

## Clinical research

# Prevalence of comorbidities and symptoms stratified by severity of illness amongst adult patients with COVID-19: a systematic review

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## Abstract

**Introduction:** We performed a systematic review of comorbidities and symptoms of adult patients with coronavirus disease 2019 (COVID-19) to evaluate comorbidities, symptoms, and severity.

**Material and methods:** We searched databases and extracted comorbidities and symptoms from the included studies. We stratified the similar signs and symptoms in groups and on the basis of severity and compared them with stratified analysis. Individual case reports and case series with < 5 patients were excluded.

**Results:** A total of 163 studies with 43,187 patients were included. Mean age was 54.6 years. There were significantly fewer women in the study (43.9% vs. 56.1%,  $p < 0.0001$ ). Prevalent cardiovascular comorbidities were hypertension (31.9%), obesity (27.9%), hyperlipidemia (26.4%), smoking (18.9%), diabetes mellitus (17.2%), atherosclerotic disease (9.2%) and arrhythmia (5.0%). The most frequently reported constitutional symptoms of COVID-19 were fever (73.9%), fatigue (33.4%), malaise (29.9%), myalgia and/or arthralgia (19.2%), generalized weakness (19.0%), and chills (11.3%). For the cardiovascular system, chest pain and/or tightness were most often reported (19.6%), followed by palpitations (5.2%). Hypertension and diabetes were common in severe disease. Obesity and congestive heart failure were not observed in any non-severe cases. Severe cases compared to non-severe cases more frequently had fever (87.8% vs. 58.5%,  $p < 0.001$ ), shortness of breath (47.4% vs. 20.6%,  $p < 0.001$ ), cough (66.8% vs. 62.9%,  $p < 0.001$ ), sputum production (35.4% vs. 26.5%,  $p < 0.001$ ) and rhinorrhea (32.2% vs. 7.3%,  $p < 0.001$ ).

**Conclusions:** Hypertension, diabetes, and atherosclerotic diseases are common comorbidities across the world, with obesity as the second most common in the US and more common in men.

**Key words:** symptoms, comorbidities, severity, COVID-19, SARS-CoV-2.

## Introduction

Coronavirus disease 2019 (COVID-19) is now a global pandemic caused by a novel coronavirus. The first case of COVID-19 was reported

in December 2019 in Wuhan, China. Since then, it has affected over 138,010,168 people and caused over 2,970,000 deaths across the world [1]. Similar to other coronaviruses, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily affects the pulmonary system. However, multi-system involvement, including cardiac, vascular, and neurological complications, has been reported [2]. The clinical manifestations range from asymptomatic infection or mild disease with fever, myalgias, and cough to severe disease characterized by shortness of breath, hypoxemia, acute respiratory distress syndrome requiring mechanical ventilation, multi-organ failure, and death [3]. However, due to this disease's novelty, within the first year of the initial description, the prevalence of various symptoms and comorbidities associated with the disease remains unclear.

Several studies have evaluated the prevalence of various symptoms. A systematic review of 3600 patients reported fever, cough, and fatigue as most common [4]. Similarly, another meta-analysis of 78 studies found the prevalence of gastrointestinal symptoms to be 1 out of every 5 COVID-19 patients [5]. Another systematic review described the prevalence of acute myocardial injury in COVID-19 infection and found a pooled prevalence of nearly 20% [6]. Given the variable presentations and unclear prevalence of comorbidities and the accrual of interim experience, we performed a systematic review to assess the contemporary prevalence of comorbidities and symptoms from all the published studies.

## Material and methods

We performed a systematic review following the Cochrane Handbook for Systematic Reviews and Intervention statement in health care interventions [7].

### Selection criteria

We included observational studies, case series (retrospective, prospective, descriptive), randomized controlled trials, and survey studies that included adults' comorbidities or symptoms with confirmed COVID-19 infection. Individual case reports and case series with < 5 patients were excluded.

### Data Sources and Search Strategy

A comprehensive literature search was done on Ovid MEDLINE(R) and Epub Ahead of Print, In-Process; Other Non-Indexed Citations and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from March 2019 to June 18, 2020. The main keywords used in the search

were: (Corona virinae or corona virus or Coronavirinae or coronavirus or COVID or nCoV or 2019; or novel or new) or (Corona virinae or & corona virus; or Coronavirinae or coronavirus or COVID or nCoV) and wuhan) or Corona virinae19; or ;Corona virinae 2019 or &quot;corona virus19 or &;corona virus2019; or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCoV19 or nCoV2019 or;2019-nCoV or 2019nCoV or SARS Corona virus or SARS Coronavirus or SARS-COV-2. Two investigators (D.R. and R.P.) reviewed the titles and abstracts of the identified studies independently and screened them as per the selection criteria mentioned above. Any conflict was resolved with the consensus of a third investigator (R.T.).

### Data abstraction

Data from included studies were independently abstracted by two investigators (D.R. and M.W.T.). The abstracted data included study design and setting, month and year of publication, duration of the study period, gender, comorbidities, symptoms and severity, mortality, survival, and discharge data. Data extraction excluded studies with pediatric patients. All comorbidities were initially abstracted separately, then grouped based on system involvement for data analysis. Similarly, all symptoms were extracted separately, then subsequently grouped for analysis.

### Statistical analysis

The frequency of variable occurrence was calculated using percentages. For comorbidity analysis, studies with fewer than 3 reported comorbidities were excluded. Primary analysis involved the calculation of the presence of comorbidities and symptoms in the pooled data. Comorbidities and symptoms were compared based on the severity of the patients studied. For this stratification, we included studies reporting symptoms or comorbidities exclusively for severe or non-severe cases. Studies with severe and non-severe cases with inseparable comorbidity or severity data were excluded. A  $\chi^2$  test was performed with  $\alpha$  set at 0.05. All analyses were performed using SPSS version 25.

## Results

The preliminary database search resulted in 4032 studies; 24 other studies were identified from other sources; after the titles' preliminary screening, 233 full-text studies were reviewed. Of these, 163 studies were included in the systematic reviews and in the primary analysis of symptoms [8–170]. For comorbidity analysis, 41 of 163 studies were excluded based on fewer than three reported comorbidities criteria, as described above,

yielding 122 studies. A flow chart of the study selection is shown in Figure 1. The details of the included studies are provided in Table I.

### Study characteristics

A total of 163 studies with 43,187 patients were included. Of these, 117 were from China, 19 from the European region, 14 from the US, 2 from other countries, and the remaining 11 were from Australia, Brazil, Iran, Japan, S Korea, Singapore, and Taiwan. The earliest study recruitment started on December 11, 2019 and ended on April 19, 2020. There were 80 retrospective single-center case series; 43 retrospective multicenter case series, 7 retrospective multicenter cohorts, 3 retrospective single-center cohorts, 6 prospective single-center series, 3 prospective single-center series, 4 prospective single-center cohort studies, 1 prospective multicenter cohort study, 7 randomized controlled trials of various design, 1 open-label non-randomized control study, 1 descriptive case series, and 1 prospective single-center open-label study (Table I). A total of 128 studies included only hospitalized patients, 13 included both hospitalized and non-hospitalized patients, 2 included only non-hospitalized patients, and 20 studies did not list hospitalization status.

### Patient baseline characteristics and outcomes

For a total of 40,632 patients, the mean age was 54.6 years, with a range of 18–98 years. A total of 8 studies, including adult patients with 2,325 patients, did not provide age data. Data regarding gender were not available in 8 studies. There were significantly fewer women in the study (43.9% vs. 56.1%,  $p < 0.0001$ ). Hospitalization outcomes were reported in 116 studies for 37,349 patients; 48.5% (28,779) were discharged, 29% (18,810) remained in the hospital, and 12.1% (4284) died at the end of the study period for these studies. The details regarding invasive mechanical ventilation (IMV) were reported in 61 studies with 30,190 patients, of whom 9.89% (3,359) underwent IMV.

### Comorbidities and symptoms for all patients

Prevalent cardiovascular comorbidities were hypertension (31.9%), obesity (27.9%), hyperlipidemia (26.4%), smoking (18.9%), diabetes mellitus (17.2%), atherosclerotic disease (9.2%) and arrhythmia (5.0%). Asthma (7.8%), followed by chronic obstructive lung disease (COPD) or chronic lung disease (CLD) (6.2%), were the most common respiratory comorbidities. The gastrointestinal comorbidities of hepatitis, liver disease and fatty liver disease had a prevalence of 2.4%. Chronic

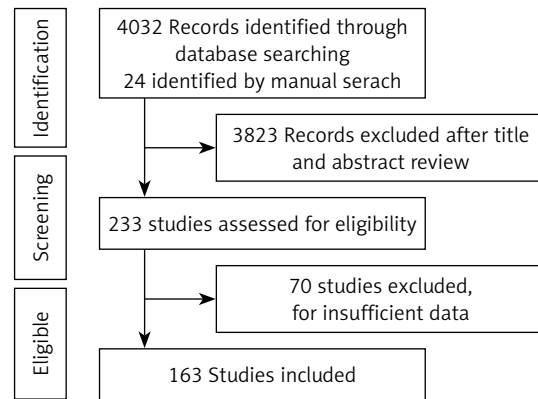


Figure 1. Flow chart low study

kidney disease and/or end-stage renal disease were reported in 6.2% of patients. Cerebrovascular disease or cerebrovascular accidents were reported in 3.5% of patients. Cancer and/or malignancy were reported in 4.4%, and HIV and/or immunodeficiency were observed in 1.6% of patients.

The most often reported constitutional symptoms of COVID-19 were fever (73.9%), fatigue (33.4%), malaise (29.9%), myalgia and/or arthralgia (19.2%), generalized weakness (19.0%), and chills (11.3%). For the cardiovascular system, chest pain and/or tightness were most often reported (19.6%), followed by palpitations (5.2%). Cough (60.3%), sputum production (29.7%), shortness of breath (27.3%), loss of smell and/or taste (25.1%), rhinorrhea (12.9%), and sore throat (12.3%) were the most often reported respiratory symptoms. The most common gastrointestinal symptoms were anorexia or loss of appetite (29.4%), followed by diarrhea (14.8%), nausea and/or vomiting (13.2%), and abdominal pain (7.4%). Commonly reported neurological symptoms were headache (12.8%), confusion (9.4%), and dizziness (8.2%). The details of the prevalence of constitutional, cardiovascular, respiratory, and gastrointestinal symptoms, and their related comorbidities, along with the number of studies, are shown in Tables II and III, respectively.

### Subgroup analysis by severity

For stratification based on severity for comorbidities and symptoms, only 30 studies met the inclusion criteria, with a total of 5,819 cases. Table IV shows the prevalence of comorbidities and symptoms in both groups.

### Comorbidities

Hypertension was the most commonly observed comorbidity among severe cases (45.2% vs. 8.1%,  $p < 0.001$ ). Diabetes mellitus was also more common in severe disease (19.5% vs. 3.5%,  $p < 0.001$ ). Obesity and congestive heart failure

**Table I.** Baseline characteristics of included studies

| Author name, year  | Study period     | Type of study   | Patients <i>N</i> | Female patients ( <i>N</i> ) | Hospitalization status | Severity |
|--|------------------|---|-------------------|------------------------------|------------------------|----------|
| Akalin <i>et al.</i> , 2020  | Mar 16–Apr 1     | Retrospective single-center case series                       | 36                | 10                           | 3                      | B        |
| An Ping <i>et al.</i> , 2020   | Jan 17–Jan 24    | Retrospective single-center case series                       | 9                 | 5                            | 1                      |          |
| Bangalore <i>et al.</i> , 2020   |                  | Retrospective single-center case series                       | 18                | 3                            |                        |          |
| Beigel JH <i>et al.</i> , 2020   | Feb 21–Apr 19    | RCT double blinded  | 1063              | 377                          | 1                      | B        |
| Bhatraju PK <i>et al.</i> , 2020   | Feb 24–Mar 9     | Retrospective multi-center case series                        | 24                | 9                            | 1                      | S        |
| Borba MGS <i>et al.</i> , 2020   | Mar 23–Apr 5     | Parallel, double-masked, randomized, phase IIb clinical trial | 81                | 20                           | 1                      | S        |
| Cai Qingxian <i>et al.</i> , 2020  | Jan 30–Feb 14    | Open labelled non-randomized control study                    | 80                | 45                           | 1                      | B        |
| Cai Qingxian <i>et al.</i> , 2020  | Jan 11–Feb 6     | Retrospective single-center case series                       | 298               | 153                          | 1                      | B        |
| Cao Jianlei <i>et al.</i> , 2020   | Jan 3–Feb 1      | Retrospective single-center case series                       | 102               | 49                           | 1                      | B        |
| Chan Fuk-Woo J <i>et al.</i> , 2020  |                  | Retrospective single-center case series                       | 6                 | 3                            | 1                      |          |
| Chang De <i>et al.</i> , 2020  | Jan 16–Jan 29    | Retrospective multi-center case series                        | 13                | 3                            | 1                      |          |
| Chen J <i>et al.</i> , 2020  | Jan 20–Feb 7     | Retrospective single-center case series                       | 249               | 123                          | 1                      | B        |
| Chen L <i>et al.</i> , 2020  | Dec 8–Mar 20     | Retrospective multi-center case series                        | 118               |                              |                        | B        |
| Chen Nanshan <i>et al.</i> , 2020  | Jan 1–Jan 20     | Retrospective single-center case series                       | 99                | 32                           | 1                      | B        |
| Chen Qing <i>et al.</i> , 2020   |                  | Retrospective single-center case series                       | 9                 | 4                            | 1                      | NS       |
| Chen Qingqing <i>et al.</i> , 2020   | Jan 1–Mar 11     | Retrospective multi-center case series                        | 145               | 66                           | 1                      | B        |
| Chen Tao <i>et al.</i> , 2020  | Jan 13–Feb 12    | Retrospective single-center case series                       | 274               | 103                          |                        | S        |
| Chen TL <i>et al.</i> , 2020   | Jan 1–Feb 10     | Retrospective single-center case series                       | 203               | 95                           |                        | B        |
| Cholankeril George <i>et al.</i> , 2020  | Mar 4–Mar 24     | Retrospective single-center case series                       | 116               | 54                           | 1                      | B        |
| Chu J <i>et al.</i> , 2020   | Jan 7–Feb 11     | Retrospective single-center case series                       | 54                | 18                           | 1                      | B        |
| COVID-19 National Emergency Response Center, Epidemiology and Case Management Team, Korea Centers for Disease Control and Prevention | Before 2/14/2020 | Retrospective multi-center case series                        | 28                | 13                           | 3                      | B        |
| COVID-19 National Incident Room Surveillance Team  |                  | Retrospective single-center case series                       | 295               |                              | 3                      | B        |

Table I. Cont.

| Author name, year                         | Study period      | Type of study                             | Patients <i>N</i> | Female patients ( <i>N</i> ) | Hospitalization status | Severity |
|---|-------------------|---|-------------------|------------------------------|------------------------|----------|
| Dai H <i>et al.</i> , 2020                | Jan 10–Feb 7      | Retrospective multi-center case series    | 234               | 98                           |                        |          |
| Deng Qing <i>et al.</i> , 2020            | Jan 6–Feb 20      | Retrospective single-center case series   | 112               | 55                           | 1                      | B        |
| Dong X <i>et al.</i> , 2020               |                   | Retrospective multi-center case series    | 11                | 6                            | 1                      |          |
| Du Rong-Hui <i>et al.</i> , 2020          | Dec 25–Feb 7      | Prospective single center cohort          | 179               | 82                           | 1                      | B        |
| Du Y <i>et al.</i> , 2020                 | Jan 9–Feb 15      | Retrospective single-center case series   | 85                | 23                           | 1                      | S        |
| Escalera-Antezana JP <i>et al.</i> , 2020 | Mar 2–Mar 15      | Retrospective multi-center case series    | 12                | 6                            | 2                      | NS       |
| Hua Fan <i>et al.</i> , 2020              | Dec 30–Feb 16     | Retrospective single-center case series   | 101               | 37                           | 1                      | S        |
| Fei Xiao <i>et al.</i> , 2020             | Feb 1–Feb 14      | Retrospective single-center case series   | 73                | 32                           | 1                      | B        |
| Feng Pan <i>et al.</i> , 2020             | Jan 12–Feb 6      | Retrospective single-center case series   | 21                | 15                           | 1                      | NS       |
| Feng Yun <i>et al.</i> , 2020             | Jan 1–Feb 15      | Retrospective multi-center case series    | 476               | 205                          | 1                      | B        |
| Fernández-Ruiz Mario <i>et al.</i> , 2020 | March 5–March 23  | Retrospective single-center case series   | 18                | 4                            | 1                      | B        |
| Gautret Philippe <i>et al.</i> , 2020     | Feb–March         | Prospective single center cohort          | 80                | 37                           | 1                      | B        |
| Geleris <i>et al.</i> , 2020              | Mar 7–Apr 8       | Cross-sectional Multi-center case series  | 1376              | 595                          | 1                      | B        |
| Giacomelli A <i>et al.</i> , 2020         |                   | Cross-sectional single-center case series | 59                | 19                           | 1                      |          |
| Goyal <i>et al.</i> , 2020                | Mar 3–mar 27      | Retrospective single-center case series   | 393               | 155                          | 1                      | B        |
| Griiti Giuseppe <i>et al.</i> , 2020      |                   | Retrospective single-center cohort        | 21                | 3                            | 1                      | B        |
| Guan W <i>et al.</i> , 2020               | Dec 11–Jan 29     | Retrospective multi-center case series    | 1099              | 459                          | 3                      | B        |
| Guo Tao <i>et al.</i> , 2020              | Jan 23–Feb 25     | Retrospective single-center case series   | 187               | 96                           | 1                      | B        |
| Hajifathalian K <i>et al.</i> , 2020      | Mar 4–Apr 9       | Retrospective multi-center case series    | 1059              | 448                          | 3                      | B        |
| Han Chaoqun <i>et al.</i> , 2020          | Feb 13–Feb 29     | Retrospective single-center case series   | 206               | 115                          | 1                      | NS       |
| Hong Kyung Soo <i>et al.</i> , 2020       | Mar–20            | Retrospective single-center case series   | 98                | 60                           | 1                      | B        |
| Horby P <i>et al.</i> , 2020              | Early 2020–June 8 | Randomized controlled open labelled trial | 6425              | 2337                         | 1                      | B        |
| Huang Chaolin <i>et al.</i> , 2020        | Dec 16–Jan 2      | Prospective single center cohort          | 41                | 11                           | 1                      | B        |
| Huang Yihui <i>et al.</i> , 2020          | Dec–Jan           | Retrospective single-center case series   | 34                | 14                           | 3                      | B        |

Table I. Cont.

| Author name, year   | Study period    | Type of study                            | Patients N | Female patients (N) | Hospitalization status | Severity |
|---|-----------------|--|------------|---------------------|------------------------|----------|
| Israelsen S B <i>et al.</i> , 2020  | Mar 10–April 23 | Retrospective single-center case series  | 175        | 90                  | 1                      | B        |
| Javanian M, <i>et al.</i> 2020  | Feb 25–Mar 12   | Retrospective multi-center case series   | 110        | 49                  | 1                      |          |
| Jin Xi <i>et al.</i> , 2020   | Jan 17–Feb 8    | Retrospective multi-center case series   | 651        | 320                 | 1                      | B        |
| Kaye <i>et al.</i> , 2020   | Mar 25–Apr 3    | Retrospective multi-center case series   | 237        | 129                 |                        |          |
| Kim ES <i>et al.</i> , 2020 (Korea National Committee for Clinical Management of COVID-19 (KNCCMC)) | Feb             | Prospective multi-center case series     | 28         | 13                  | 1                      | B        |
| Klopfenstein T <i>et al.</i> , 2020   | Mar 1–Mar 17    | Retrospective single-center case series  | 114        |                     | 1                      | B        |
| Kluytmans-van den Bergh M <i>et al.</i> , 2020  | Mar 7–Mar 12    | Cross-sectional multi-center case series | 86         | 71                  | 3                      | NS       |
| Kuang Y <i>et al.</i> , 2020  | Jan 1–Feb 10    | Retrospective multi-center cohort        | 944        | 476                 |                        | B        |
| Kujawski Stephanie <i>et al.</i> , 2020   | Jan 20–Feb 5    | Retrospective multi-center case series   | 12         | 4                   | 3                      | B        |
| Lechien JR <i>et al.</i> , 2020   |                 | Retrospective multi-center case series   | 417        | 263                 | 1                      | NS       |
| Lei H <i>et al.</i> , 2020  | Jan 25–Jan 27   | Retrospective multi-center case series   | 8          | 2                   | 1                      |          |
| Lei S <i>et al.</i> , 2020  | Jan 1–Feb 5     | Retrospective multi-center case series   | 34         | 20                  | 1                      | B        |
| Lei Wang <i>et al.</i> , 2020   | Jan 21–Feb 5    | Retrospective single-center case series  | 18         | 8                   | 1                      |          |
| Lei Z <i>et al.</i> , 2020  | Jan 22–Feb 12   | Retrospective single-center case series  | 20         | 10                  |                        |          |
| Li Kunhua <i>et al.</i> , 2020  | Jan–Feb         | Retrospective multi-center case series   | 83         | 39                  | 1                      | B        |
| Li X <i>et al.</i> , 2020   | Jan 14–Feb 13   | Retrospective single-center case series  | 25         | 15                  | 1                      | S        |
| Li Xiaochen <i>et al.</i> , 2020  | Jan 26–Feb 5    | Retrospective single-center cohort       | 548        | 269                 | 1                      | B        |
| Lian J <i>et al.</i> , 2020   | Jan 17–Jan 31   | Retrospective single-center case series  | 465        | 222                 |                        | B        |
| Lian J <i>et al.</i> , 2020   | Jan 17–Feb 12   | Retrospective multi-center case series   | 788        | 381                 |                        |          |
| Liang WH, <i>et al.</i> , 2020  | Nov 21–Jan 31   | Retrospective multi-center case series   | 1590       | 674                 |                        | B        |
| Lin Lu <i>et al.</i> , 2020   | Jan 17–Feb 15   | Retrospective single-center case series  | 95         | 50                  | 1                      | B        |
| Liu Jui-Yao <i>et al.</i> , 2020  | Jan 21–Apr 6    | Retrospective multi-center case series   | 321        | 170                 |                        | NS       |
| Liu Kai <i>et al.</i> , 2020  | Jan 15–Feb 18   | Retrospective single-center case series  | 56         | 25                  | 1                      | B        |

Table I. Cont.

| Author name, year                      | Study period        | Type of study                              | Patients <i>N</i> | Female patients ( <i>N</i> ) | Hospitalization status | Severity |
|--|---------------------|--|-------------------|------------------------------|------------------------|----------|
| Liu Kiu <i>et al.</i> , 2020           | Dec 30 –Jan 24      | Retrospective multi-center case series     | 137               | 76                           | 1                      | B        |
| Liu Yingxia <i>et al.</i> , 2020       | December 26–January | Retrospective single-center case series    | 12                | 4                            | 1                      | B        |
| Liu Zhe <i>et al.</i> , 2020           | Jan 16–Feb 13       | Retrospective multi-center case series     | 72                | 33                           | 1                      | B        |
| Lo Li <i>et al.</i> , 2020             | Jan 21–Feb 16       | Prospective single center case series      | 10                | 7                            | 1                      | B        |
| Luo Shihua <i>et al.</i> , 2020        | Jan 1–Feb 20        | Retrospective single-center case series    | 183               | 81                           | 1                      | B        |
| Lu-Xiaofan <i>et al.</i> , 2020        | Jan 25–Feb 25       | Retrospective single-center case series    | 244               | 116                          | 1                      | S        |
| Ma J <i>et al.</i> , 2020              | Jan 1–Mar 30        | Retrospective single-center case series    | 37                | 20                           | 1                      | B        |
| Mahevas M <i>et al.</i> , 2020         | Mar 12–Mar 31       | Retrospective multi-center case series     | 173               | 101                          | 1                      | B        |
| Mathian A <i>et al.</i> , 2020         | Mar 29–Apr 6        | Cross-sectional single-center case series  | 17                | 13                           | 3                      | B        |
| Meng Yifan <i>et al.</i> , 2020        | Jan 16–Feb 4        | Retrospective single-center case series    | 168               | 82                           | 1                      | S        |
| Mi Bobib <i>et al.</i> , 2020          | Jan 1–Feb 27        | Retrospective multi-center case series     | 10                | 8                            | 1                      | B        |
| Million M <i>et al.</i> , 2020         | Mar 3–Mar 31        | Retrospective multi-center cohort          | 1061              | 569                          | 3                      | B        |
| Mo P <i>et al.</i> , 2020              | Jan 1 –Feb 5        | Retrospective single-center case series    | 155               | 69                           | 1                      | B        |
| Moein S <i>et al.</i> , 2020           | Mar 21–Apr 5        | Prospective single center case series      | 60                | 20                           | 1                      | B        |
| Morena V <i>et al.</i> , 2020          | Mar 10–Mar 23       | Prospective single center open label study | 51                | 11                           |                        | S        |
| Nobel Yael <i>et al.</i> , 2020        | Mar 10–Mar 21       | Retrospective single-center cohort         | 278               | 133                          |                        | B        |
| Pan Lei <i>et al.</i> , 2020           | Jan 18–Feb 28       | Cross-sectional multicenter case series    | 103               | 48                           | 1                      | B        |
| Pung Rachel <i>et al.</i> , 2020       | Jan–Feb             | Retrospective multi-center case series     | 17                | 10                           | 2                      | NS       |
| Qi X <i>et al.</i> , 2020              | Jan 23–Feb 18       | Retrospective multi-center case series     | 70                |                              | 1                      | B        |
| Qian GQ <i>et al.</i> , 2020           | Jan 20–Feb 11       | Retrospective multi-center case series     | 91                | 54                           | 1                      | B        |
| Redd WD <i>et al.</i> , 2020           | Feb 11–Feb 29       | Randomized, parallel, open label trial     | 150               | 68                           | 1                      | B        |
| Richardson Safiya <i>et al.</i> , 2020 | Before April 2      | Retrospective multicenter cohort           | 318               | 144                          | 1                      | B        |
| Rodríguez-Cola M <i>et al.</i> , 2020  | Mar 1–Apr 4         | Retrospective multi-center case series     | 5700              | 2263                         | 1                      | B        |
| Ronald LT <i>et al.</i> , 2020         | Mar 20 –Apr 4       | Prospective single center case series      | 7                 | 2                            | 1                      | B        |



Table I. Cont.

| Author name, year                  | Study period   | Type of study                                       | Patients N | Female patients (N) | Hospitalization status | Severity |
|------------------------------------|----------------|---|------------|---------------------|------------------------|----------|
| Rosenberg ES <i>et al.</i> , 2020  | Mar 31–Apr 10  | Electronic survey                                   | 145        | 94                  |                        |          |
| Sciascia S <i>et al.</i> , 2020    | Mar 15–Mar 28  | Retrospective multi-center cohort                   | 1438       | 580                 | 1                      | B        |
| Shaobo Shi <i>et al.</i> , 2020    |                | Double-blind, placebo-controlled, multicenter trial | 63         | 7                   | 1                      | S        |
| Shi Heshui <i>et al.</i> , 2020    | Jan 1–Feb 23   | Retrospective single-center case series             | 671        | 349                 | 1                      | B        |
| Shi Shaobo <i>et al.</i> , 2020    | Dec 20–Jan 23  | Retrospective single-center case series             | 81         | 39                  | 1                      | NS       |
| Shu Lei <i>et al.</i> , 2020       | Jan 20–Feb 10  | Retrospective single-center case series             | 416        | 211                 | 1                      | B        |
| Song F <i>et al.</i> , 2020        | Feb 13–Feb 29  | Retrospective single-center case series             | 545        | 281                 | 1                      | NS       |
| Spiteri Gianfranco 2020            | Jan 20–Jan 27  | Retrospective single-center case series             | 51         | 26                  | 1                      | NS       |
| Tabata Sakiko <i>et al.</i> , 2020 | Jan 24 –Feb 21 | Retrospective multi-center case series              | 38         | 13                  | 3                      | NS       |
| Tang Wei <i>et al.</i> , 2020      | Feb 11–Feb 25  | Retrospective single-center case series             | 104        | 50                  | 1                      | B        |
| Tian S <i>et al.</i> , 2020        | Jan 20–Feb 10  | Retrospective multi-center case series              | 262        | 135                 |                        | B        |
| Toniati Paola <i>et al.</i> , 2020 | Mar 9–Mar 20   | Multicenter prospective non-randomized study        | 100        | 12                  | 1                      | S        |
| Tu Wen-Jun <i>et al.</i> 2020      | Jan 3–Feb 24   | Retrospective single-center case series             | 174        | 95                  | 1                      | B        |
| Wan S <i>et al.</i> , 2020         | Jan 23–Feb 8   | Retrospective single-center case series             | 135        | 63                  | 3                      |          |
| Wan Yunle <i>et al.</i> , 2020     | Jan 19–Mar 6   | Retrospective multi-center case series              | 232        | 101                 | 1                      | B        |
| Wang Dawei <i>et al.</i> , 2020    | Jan 1–Jan 28   | Retrospective single-center case series             | 138        | 63                  | 1                      | B        |
| Wang J <i>et al.</i> , 2020        | Jan–Feb        | Prospective multicenter case series                 | 93         | 36                  |                        |          |
| Wang L <i>et al.</i> , 2020        | Jan 1–Feb 6    | Retrospective single-center case series             | 339        | 173                 | 1                      | B        |
| Wang Lizhen <i>et al.</i> , 2020   | Jan 31–Feb 12  | Retrospective single-center case series             | 26         | 15                  | 1                      |          |
| Wang Luwen <i>et al.</i> , 2020    | Jan 14–Feb 13  | Prospective single center cohort                    | 116        | 49                  | 1                      | B        |
| Wang Min <i>et al.</i> , 2020      | Jan 21–Feb 2   | Retrospective multi-center case series              | 66         | 23                  | 1                      |          |
| Wang Ruirui <i>et al.</i> , 2020   | Jan 20–Feb 9   | Retrospective single-center case series             | 125        | 71                  | 1                      | B        |
| Yang Wenjie <i>et al.</i> , 2020   | Jan 17–Feb 10  | Retrospective multi-center cohort                   | 149        | 68                  | 1                      | NS       |
| Wang X <i>et al.</i> , 2020        | Feb 7–Feb 12   | Retrospective single-center case series             | 1012       | 488                 | 1                      | NS       |



Table I. Cont.

| Author name, year                  | Study period  | Type of study   | Patients <i>N</i> | Female patients ( <i>N</i> ) | Hospitalization status | Severity |
|------------------------------------|---------------|---|-------------------|------------------------------|------------------------|----------|
| Wang X <i>et al.</i> , 2020        | Jan 10–Feb 24 | Retrospective multi-center case series                          | 80                | 49                           | 1                      |          |
| Wang Yang <i>et al.</i> , 2020     | Jan 25–Feb 25 | Retrospective single-center case series                         | 344               | 165                          | 1                      | S        |
| Wang Yanrong <i>et al.</i> , 2020  | Jan 11–Feb 29 | Retrospective single-center case series                         | 55                | 22                           | 1                      | NS       |
| Wang Yeming <i>et al.</i> , 2020   | Feb 6–Mar 12  | Randomized, double-blind, placebo-controlled, multicenter trial | 236               | 96                           | 1                      | B        |
| Wang Z <i>et al.</i> , 2020        | Jan 16–Jan 29 | Retrospective single-center case series                         | 69                |                              | 1                      |          |
| Wei XS <i>et al.</i> , 2020        | Jan 19–Feb 7  | Retrospective single-center case series                         | 84                | 56                           | 1                      |          |
| Wei Jia-Fu <i>et al.</i> , 2020    | Jan 16–Mar 10 | Prospective multicenter cohort                                  | 101               | 47                           | 1                      | B        |
| Wentao Ni <i>et al.</i> , 2020     |               | Retrospective single-center case series                         | 179               |                              | 1                      | B        |
| Wolfel Roman <i>et al.</i> , 2020  | Jan 23–Jan 26 | Retrospective single-center case series                         | 9                 |                              | 1                      | NS       |
| Wu Chaomin <i>et al.</i> , 2020    | Dec 25–Jan 26 | Retrospective single-center case series                         | 201               | 73                           |                        | S        |
| Wu J <i>et al.</i> , 2020          | Jan 22–Feb 14 | Retrospective multi-center case series                          | 80                | 41                           | 1                      | B        |
| Wu Jiong <i>et al.</i> , 2020      | Jan –Feb      | Retrospective multi-center case series                          | 80                | 38                           | 1                      | B        |
| Wu Yongjian <i>et al.</i> , 2020   | Jan 16–Mar 15 | Prospective single center case series                           | 74                | 35                           | 1                      | B        |
| Xia Xiao-ying <i>et al.</i> , 2020 | Jan 23–Feb 18 | Retrospective single-center case series                         | 10                | 4                            | 1                      | B        |
| Xie Hansheng <i>et al.</i> , 2020  | Feb 2–Feb 23  | Retrospective single-center case series                         | 79                | 35                           | 1                      | NS       |
| Xiong Fei <i>et al.</i> , 2020     | Jan 1–Mar 10  | Retrospective multi-center cohort                               | 131               | 56                           | 1                      | B        |
| Xiong Ying <i>et al.</i> , 2020    | Jan 11–Feb 5  | Retrospective single-center case series                         | 42                | 17                           | 1                      | B        |
| Xu T <i>et al.</i> , 2020          | Jan 23–Feb 18 | Retrospective single-center case series                         | 51                | 26                           | 1                      |          |
| Xu Xi <i>et al.</i> , 2020         | Jan 23–Feb 4  | Retrospective single-center case series                         | 90                | 51                           | 1                      | B        |
| Xu Xiaoling <i>et al.</i> , 2020   | Feb 5–Feb 14  | Prospective single center case series                           | 21                | 3                            | 1                      | S        |
| Xu XW <i>et al.</i> , 2020         | Jan 10–Jan 26 | Retrospective single-center case series                         | 62                | 27                           | 1                      | NS       |
| Xun Ding 2020                      | Feb–March     | Retrospective single-center case series                         | 112               | 61                           |                        |          |
| Yan CH <i>et al.</i> , 2020        | Mar 3–mar 29  | Cross-sectional single-center case series                       | 59                | 29                           | 3                      |          |

Table I. Cont.

| Author name, year                    | Study period   | Type of study                           | Patients N | Female patients (N) | Hospitalization status | Severity |
|--------------------------------------|----------------|---|------------|---------------------|------------------------|----------|
| Yan Yongli <i>et al.</i> , 2020      | Jan 10–Feb 24  | Retrospective single-center case series | 193        | 79                  | 1                      | S        |
| Yang Fan <i>et al.</i> , 2020        | Jan 1 –April15 | Retrospective single-center case series | 52         | 24                  | 1                      | B        |
| Yang X 2020                          | Dec 24–Jan 26  | Retrospective single-center case series | 52         | 17                  | 1                      | S        |
| Young BE <i>et al.</i> , 2020        | Jan 23–Feb 3   | Retrospective multi-center case series  | 18         | 9                   | 1                      | NS       |
| Yu Yuan <i>et al.</i> , 2020         | 27–Feb         | Prospective multicenter case series     | 226        | 87                  | 1                      | S        |
| Zha Lei <i>et al.</i> , 2020         | Jan 24–Feb 24  | Retrospective multi-center case series  | 31         | 11                  | 1                      | NS       |
| Zhang Guqin <i>et al.</i> , 2020     | Jan 2–Feb 10   | Retrospective multi-center case series  | 221        | 113                 | 1                      | B        |
| Zhang JingCheng <i>et al.</i> , 2020 | Jan 27–Feb 10  | Retrospective single-center case series | 14         | 7                   | 1                      | NS       |
| Zhang Jin-Jin <i>et al.</i> , 2020   | Jan 16–Feb 3   | Retrospective single-center case series | 140        | 69                  | 1                      | B        |
| Zhang Jun <i>et al.</i> , 2020       | Jan 28–Feb 24  | Retrospective single-center case series | 13         |                     | 1                      | B        |
| Zhang L <i>et al.</i> , 2020         | Jan 13–Feb 26  | Retrospective multi-center case series  | 28         | 11                  | 1                      | B        |
| Zhang Xiaoli <i>et al.</i> , 2020    | Jan 17–Feb 8   | Retrospective multi-center case series  | 645        | 317                 | 1                      | B        |
| Zhao Xin-Ying <i>et al.</i> , 2020   | Jan 16–Feb 10  | Retrospective single-center case series | 91         | 42                  | 1                      | B        |
| Zhao D <i>et al.</i> , 2020          | Jan 23–Feb 5   | Retrospective multi-center case series  | 19         | 8                   | 1                      |          |
| Zhao Wei <i>et al.</i> , 2020        |                | Retrospective single-center case series | 101        | 45                  | 1                      |          |
| Zheng F <i>et al.</i> , 2020         | Jan 17–Feb 7   | Retrospective single-center case series | 161        | 81                  | 1                      | B        |
| Zheng Y <i>et al.</i> , 2020         | Jan 16–Feb 20  | Retrospective single-center case series | 99         | 48                  | 1                      | B        |
| Zhou Fei <i>et al.</i> , 2020        | Dec 29–Jan 31  | Retrospective multi-center cohort       | 191        | 119                 | 1                      | S        |
| Zhou Shuchang <i>et al.</i> , 2020   | Jan 16–Feb 12  | Retrospective single-center case series | 100        | 46                  | 1                      | NS       |
| Zhou Shuchang <i>et al.</i> , 2020   | Jan 16–Jan 30  | Retrospective single-center case series | 62         | 23                  | 1                      | B        |
| Zhou Y <i>et al.</i> , 2020          | Jan 28–Mar 2   | Prospective single center case series   | 21         | 8                   | 1                      | S        |
| Zhou Zili <i>et al.</i> , 2020       | Dec 20–Feb 9   | Retrospective single-center case series | 254        | 139                 | 1                      |          |
| Zou Lirong <i>et al.</i> , 2020      | Jan 7–Jan 26   | Retrospective single-center case series | 18         | 9                   |                        |          |

Hospitalization: 1: inpatient, 2: outpatient, 3: combined inpatient, and outpatient. S – severe, NS – non-severe, B – Both, N – number, RCT – randomized controlled trial, COVID-19: coronavirus disease 2019.

**Table II.** Symptoms based on systems involved overall in patients with coronavirus disease 2019

| Symptom   | %Age   | Number of patients (N) | Total patients | Number of studies |
|---|--------|------------------------|----------------|-------------------|
| <b>Constitutional:</b>                          |        |                        |                |                   |
| Fever   | 73.9.0 | 16999                  | 22987          | 134               |
| Myalgia/arthralgia                              | 19.20  | 3657                   | 19064          | 96                |
| Fatigue   | 33.40  | 4266                   | 12785          | 69                |
| Chills  | 11.30  | 546                    | 4816           | 19                |
| Generalized weakness                            | 19.00  | 434                    | 2286           | 9                 |
| Malaise   | 29.90  | 272                    | 909            | 8                 |
| <b>Respiratory/upper respiratory infection:</b> |        |                        |                |                   |
| Cough   | 60.30  | 13739                  | 22778          | 134               |
| Dyspnea   | 27.30  | 5440                   | 19926          | 111               |
| Sore throat                                     | 12.30  | 1877                   | 15302          | 78                |
| Sputum production                               | 29.70  | 3789                   | 12730          | 64                |
| Nasal congestion                                | 6.60   | 507                    | 7658           | 19                |
| Hemoptysis                                      | 1.90   | 134                    | 7191           | 22                |
| Rhinorrhea                                      | 12.90  | 529                    | 4089           | 34                |
| Loss of smell or taste                          | 25.10  | 740                    | 2952           | 13                |
| Conjunctival congestion                         | 0.90   | 26                     | 2927           | 4                 |
| <b>Cardiovascular:</b>                          |        |                        |                |                   |
| Chest pain/tightness                            | 19.60  | 1251                   | 6394           | 47                |
| Palpitations                                    | 5.20   | 22                     | 422            | 4                 |
| <b>Gastrointestinal:</b>                        |        |                        |                |                   |
| Diarrhea  | 14.80  | 2903                   | 19544          | 112               |
| Nausea/vomiting                                 | 13.20  | 1992                   | 15081          | 76                |
| Abdominal pain                                  | 7.40   | 504                    | 6783           | 34                |
| Anorexia  | 29.40  | 1857                   | 6319           | 37                |
| <b>Neurologic:</b>                              |        |                        |                |                   |
| Headache  | 12.80  | 2005                   | 15704          | 75                |
| Confusion                                       | 9.40   | 191                    | 2025           | 6                 |
| Dizziness                                       | 8.20   | 293                    | 3564           | 22                |

(CHF) were not observed in any non-severe cases among the studies included for this analysis but were present in severe cases (30.5% and 5.2%, respectively). Smoking was more commonly observed in non-severe cases than severe cases (13.5% vs. 3.8%,  $p < 0.001$ ). COPD was similar in non-severe and severe cases (9.2% vs. 12.0%,  $p = 0.083$ ).

### Symptoms

Among all the symptoms compared, non-respiratory symptoms were more commonly observed among non-severe cases (headaches, anorexia, abdominal pain, loss of smell/taste). Severe compared to non-severe cases more frequently had fever (87.8% vs. 58.5%,  $p < 0.001$ ), shortness of breath (47.4% vs. 20.6%,  $p < 0.001$ ), cough (66.8% vs. 62.9%,  $p < 0.001$ ), sputum production (35.4%

vs. 26.5%,  $p < 0.001$ ) and rhinorrhea (32.2% vs. 7.3%,  $p < 0.001$ ). Both groups had a similar prevalence of chest pain (21.1% severe vs. 19.3% non-severe,  $p = 0.34$ ), diarrhea (20.2% severe vs. 19.4% non-severe,  $p = 0.515$ ), and nausea/vomiting (8.8% severe vs. 8.4% non-severe,  $p = 0.643$ ).

### Discussion

Since the emergence of SARS-CoV-2 infection in China and its spread worldwide, the knowledge regarding disease course, clinical characteristics, and treatment options has continued to evolve. We performed a comprehensive systematic review of published studies with COVID-19 patients. This systematic review summarized the prevalence of clinical symptoms and comorbidities in COVID-19 patients, stratified by the severity of symptoms [164–170].

**Table III.** Prevalence of comorbidities overall in patients with coronavirus disease 2019

| Comorbidity                         | %     | N    | Total | Count |
|-------------------------------------|-------|------|-------|-------|
| <b>Cardiovascular:</b>              |       |      |       |       |
| Hypertension                        | 31.90 | 9818 | 30792 | 105   |
| Diabetes mellitus                   | 17.20 | 5122 | 29796 | 107   |
| Atherosclerotic disease             | 9.20  | 2642 | 28806 | 102   |
| Smoking                             | 18.90 | 2980 | 15728 | 31    |
| Obesity                             | 27.90 | 2758 | 9870  | 9     |
| Heart failure                       | 5.90  | 554  | 9403  | 9     |
| Arrhythmia                          | 5.01  | 65   | 1297  | 5     |
| Hyperlipidemia                      | 26.40 | 199  | 753   | 9     |
| <b>Respiratory:</b>                 |       |      |       |       |
| COPD/CLD                            | 6.20  | 1643 | 26570 | 83    |
| Asthma                              | 7.80  | 555  | 7136  | 11    |
| <b>Gastrointestinal:</b>            |       |      |       |       |
| Hepatitis/liver disease/fatty liver | 2.40  | 459  | 19310 | 60    |
| <b>Renal:</b>                       |       |      |       |       |
| CKD/ESRD                            | 6.20  | 1445 | 23149 | 58    |
| <b>Neurologic:</b>                  |       |      |       |       |
| CVA/cerebrovascular disease         | 3.50  | 320  | 9152  | 40    |
| <b>Other:</b>                       |       |      |       |       |
| Cancer/malignancy                   | 4.40  | 1062 | 23962 | 66    |
| HIV/immunodeficiency                | 1.60  | 216  | 13506 | 23    |

COPD – chronic obstructive pulmonary disease, CLD – chronic lung disease, CKD – chronic kidney disease, ESRD – end-stage renal disease, CVA – cerebrovascular accident, HIV – human immunodeficiency virus.

This analysis found that the prevalence of COVID-19 was higher in men compared to women. Hypertension, obesity, hyperlipidemia, smoking, diabetes mellitus, and atherosclerotic diseases are the most common comorbidities overall. Fever, cough, fatigue, malaise, sputum production, shortness of breath, and anosmia are the most common symptoms overall. After stratification of patients on the basis of severity, hypertension, diabetes, obesity, and CHF were the most common comorbidities in severe illness. In contrast, smoking is more common in non-severe illnesses. Fever, shortness of breath, cough, sputum production, and rhinorrhea are more commonly reported in patients with severe illness, whereas headache, anorexia, abdominal pain, and loss of smell/taste are reported more often in patients with non-severe illness.

We report a higher prevalence of COVID-19 in men compared to women. An analysis of 14,712 patients revealed men to have significantly higher mortality than women even after adjusting for comorbidities [171]. Gender differences have been reported in the prior influenza pandemic, suggesting that men are more susceptible to viral respiratory illness; this is attributed to females generating stronger innate and adaptive immune responses [172, 173]. Thus, it could be why SARS-

CoV-2, being a respiratory virus, was noted to have a higher prevalence in men in our study. One study evaluating 524 SARS-CoV-2 patients ages 51 to 70 found that males were significantly more likely to be hospitalized and had increased mortality regardless of age [174]. It could be hypothesized that women have a robust immune response to viruses as seen with the influenza virus as well; hence that could be the reason for the protection of females against SARS-CoV 2 infection.

We found the most common comorbidities to be hypertension and diabetes; these results are consistent with prior studies with a similar prevalence of hypertension and diabetes ranging from 13% to 27% and 7% to 12%, respectively [4, 175]. The slightly higher prevalence of hypertension and diabetes in this study could be attributed to the inclusion of studies worldwide. In contrast, prior studies included only studies from China. The prevalence of obesity was 27.9% from 9 studies; interestingly, all these studies were from the US. Obesity has also been postulated to be a risk factor for COVID-19 by the dysregulation of the immune system due to excess adiposity and decreased diaphragm contractility [176]. Smoking was more common in non-severe patients; the “smoker’s paradox” has been proposed as a possible mechanism suggesting smoking to have

a protective effect, although this hypothesis continues to remain controversial [177].

Hypertension, hyperlipidemia, smoking, diabetes mellitus, and obesity are well-known cardiovascular risk factors [178]. Heart disease, stroke, and diabetes are known risk factors for influenza and its complications. SARS-CoV-2, being a respiratory virus, could also be hypothesized to have a similar risk factor [179]. Several hypotheses have been proposed for the cardiovascular complications of SARS-CoV-2, including angiotensin-converting enzyme-2 mediated cardiac damage, direct viral injury to myocardium, and hypoxemia mediated damage. However, none of these hypotheses have been proven yet [6, 180, 181]. Our findings suggest a higher prevalence of cardiovascular comorbidities in severe cases, which could be likely because of myocardial injury in these patients. The presence of comorbidities, including hypertension, diabetes mellitus, and atherosclerotic disease, was noted to be significantly higher in the severely ill patient population, which is corroborated by prior studies [19, 24, 35, 182].

Our study is in concordance with a prior meta-analysis of 43 studies with 3600 patients reporting fever, cough, and fatigue to be the most common clinical symptoms, suggesting COVID-19 to have primary respiratory system involvement [4]. In our study, fever was the most common presenting symptom as well [4, 35, 54, 109]. Respiratory symptoms of shortness of breath, cough, sputum production, and rhinorrhea were more common in severe illnesses, whereas non-respiratory symptoms are more common in non-severe disease. This could be because dyspnea and the need for supplemental oxygen are the criteria for severe illness. Initial studies were suggestive of COVID-19 being primarily a respiratory illness; however, recent studies suggest COVID-19 to be a multi-system disorder with the involvement of cardiovascular, gastrointestinal, musculoskeletal, and nervous systems. We report the involvement of respiratory, cardiovascular, gastrointestinal, musculoskeletal, and nervous systems, suggesting that COVID-19 is a multi-system disease with primary respiratory system involvement.

Our study reports a low prevalence (25.1% in 7952 from 13 studies) of loss of smell or taste; this is likely because of the inclusion of outpatient and survey studies in our review. A review focusing on olfactory dysfunction reported that up to 80% of patients with COVID-19 might develop subjective olfactory dysfunction in the disease's initial stages [183]. The lower prevalence in our study can be attributed to the inclusion of more inpatient studies in our analysis, as loss of smell tends to be an early-onset symptom and not recognized in inpatients. A review focusing on musculoskeletal symptoms of 12,046 patients reported occurrence

**Table IV.** Comorbidities and symptoms by severity vs. non-severity in patients with coronavirus disease 2019

| Parameter               | Non-severe | Severe | P-value |
|-------------------------|------------|--------|---------|
| <b>Comorbidity:</b>     |            |        |         |
| Hypertension            | 8.1%       | 45.2%  | < 0.001 |
| Diabetes mellitus       | 3.5%       | 19.5%  | < 0.001 |
| Atherosclerotic disease | 5.2%       | 10.9%  | < 0.001 |
| Smoking                 | 13.5%      | 3.8%   | < 0.001 |
| Obesity                 | 0.0%       | 30.5%  | –       |
| Heart failure           | 0.0%       | 5.2%   | –       |
| COPD/CLD                | 9.2%       | 12.0%  | 0.083   |
| Liver disease           | 2.8%       | 3.0%   | 0.814   |
| CKD/ESRD                | 0.8%       | 8.7%   | < 0.001 |
| Malignancy              | 3.8%       | 3.7%   | 0.899   |
| <b>Symptom:</b>         |            |        |         |
| Fever                   | 58.5%      | 87.8%  | < 0.001 |
| Myalgia/Arthralgia      | 25.8%      | 19.0%  | < 0.001 |
| Fatigue                 | 40.4%      | 45.1%  | 0.091   |
| Cough                   | 62.9%      | 66.8%  | 0.03    |
| Shortness of breath     | 20.6%      | 47.4%  | < 0.001 |
| Sore throat             | 12.6%      | 14.0%  | 0.279   |
| Sputum production       | 26.5%      | 35.4%  | < 0.001 |
| Nasal congestion        | 4.8%       | 4.8%   | 0.998   |
| Rhinorrhea              | 7.3%       | 32.2%  | < 0.001 |
| Loss of smell/taste     | 71.5%      | 18.6%  | < 0.001 |
| Chest pain/tightness    | 19.3%      | 21.1%  | 0.34    |
| Diarrhea                | 19.4%      | 20.2%  | 0.515   |
| Nausea/vomiting         | 8.4%       | 8.8%   | 0.643   |
| Abdominal pain          | 10.3%      | 4.2%   | < 0.001 |
| Anorexia                | 41.0%      | 27.1%  | < 0.001 |
| Headache                | 20.4%      | 10.6%  | < 0.001 |
| Hemoptysis              | 3.2%       | 2.5%   | 0.725   |
| Chills                  | 15.9%      | 6.9%   | 0.001   |

*COPD – chronic obstructive pulmonary disease, CLD – chronic lung disease, CKD – chronic kidney disease, ESRD – end-stage renal disease.*

of fatigue in 25.6% and arthralgia and/or myalgia in 15.5% of patients. Our study also showed a similar prevalence of these symptoms, although they seem to be nonspecific and represent viral prodromal symptoms for most of the respiratory viruses [184].

Our study's strength lies in its large patient population of more than 40,000 cases, including inpatients and outpatients, severe and non-severe cases, and spread over multiple continents. Our study has certain limitations as the majority of studies included in our study are observational. Even though our study included patients across the world, the majority of studies originate from

China. Of concern, many of the studies were incomplete and did not include a comprehensive picture of the patients such as outcomes on discharge. Additionally, most of the studies were in inpatient settings, thus under-representing cases within the community. Lastly, the literature evolving around COVID-19 is very dynamic and rapidly evolving, especially in terms of outcomes.

In conclusion, the prevalence of COVID-19 was found to be higher in men. Hypertension, diabetes, and atherosclerotic diseases are common comorbidities globally, and obesity is the second most common in the US. There is a higher prevalence of comorbid hypertension and diabetes amongst severely ill patients and a higher prevalence of fever, myalgia/arthralgia, shortness of breath, and cough symptoms in severely ill patients. We believe that further high-quality prospective studies are needed to identify the demographics and regional differences and ascertain characteristics of outpatient COVID-19 individuals.

### Conflict of interest

The authors declare no conflict of interest.

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