in which Guan et al analyzed data from 1590 patients with COVID-19 in China between 11 December 2019 and 31 January 2020, the incidence of headache was 15.4%. Among the 1328 patients with valid data, 205 patients reported headaches.<sup>25</sup> Up to April 12, 2020, based on the 11th epidemiological report issued by COVID-19 National Incident Room Surveillance Team, 6394 confirmed cases

were reported in Australia, in which 36% reported headache ( $n = 2010$ ).<sup>26</sup> Table 1 summarizes the five types of pain in different studies of COVID-19. The incidence rate of headache is 1.7–33.9% (Figure 1).<sup>16,27</sup>

The mechanism of COVID-19-induced headache remains unclear. We list some possible reasons. First, the levels of cytokines in the serum of patients with COVID-19 were elevated, including tumor necrosis factor, interleukin 2, and granulocyte macrophage-colony stimulating factor.<sup>10,28,29</sup> These cytokines released by immune cells in response to viral infections may cause headache.<sup>30,31</sup> Second, when SARS-CoV-2 invades lung tissue, it may cause alveolar gas exchange disorders, leading to hypoxia in the brain, increasing the anaerobic metabolism of mitochondria in brain cell and accumulation of acid metabolites. It will cause obstruction of cerebral blood flow, swelling of brain cells, cerebrovascular dilatation and headache due to ischemia and congestion.<sup>32</sup> Moreover, headache may result from the direct invasion of SARS-CoV-2 into the nervous system. Besides headache, some patients also presented neurological symptoms, such as dizziness, nausea, and vomiting.<sup>33,34</sup> The results of autopsy on patients with COVID-19 revealed the congestion and edema of brain tissue, where some neurons degenerate. And some researchers detected SARS-CoV-2 in the cerebrospinal fluid of confirmed patients by genome sequencing.<sup>32</sup> Neuronal pathway is an important way for neurotropic viruses to enter the central nervous system. Two experimental studies showed that SARS-CoV or Middle East respiratory syndrome coronavirus (MERS-CoV) could enter some brain areas in transgenic mice via the olfactory nerves when administered intranasally.<sup>35,36</sup> Considering the similar structure and pathogenesis of SARS-CoV-2, SARS-CoV and MERS-CoV,<sup>37</sup> this mechanism can also be applied to this novel coronavirus. The main routes of COVID-19 transmission among people are close contact and droplet contagion. The trigeminal nerve or the solitary tract is infected due to the contact of the eye conjunctiva or tongue taste buds with droplets containing SARS-CoV-2, the virus can infect the central nervous system (CNS) through retrograde traveling. As the respiratory droplets containing SARS-CoV-2 reach the nasal mucosa, the virus may directly infect olfactory sensory neurons and then enter the brain from olfactory nerve.<sup>38</sup> In a transgenic mouse model of human angiotensin converting enzyme 2 (ACE2) infected by SARS-CoV, the olfactory nerve was the route for the virus to enter and infect the CNS; however, there were

**Table 1** The Incidence Rate of Pain Symptoms for Patients with COVID-19 in Different Studies

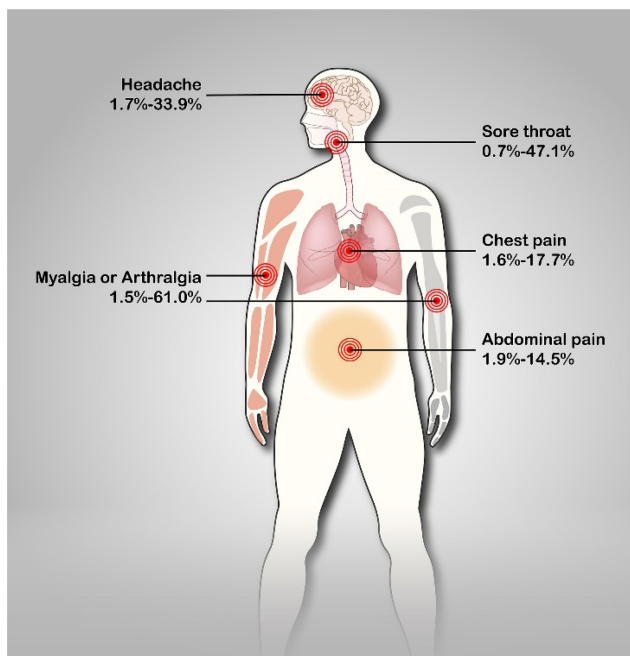
Ranking	Author	Recruited Time	Country	Number of COVID-19 Patients	Number of Headache (Incidence, %)	Number of Sore Throat (Incidence, %)	Number of Chest Pain (Incidence, %)	Number of Myalgia or Arthralgia Pain (Incidence, %)	Number of Abdominal Pain (Incidence, %)
1	Tian <sup>98</sup>	2020.01.20–2020.02.10	China	262	6.5%	NR	NR	NR	NR
2	Xu <sup>99</sup>	2020.01–2020.02	China	50	10.0%	8.0%	NR	16.0%	NR
3	Yang <sup>100</sup>	2020.01.17–2020.02.10	China	149	8.7%	14.1%	3.4%	3.4%	NR
4	Wang <sup>33</sup>	2020.01.01–2020.01.28	China	138	6.5%	17.4%	NR	34.8%	2.2%
5	Zhang <sup>89</sup>	2020.01.16–2020.02.03	China	140	NR	NR	NR	NR	5.8%
6	Guan <sup>101</sup>	2019.12.11–2020.01.29	China	1099	13.6%	13.9%	NR	14.9%	NR
7	Wu <sup>102</sup>	2020.01.22–2020.02.14	China	80	NR	13.8%	3.8%	22.5%	NR
8	Huang <sup>103</sup>	2019.12–2020.01	China	34	5.9%	NR	NR	NR	NR
9	Liu <sup>104</sup>	2019.12.30–2020.01.24	China	137	9.5%	NR	NR	NR	NR
10	Mo <sup>34</sup>	2020.01.01–2020.02.05	China	155	9.8%	NR	3.7%	61.0%	1.9%
11	Zhou <sup>105</sup>	2019.12.29–2020.01.31	China	191	NR	NR	NR	15.2%	NR
12	Xu <sup>106</sup>	2020.01.23–2020.02.18	China	51	NR	5.9%	NR	15.7%	NR
13	Wan <sup>107</sup>	2020.01.23–2020.02.08	China	135	32.5%	17.7%	NR	NR	NR
14	Huang <sup>10</sup>	Up to 2020.01.02	China	41	7.9%	NR	NR	NR	NR
15	Xu <sup>16</sup>	2020.01.10–2020.01.26	China	62	33.9%	NR	NR	NR	NR
16	Chen <sup>108</sup>	2020.01.20–2020.02.06	China	249	NR	6.4%	NR	NR	NR
17	COVID-19 National Incident Room Surveillance Team <sup>109</sup>	Up to 2020.03.14	Australia	295	19.9%	46.2%	5.8%	14.7%	3.9%
18	Zhou <sup>110</sup>	2020.01.16–2020.01.30	China	62	NR	NR	NR	32.3%	NR
19	Qin <sup>28</sup>	2020.01.10–2020.02.12	China	452	11.4%	4.8%	NR	21.4%	5.0%
20	Han <sup>111</sup>	2020.01.04–2020.02.03	China	108	13.0%	13.0%	NR	11.1%	NR

(Continued)

Table 1 (Continued).

Ranking	Author	Recruited Time	Country	Number of COVID-19 Patients	Number of Headache (Incidence, %)	Number of Sore Throat (Incidence, %)	Number of Chest Pain (Incidence, %)	Number of Myalgia or Arthralgia Pain (Incidence, %)	Number of Abdominal Pain (Incidence, %)
21	Song <sup>112</sup>	2020.01.20–2020.01.27	China	51	NR	5.9%	NR	NR	NR
22	Qian <sup>113</sup>	2020.01.20–2020.02.11	China	91	7.7%	NR	NR	5.5%	NR
23	Chen <sup>11</sup>	2020.01.01–2020.01.20	China	99	8.1%	5.1%	2.0%	11.1%	NR
24	Spiteri <sup>114</sup>	up to 2020.02.21	WHO European Region	38	19.4%	6.5%	NR	NR	NR
25	Xu <sup>115</sup>	2020.01.23–2020.02.04	China	90	4.4%	25.6%	NR	27.8%	NR
26	Zhu <sup>116</sup>	2020.01.24–2020.02.20	China	32	3.1%	NR	NR	NR	NR
27	Pung <sup>52</sup>	Up to 2020.02.15	Singapore	36	NR	47.1%	17.7%	29.4%	NR
28	Shi <sup>117</sup>	2020.12.20–2020.01.23	China	81	6.2%	NR	NR	NR	NR
29	Zhao <sup>118</sup>	NR	China	101	NR	11.9%	NR	NR	NR
30	Wu <sup>119</sup>	2020.12.25–2020.01.26	China	201	NR	NR	NR	32.3%	NR
31	Wang <sup>120</sup>	2020.01.16–2020.02.27	China	90	4.4%	7.8%	NR	4.4%	2.2%
32	Li <sup>12</sup>	2020.01–2020.02	China	83	10.8%	NR	6.0%	18.1%	NR
33	Mao <sup>121</sup>	2020.01.16–2020.02.19	China	214	13.1%	14.5%	NR	NR	4.7%
34	Shi <sup>122</sup>	2020.01.20–2020.02.10	China	416	2.2%	2.9%	3.4%	4.6%	NR
35	Daily Situation Report on Coronavirus disease (COVID-19) in Iran <sup>123</sup>	Up to 2020.03.13	Iran	11,364	NR	NR	NR	22.0%	NR
36	Guan <sup>25</sup>	2019.12.11–2020.01.31	China	1590	15.4%	14.7%	NR	17.5%	NR
37	Wang <sup>124</sup>	2020.01.25–2020.02.09	China	114	NR	5.3%	NR	NR	NR
38	Cao <sup>125</sup>	2020.01.03–2020.02.01	China	102	NR	NR	NR	34.3%	NR
39	Zhang <sup>126</sup>	2020.01.20–2020.02.10	China	120	23.3%	16%	NR	NR	NR

40	Barrasa <sup>127</sup>	2020.03.04–2020.03.31	Spain	48	NR	NR	NR	NR	NR	4.2%	NR	NR
41	Tang <sup>128</sup>	2020.12.24–2020.02.07	China	73	NR	NR	NR	NR	NR	34.2%	NR	NR
42	Sun <sup>129</sup>	2020.01.26–2020.02.16	Multi-country	54	NR	NR	33.3%	NR	NR	NR	NR	NR
43	Chen <sup>130</sup>	2020.01.20–2020.02.17	China	98	NR	NR	8.2%	NR	NR	NR	NR	NR
44	Cai <sup>27</sup>	2020.01.11–2020.02.06	China	298	1.7%	NR	0.7%	NR	NR	NR	NR	NR
45	Chen <sup>131</sup>	2020.01.20–2020.02.09	China	42	NR	NR	14.3%	NR	NR	23.8%	NR	11.9%
46	Wang <sup>132</sup>	2020.02.07–2020.02.12	China	1012	15.0%	NR	14.2%	NR	NR	16.8%	NR	3.7%
47	Shao <sup>133</sup>	2020.01.15–2020.02.25	China	136	NR	NR	NR	NR	NR	60.3%	NR	5.9%
48	Wang <sup>134</sup>	2020.01.20–2020.02.09	China	125	NR	NR	13.6%	NR	1.6%	3.2%	NR	NR
49	Du <sup>135</sup>	2019.12.25–2020.02.15	China	109	7.3%	NR	NR	NR	NR	17.4%	NR	NR
50	Jia <sup>136</sup>	2020.01.29–2020.02.23	China	44	11.4%	NR	9.1%	NR	NR	15.9%	NR	NR
51	Li <sup>66</sup>	2020.12.28–2020.02.10	China	131	NR	NR	NR	NR	NR	1.5%	NR	NR
52	Feng <sup>137</sup>	2020.01.01–2020.02.15	China	476	NR	NR	8.1%	NR	4.8%	12.6%	NR	NR
53	Zheng <sup>138</sup>	2020.01.17–2020.02.07	China	161	7.5%	NR	NR	NR	NR	11.2%	NR	NR
54	Du <sup>139</sup>	2020.01.09–2020.02.15	China	85	4.7%	NR	2.4%	NR	2.4%	16.5%	NR	3.5%



**Figure 1** The incidence rate of pain symptoms for patients with COVID-19.

still many infection sites indirectly connected to the olfactory bulb, indicating body fluid pathway for viral infection (such as blood, lymph and cerebral spinal fluid).<sup>35,39</sup> SARS-CoV-2 has the same functional receptor as SARS-CoV - ACE2.<sup>40</sup> The significant presence of blood and lymphatic capillaries in the nasal mucosa provides a favorable environment for the virus invasion and help to enter the blood stream after interaction with ACE2 expressed on endothelial cells. When the virus spreads in the respiratory tract, it can also bind to ACE2 expressed on the epithelial cells and enter the blood stream. SARS-CoV-2 can spread to the CNS through vascular pathways. Likewise, the virus in the gastrointestinal tract can also enter the CNS through blood vessels, lymphoid pathways, and the vagus nerve.<sup>39</sup>

Headache is not a typical symptom of patients with COVID-19, but it cannot be easily ignored. A confirmed case reported that he only experienced strong headache and fatigue, without fever, coughing or breathing problems in the early days. Then, he displayed anosmia and slowly emerged common symptoms.<sup>41</sup> This condition indicates that headache and anosmia are the early signs of COVID-19 in some patients. Doctors should also focus on patients who report early neurological symptoms, because the virus shows a potential neurotropism, and may eliminate medullary neurons and threaten the patient's life during the incubation period.<sup>42</sup> In addition,

Hu et al found that headache was a predictor of intermittent negative state in patients with COVID-19, with probability of 60%. Intermittent negative status was described as COVID-19 patient who showed negative on reverse-transcription-polymerase-chain-reaction test was re-detected virus RNA. It showed that a large proportion of patients with headache had delayed clearance of SARS-CoV-2 and poor prognosis, suggesting doctors still give attention to patients who tested negative with COVID-19, and prolong their isolation and hospitalization.<sup>43</sup>

## Sore Throat

Sore throat refers to the pain caused by inflammation of tissues located behind the throat,<sup>44</sup> and up to 80% of the cases is caused by viruses (eg, coronavirus, influenza, and rhinovirus).<sup>45,46</sup> Internationally, sore throat complaints account for 1–4% of all primary care reports.<sup>47</sup> Within a year, approximately 30% of the general population experiences sore throat once because of viral infection, and the course is usually self-limited.<sup>48</sup> Patients with sore throat may also experience redness, swelling, scratchy, coughing, and hoarseness.<sup>49,50</sup> In China, Guan et al described the clinical characteristics of 1099 patients with COVID-19 in a selected cohort on 29 January 2020. A total of 153 patients reported sore throat, and the incidence rate was approximately 13.9%.<sup>9</sup> On 1–30 March 2020, Garg et al collected data from 1482 hospitalized patients with COVID-19 in the United States. The symptoms of 180 adults were presented using the COVID-19-associated hospitalization surveillance network, sore throat was 17.8% (n=32).<sup>51</sup> Table 1 shows that the incidence rate of sore throat is 0.7–47.1% (Figure 1).<sup>27,52</sup>

At present, few studies have clearly explained the mechanism for the development of sore throat in patients with COVID-19. Given that both SARS-CoV-2 and influenza virus can spread in the respiratory tract and exhibit similar symptoms,<sup>53,54</sup> we speculate that the reason of sore throat induced by influenza may be applicable to SARS-CoV-2. The body may release inflammatory mediators (eg, prostaglandins and bradykinin) in the airway in response to SARS-CoV-2 infection, thereby affecting the sensory nerve in the layers of throat tissue and causing sore throat.<sup>30,50</sup>

Sore throat is one of the common otorhinolaryngological dysfunctions in patients with COVID-19. Krajewska et al discussed the connection between otorhinolaryngological manifestations and patients with COVID-19 in a review. She mentioned that sore throat, cough, and dyspnea were often observed in young, mildly, or moderately ill patients with COVID-19. Before the confirmation

of SARS-CoV-2 in molecular analysis, patients may present these symptoms.<sup>55</sup> Yan et al also reported that patients who tested negative with COVID-19 are 4–5 times more likely to develop sore throat than those who tested positive with COVID-19.<sup>56</sup> Sore throat is not as common as fever in patients with COVID-19, but these patients should still be considered as carrier of COVID-19. In comparison with elderly patients infected with coronavirus, young adults have a higher incidence of sore throat.<sup>57,58</sup> This condition may also be a common feature of COVID-19.

## Myalgia or Arthralgia

Myalgia is a symptom of muscle pain or discomfort, and it is mostly caused by systemic or local infection.<sup>59,60</sup> It is usually diffuse rather than localized and is likely to cause referred pain.<sup>61</sup> Arthralgia is defined as joint pain or stiffness<sup>62</sup> that results in low quality of life, adverse emotions, reduced compliance, and even interruption of treatment.<sup>63,64</sup> Both myalgia and arthralgia belong to musculoskeletal pain, which is experienced by most people at least once in a lifetime, thus negatively affecting their physical, social and psychological levels.<sup>65</sup> In an epidemiological and clinical investigation, Pung et al analyzed 36 cases of COVID-19 until 15 February 2020 in Singapore. Among the 17 local patients who tested positive for SARS-CoV-2, myalgia was reported in 14 (29.4%) individuals.<sup>52</sup> Mo et al retrospectively analyzed the characteristics of confirmed cases in China, including 155 patients with COVID-19 from 1 January 2020 to 5 February 2020. Fifty patients experienced myalgia or arthralgia, accounting for 61.0% of 82 patients with valid data.<sup>34</sup> Table 1 shows that the incidence rate range of myalgia/arthralgia is 1.5–61.0% (Figure 1).<sup>34,66</sup> Myalgia during viral infection is usually mediated by interleukin-6, which upregulates and causes myalgia or arthralgia.<sup>67,68</sup> Creatine kinase (CK) and lactate dehydrogenase (LDH) can assess skeletal muscle damage.<sup>69</sup> Mao et al found that patients with COVID-19 having muscle symptoms had higher levels of CK and LDH than those without muscle symptoms. Myalgia might be caused by skeletal muscle injury.<sup>40</sup> ACE2 is also present in skeletal muscle,<sup>70</sup> and SARS-CoV-2 may bind with ACE2 to infect skeletal muscle. However, the autopsy result of SARS-CoV-infected patients did not indicate SARS-CoV infection in skeletal muscle.<sup>71</sup> Hence, the mechanism still needs further study. Second, myalgia may also occur when cytokines stimulate the production of prostaglandin E2, and prostaglandin E2 mediate pain via peripheral pain receptors.<sup>30</sup> In addition, skeletal muscle injury is also a manifestation of nervous system damage.<sup>40</sup> SARS-CoV-2 can invade the central nervous

system through peripheral nerves or directly attack the nervous system by binding to ACE2 to cause skeletal muscle injury.

Myalgia is closely related to SARS-CoV-2 test positivity and can be used as one of the strongest predictors.<sup>72</sup> General myalgia is very common in patients with COVID-19, but focal myalgia should alert the doctor that the patient may have rhabdomyolysis.<sup>73</sup> Rhabdomyolysis is a potentially fatal syndrome, and its important indices are the concentration of serum CK or appearance of myoglobinuria.<sup>74</sup> The CK level may indicate the severity of rhabdomyolysis.<sup>75</sup> In comparison with non-severely infected patients, patients with severe infection have higher levels of CK and LDH.<sup>40</sup> Therefore, the severity of myalgia may predict the severity of COVID-19 infection. Arthralgia is not a common symptom, and approximately 2.5% of patients with COVID-19 presented joint pain in Thailand up to 28 February 2020.<sup>76</sup> Doctors should not ignore arthralgia when diagnosing COVID-19 to avoid misdiagnosis.

## Chest Pain

Chest pain refers to discomfort or pain between the neck and upper abdomen. During a lifetime, this condition affects 20–40% of the general population. Moreover, patients with chest pain often suffer from health-related quality of life impairment.<sup>77</sup> Between January 20 2020, and February 10 2020, Shi et al conducted a retrospective cohort study that included 416 confirmed COVID-19 cases in Wuhan, China. Fourteen patients experienced chest pain, accounting for 13.4%.<sup>78</sup> Up to 29 March 2020, the COVID-19 National Incident Room Surveillance Team reported 4159 confirmed cases in Australia. Among the 2257 patients with COVID-19 who reported symptoms, 5% experienced chest pain.<sup>79</sup> Table 1 shows that the incidence rate range of chest pain is 1.6–17.7% (Figure 1).<sup>52,80</sup>

The mechanism of chest pain caused by the invasion of the SARS-CoV-2 remains unclear. We speculate that chest pain may result from cardiac injury or pleural inflammatory infection.<sup>12,78</sup> A high ACE2 expression has been observed in the heart.<sup>70</sup> The result of autopsy in patients who died from SARS revealed SARS-CoV viral RNA in the heart samples.<sup>81</sup> This finding indicates that the virus mediated by ACE2 can invade cardiomyocytes directly and cause cardiac injury. Moreover, the inflammatory markers (eg, C-reactive protein, leukocytes, and procalcitonin), which may be due to the cytokine storm syndrome, increase substantially in patients with cardiac injury. The enhanced release and activation of inflammatory cytokines can damage myocardial cells.<sup>78</sup> Furthermore, some inflammatory mediators released into the

pleural space can trigger pain receptors on the pleura, thus causing chest pain.<sup>82</sup> In addition, cardiac injury can be attributed to respiratory dysfunction and hypoxemia instigated by COVID-19.<sup>83</sup>

The symptoms of chest pain and dyspnea represent severe COVID-19.<sup>84</sup> In comparison with general patients, severe/critical patients have higher incidence of chest pain;<sup>12</sup> in comparison with survivors, the prevalence of chest pain in non-survivors is approximately three times higher.<sup>84</sup> Therefore, chest pain may be a risk factor for developing severe/critical COVID-19 or death. The National Health Commission of China reported that 11.8% of non-survivors without underlying cardiovascular disease had severe heart injury.<sup>83</sup> In patients infected with SARS-CoV-2, cardiovascular disease has high incidence and can easily lead to deterioration. In addition, Wu et al recruited 25 SARS survivors in 2014 and found that SARS-CoV could cause long-term damage to the patient's cardiovascular system.<sup>85</sup> It indicates that recovered patients with COVID-19 are likely to have sequelae of the cardiovascular system. For patients with chest pain, doctors should keep alert and not neglect the cardiovascular protection during treatment.

## Abdominal Pain

Abdominal pain is the symptom of disordered gastrointestinal motility and sensation that affects almost everyone once in a lifetime.<sup>86,87</sup> This condition is associated with complications (eg, depression, anxiety, fibromyalgia) and the decline in the quality of life.<sup>87,88</sup> Qin et al completed a retrospective study and recruited 452 confirmed patients with COVID-19 between 10 January 2020 and 12 February 2020 in Wuhan, China. Among these patients, 23 cases involved abdominal pain, and the incidence rate was 5.1%.<sup>28</sup> To explore the clinical characteristics and allergy status of patients with COVID-19, Zhang et al investigated the medical records of 140 confirmed patients in the No. 7 Hospital of Wuhan in China. Eight patients presented abdominal pain in the 139 valid data, and the incidence rate was 5.8%.<sup>89</sup> Table 1 shows that the incidence rate range of abdominal pain is 1.9–14.5% (Figure 1).<sup>34,90</sup>

Few studies have clearly explained the mechanism of abdominal pain caused by SARS-CoV-2. Of 1141 confirmed patients with COVID-19 in China, Luo et al found 183 (16%) cases had gastrointestinal symptoms only, of which 25% presented abdominal pain.<sup>91</sup> It indicates that SARS-CoV-2 invades the gastrointestinal tract and caused abdominal pain. ACE2 is abundantly expressed in the gastrointestinal tract, especially in the small and large intestines.<sup>92,93</sup> Therefore, SARS-CoV-2 can attack the digestive system by combing

with ACE2 and cause pain. In children, pneumonia is the most common extra-abdominal cause of abdominal pain. The enlarged mesenteric lymph nodes are considered a potential mechanism in the presence of abdominal pain in children with pneumonia.<sup>94</sup> However, further research is needed on whether this mechanism is applicable to adult patients with COVID-19.

In comparison with non-severely infected patients, patients with severe infection more likely to report abdominal pain. Patients without digestive symptoms usually have better prognosis than those with digestive symptoms.<sup>95</sup> In addition, based on the review of the medical records of Oslo University Hospital during the outbreak of acute abdominal pain, 76 patients came to the hospital with the chief complaint of acute abdominal pain, and nine patients were diagnosed with COVID-19 (11.8%).<sup>96</sup> At the early stage of the epidemic, some patients may only report atypical symptoms but should still be suspected of being potential patients with COVID-19. It suggested that patients with symptoms of abdominal pain should also be diagnosed with oropharyngeal and nasopharyngeal swabs. On the other hand, it has been reported that confirmed cases tested positive for SARS-CoV-2 RNA in stool specimens, indicating that individuals could be infected via the fecal–oral route.<sup>97</sup> SARS-CoV-2 is highly contagious, suggesting that everyone should wash their hands before and after going to the toilet and not touch mucous membranes, such as nose and eyes, with dirty hands. Patients with COVID-19 should use a single toilet in the quarantine area and dispose their waste properly as directed by the appropriate authorities.<sup>95</sup>

## Conclusion

In summary, the virus not only invades the respiratory system and cause fever, cough, sore throat, and other pneumonia-associated symptoms, but also infects other systems in humans and results in corresponding symptoms, including nervous system (eg, headache, dizziness, and confusion), digestive system (eg, diarrhea, abdominal pain, and loss of appetite), and cardiovascular system (eg, palmus, chest pain, and cardiac injury).<sup>10,11</sup> Chest pain, myalgia, and abdominal pain are likely to occur in patients with severe infections, foreshadowing a wider range of virus invasion. These conditions may be risk factors for developing severe or critical COVID-19. Sore throat is more common in mild patients than in severe patients. It may be attributed to the invasion of the virus is limited to respiratory system in mild patients, and other systems are not damaged. Moreover, the spread of the virus through feces also suggests that need for more effective



protective measures to prevent further spread of COVID-19 and control infection. The incidence rate is 1.7–33.9% for headache, 0.7–47.1% for sore throat, 1.5–61.0% for myalgia/arthralgia, 1.6–17.7% for chest pain, and 1.9–14.5% for abdominal pain. Different pain reflects the damage of different body systems. However, pain in patients with COVID-19 may also be caused by treatment-related persistent pain and discomfort, intermittent procedural pain, and chronic pain before admission to the intensive care unit.<sup>68</sup> So, it is particularly important to determine the source of pain in the long and complicated treatment process. Although these pain symptoms are not as typical as fever and cough, doctors should not ignore them to avoid misdiagnosis or delayed diagnosis. They are also the signal that could alert doctors to pay attention to strengthen self-protection to reduce infection risks. The symptoms can also provide basis for doctors to take more targeted measures, treat and cure patients reasonably. In addition, once the general population has these symptoms, they should also consider that they are potential patients with COVID-19, should isolate themselves and seek medical attention as soon as possible.

## Abbreviations

SARS, severe acute respiratory syndrome; MERS-COV, Middle East respiratory syndrome coronavirus; CNS, central nervous system; ACE2, angiotensin converting enzyme 2; CK, creatine kinase; LDH, lactate dehydrogenase.

## Data Sharing Statement

All data generated or analysed during this study are included in this published article.

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## Disclosure

The authors report no conflicts of interest in this work.

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