Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

MAYO CLINIC

Prevalence and Mortality of COVID-19 Patients With Gastrointestinal Symptoms: A Systematic Review and Meta-analysis

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Abstract

Objective: To perform a systematic review and meta-analysis evaluating the prevalence of gastrointestinal (GI) symptoms and mortality in patients with coronavirus disease 2019 (COVID-19) diagnosed.

Methods: A systematic search of MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus was performed from December 1, 2019 to May 7, 2020. Observational studies including adults with COVID-19 infection and reporting GI symptoms were included. The primary outcome was assessing the weighted pooled prevalence (WPP) of GI symptoms in patients with COVID-19 infection. Secondary outcomes were WPP of overall mortality, and mortality in patients with COVID-19 infection with GI symptoms.

Results: A total of 78 studies with 12,797 patients were included. Among GI symptoms (at onset of illness in 6, at admission in 17, data given separately for both in 3, and data unavailable in 52 studies), the WPP of diarrhea was 12.4% (95% CI, 8.2% to 17.1%), I^2=94%; nausea and/or vomiting, 9.0% (95% CI, 5.5% to 12.9%), I^2=93%; loss of appetite, 22.3% (95% CI, 11.2% to 34.6%, I^2=94%; and abdominal pain, 6.2% (95% CI, 2.6% to 10.3%), I^2=92%. Mortality among patients with GI symptoms (0.4%; 95% CI, 0% to 1.1%; I^2=74%) was similar to overall mortality (2.1%; 95% CI, 0.2% to 4.7%; I^2=94%), P=.15. Most studies had high risk of bias and overall quality of evidence was low to very low for all outcomes.

Conclusion: Gastrointestinal symptoms are seen in up to 1 in 5 patients with COVID-19 infection. More high-quality evidence is needed to confirm these findings and explore factors causing mortality in these patients.

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Coronavirus disease 2019 (COVID-19) is an infection caused by the novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first case of COVID-19 infection was reported in December 2019 in Wuhan, China. Since then, the disease has been declared a pandemic, affecting more than 4,700,000 people and causing more than 300,000 deaths globally (as of May 21, 2020).[1,2] Similar to other coronaviruses, SARS-CoV-2 primarily affects the pulmonary system, but multisystem involvement has been reported. The spectrum of disease includes asymptomatic colonization; mild disease with fever, cough, and fatigue; and severe disease characterized by dyspnea, hypoxemia, acute respiratory distress syndrome, need for mechanical ventilation, and death.[3]

The presence of gastrointestinal (GI) manifestations in COVID-19–infected patients has been noted in several reports recently, with 16% to 50% of patients reporting one or more GI symptom at presentation or during the illness.[4] Recognition of these symptoms has important implications for the identification of individual cases and would influence testing and isolation strategies, which are continually evolving based

on emerging data. One recent meta-analysis of 4243 patients found the pooled prevalence of all GI symptoms to be 17.6%[5]; however, most of the data included in the analysis were from Asia, limiting its generalizability. Another meta analysis of 47 studies reported the symptoms of diarrhea and nausea/vomiting to be present in 7.7% and 7.8% patients with COVID 19 infection, respectively. However, the study did not report mortality rates among these patients.[6]

Given the rapidly growing literature regarding GI symptoms in patients with COVID-19 infection, we conducted an updated systematic review and meta-analysis to assess the prevalence of GI symptoms in patients with COVID-19 infection and determine whether mortality is influenced by the presence of GI symptoms in these patients.

METHODS

All procedures used in this meta-analysis were consistent with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (Appendix, available online at http://www.mayoclinicproceedings.org).[7]

Selection Criteria

The studies considered in this meta-analysis were observational studies that included adults with confirmed COVID-19 infection and reported clinical characteristics, including GI symptoms. Studies not reporting the presence or absence of GI symptoms (because nonreporting during this pandemic would not equate to lack of GI symptoms) and individual case reports were excluded.

Data Sources and Search Strategy

A comprehensive search of several databases from December 1, 2019 to May 7, 2020, excluding animal studies, was conducted. The databases included Ovid MEDLINE 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.

The search strategy was designed and conducted by an experienced librarian (L.H.) with input from the study's principal investigators. Controlled vocabulary supplemented with keywords was used to search for studies describing GI manifestations of COVID-19 infection.

The actual strategy listing all search terms used and how they are combined is available in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org).

Two authors (R.T. and S.S.) independently reviewed titles and abstracts of the identified studies, and those that did not answer the research question of interest were excluded. The remaining articles were reviewed to determine inclusion criteria fulfillment. Reference lists of articles with information on the topic were also reviewed for additional pertinent studies. A flow diagram of included studies is shown in Figure 1.

Data Abstraction

Data were independently abstracted to a predetermined collection form by 2 investigators (R.T. and S.S.). Data collected for each study included study setting and design, month and year of publication, location, number of patients, patients with GI symptoms, symptom onset (symptoms assessed

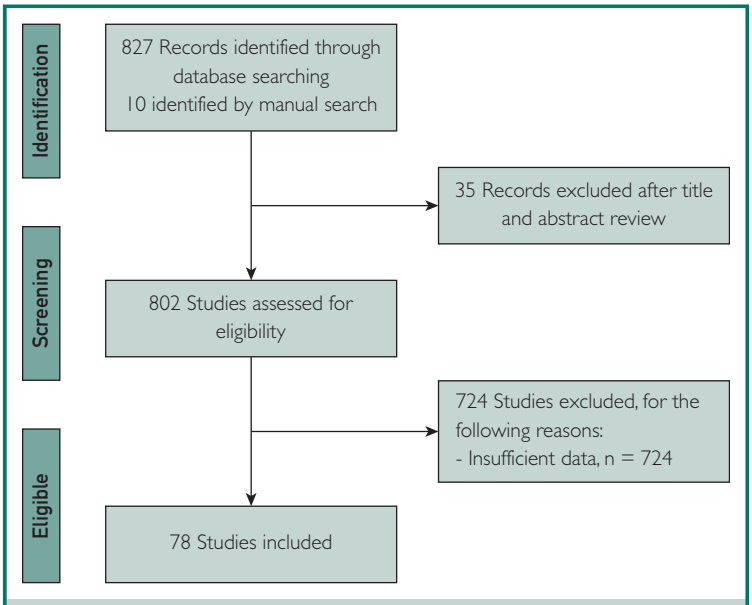

FIGURE 1. Flow diagram of study selection process.

at onset of illness or at admission to the hospital), severity of COVID-19 infection, duration of follow-up, and mortality. Severe infection was defined as admission to the intensive care unit or need for mechanical ventilation. Conflicts in data abstraction were resolved by consensus, referring to the original article.

Methodological Quality of Included Studies

Most studies included were case series, hence an appropriate risk-of-bias tool was applied (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org).[8] Risk of bias was assessed based on 4 domains: selection, ascertainment, causality, and reporting. An overall judgment of risk of bias was made based on factors deemed to be most critical for the systematic review (selection criteria, ascertainment of outcome, and follow-up duration).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to interpret the findings of the study. The principles of the GRADE system have been adopted by the Cochrane Collaboration for evaluating the quality of evidence for the outcomes reported in systematic reviews. For systematic reviews, the GRADE approach defines the quality of the body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest. The GRADE framework classifies the quality of evidence in 1 of 4 levels: high, moderate, low, and very low. Quality of a body of evidence involves consideration of the study design of included studies, methodological quality, directness of evidence, heterogeneity, inconsistency of results, and risk of publication bias.[9,10]

Data for symptom prevalence are expected to be of low quality because the evidence primarily arises from observational studies. This is particularly true in the context of an ongoing pandemic. Due to the clinical importance of the study question, such studies were included in the systematic review and meta-analysis.

Outcomes Assessed

Our primary analysis focused on assessing the weighted pooled prevalence (WPP) of GI symptoms in patients with COVID-19 infection, occurring any time during the course of illness. Secondary outcomes were the WPPs of mortality in all COVID-19–infected patients and in those with GI symptoms.

Statistical Analyses

We calculated the WPP with corresponding 95% CI for each symptom. We used the inverse variance heterogeneity model of meta-analysis with corresponding 95% CI for the overall and subgroup analyses. The inverse variance heterogeneity model is a modification of fixed-effects models that accounts for between-study heterogeneity, retains the individual weights of the studies, and decreases the variance in estimates.[11] Freeman-Tukey double arcsine transformation was used to avoid giving more weight to studies with prevalence estimates that are too large or too small. We assessed heterogeneity within groups using the I^2 statistic, which estimates the proportion of total variation across studies that is due to heterogeneity in study patients, design, or interventions rather than chance; I^2 values greater than 50% suggest substantial heterogeneity.[12] Publication bias was assessed visually using funnel plots if more than 10 studies were included in the analysis. Subgroup analyses were done for symptoms and mortality by onset of symptoms (at onset of illness) and for all all outcomes by study location (China vs non-China). Sensitivity analyses were done by excluding outlier studies and studies with high risk of bias. Calculations were performed and graphs were constructed using MetaXL meta-analysis software (version 5.3; EpiGear International Pty Ltd).

RESULTS

Search Results

The described database search strategy revealed 827 unique studies, 10 studies were identified from other sources; titles

and abstracts were screened, and relevant articles were obtained. Of the potentially relevant articles, 759 were excluded for various reasons (Figure 1), leaving 78 studies that were included in this meta-analysis (Table[4,5,13-88]).

Methodological Quality of Included Studies

The risk of bias of included studies is shown in Supplemental Table 2. Risk of bias was high in 48 studies, medium in 24 studies, and low in 6 studies.

Characteristics of Included Studies

The 78 included studies reported a total of 12,767 patients.[4,5,13-88] Of these studies, 57 were performed in mainland China; 6 in the United States; 1 in Australia; 1 in Europe; 1 in France; 1 in Germany; 1 in the Netherlands; 1 in Hong Kong; 2 in Italy; 1 in Spain; 1 in Japan; 1 in Korea; 1 in South Korea; 1 in Taiwan; and 2 in Singapore (Table). Among the studies performed in China, 24 were from Wuhan City in Hubei province; 4 included data from the entire Hubei province; 1 from Jingzhou city; 2 from Beijing City; 3 from Chongqing city; 3 from Shanghai; 3 from Zhuahi City; 2 from Nanjing province; 1 from Anhai province; 3 from Zhejiang province; 3 from Guangdong province; 1 from Zhengzou province; 1 from Hunan province; 1 from Jiangsu province; 1 from Shenzun province; and 1 from all provinces in China. The earliest study recruitment period started from December 11, 2019, and the last date of patient enrollment was April 16, 2020. Twelve studies were retrospective cohort studies, 1 was a prospective cohort study, 1 was a case-control study, and the remaining 64 were case series (Table).

The age distribution among the included patients ranged from 10 months to 96 years, and 58.4% (7455 of 12,767) were female. Of the included studies, 64 included only patients who were hospitalized (in 1 study, patients with mild symptoms were included, but they were hospitalized for monitoring and quarantine), 10 studies included both inpatients and outpatients, 1 included outpatients only, and 3 studies did not mention the location of patients. Thirty-four studies reported the severity of COVID-19 infection in patients. Among these studies, 3 included patients with severe disease only, 24 included patients with both severe and nonsevere disease, and 7 included patients with nonsevere disease only. The follow-up period was variable and ranged from 1 to 69 days; only 41 studies provided information on follow-up period.

Twelve studies (total 140 patients) reported the presence or absence of preexisting GI disease. The GI comorbid conditions reported were gastroesophageal reflux disease in 80, irritable bowel syndrome in 5, inflammatory bowel disease in 4, peptic ulcer disease in 9, *Helicobacter pylori* infection in 10, chronic liver disease in 16, hepatitis B virus infection in 1, fatty liver disease in 1, and other GI conditions in 14. The GI symptoms at onset of illness were assessed in 6 studies, at admission to the hospital in 17, data given separately for both in 3 studies and were not specified in 52 studies (Supplemental Table 3, available online at http://www.mayoclinicproceedings.org). Only 1 study reported data for how many patients had GI symptoms with and without pulmonary symptoms. In this study, 23.3% (48 of 206) of patients had GI symptoms only, 43.2% (89 of 206) had pulmonary symptoms only, and 33.5% (69 of 206) had both.

Prevalence of GI Symptoms

Of the included studies, 74 reported the prevalence of diarrheal symptoms in patients with COVID-19 infection ranging from 0% to 100%. Overall, of the 12,688 patients, 1773 reported diarrhea; the WPP was 12.4% (95% CI, 8.2% to 17.1%). There was significant heterogeneity among the studies, with I^2=94% (Figure 2). Publication bias was seen on visual inspection of a funnel plot (Supplemental Figure 1, available online at http://www.mayoclinicproceedings.org). There was 1 outlier study (Siegel et al[53]) with only 3 patients, all of whom had diarrhea (inclusion was patients presenting with predominantly GI symptoms). On removing this study, the WPP was unchanged (12.4%; 95% CI, 8.2% to 17.1%; I^2=94%; P=.90).

TABLE. Characteristics of Included Studies[a]

Serial No.	Reference, year	Country	Study Period	Type of Study	N	Age (y)[b]	Female (%)	Severity of Infection	Hospitalization	Follow-up (d)
1	An et al,[13] 2020	China	1/17/20-1/24/20	Case series	9	35.8 (28-45)	44	NS	( )	10-17
2	Chan et al,[14] 2020	China	1/10/20-1/15/20	Case series	6	50 (20-66)	50	( )	All	( )
3	Chang et al,[15] 2020	China	1/16/20-1/29/20	Case series	13	34 (34-48)	23.1	( )	No	20
4	Chen et al,[16] 2020	China	1/1/20-1/20/20	Case series	99	55 (21-82)	32	( )	All	16-25
5	Chen et al,[17] 2020	China	( )	Case series	9	54-25	77.8	NS	All	13
6	Chen et al,[18] 2020	China	1/1/20-3/11/20	Case series	145	47.5±14.6	54.5	B	All	Up to 69
7	Cheung et al,[5] 2020	Hong Kong	2/2/20-2/29/20	Case series	59	58.5 (22-96)	54.2	( )	( )	( )
8	Cholankeril et al,[19] 2020	US	3/4/20-3/24/20	Case series	116	50 (35-67)	46.5	( )	All	( )
9	C-NERC,[20] 2020	South Korea	1/10/20-2/14/20	Case series	28	42.6 (20-73)	46.1	( )	All	12.7 (range, 8-19)
10	C-NIRST,[21] 2020	Australia	Until 3/14/20	Case series (national database)	295	47 (0-94)	50	( )	225	Up to 3/14/20
11	Fan H et al,[22] 2020	China	12/30/19-2/16/20	Case series	101	65 (24-83)	36.6	S	All	( )
12	Fernandez-Ruiz et al,[23] 2020	Spain	3/5/20-3/23/20	Case series	17	71 (38-80)	24	( )	All	( )
13	Gritti et al,[24] 2020	Italy	3/11/20-3/24/20	Case series	21	64 (48-75)	14.3	( )	All	8 (median)
14	Guan et al,[25] 2020	China	12/11/19-1/29/20	Retrospective cohort	1099	47 (35-58)	41.9	B	All	13
15	Hajifathalian et al,[26] 2020	US	3/4/20-4/16/20	Case series	1059	61±18	42.3	B	768	Up to 34
16	Han et al,[27] 2020	China	2/13/20-2/29/20	Retrospective cohort	206	62.5±32.5	55.8	NS	All (for monitoring, quarantine)	19-35
17	Hsih et al,[28] 2020	Taiwan	1/20/20-2/19/20	Case series	2	45 (39-51)	50	( )	All	35
18	Huang et al,[29] 2020	China	12/16/19-1/2/20	Prospective cohort	41	49 (41-58)[c]	27	NS	All	( )
19	Huang et al,[30] 2020	China	1/21/20-2/1/20	Case series	11	NA	72.7	( )	( )	( )
20	Huang et al,[31] 2020	China	NA	Case series	2	73.5 (73-74)	100	NS	All	9
21	Huang et al,[32] 2020	China	12/21/19-1/8/20	Case series	34	56.2 (26-88)	58.8	B	33	( )
22	Jin et al,[33] 2020	China	1/17/20-2/8/20	Case series	651	46.4±14.19	49.1	B	All	( )
23	Kim ES et al,[34] 2020	Korea	1/19/20-2/17/20	Case series	28	40 (20-73)	46.4	B	All	Median time of off-isolation/ discharge was 18.5 d after symptom onset (range, 11-27)

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TABLE. Continued

Serial No.	Reference, year	Country	Study Period	Type of Study	N	Age (y)[b]	Female (%)	Severity of Infection	Hospitalization	Follow-up (d)
24	Klopfenstein et al,[35] 2020	France	3/1/20-3/17/20	Case series	114	56±18	59	( )	( )	( )
25	Kluytmans et al,[36] 2020	the Netherlands	3/7/20-3/12/20	Case series	86	49 (22-66)	83	( )	2	8 (range, 1-20)
26	Kuang et al,[37] 2020	China	1/1/20-2/10/20	Retrospective cohort	944	47 (21-96)	49.6	( )	All	( )
27	Liu et al,[38] 2020	China	12/30/19-1/24/20	Case series	137	57 (20-83)	54.4	( )	All	( )
28	Kujawski et al,[39] 2020	US	1/20/20-2/2/20	Case series	12	53 (21-68)	33.3	B	7	1-14
29	Lechien et al,[40] 2020	Europe	( )	Case series	417	36.9 (19-77)	63.1	( )	( )	( )
30	Li et al,[41] 2020	China	1/20-2/20	Case series	83	45±12.3)	47	B	All	( )
31	Lin et al,[42] 2020	China	1/17/20-2/15/20	Case series	95	45.3	52.6	( )	( )	( )
32	Liu et al,[43] 2020	China	1/11/20-1/20/20	Case series	12	49 (10-72)	33	B	All	( )
33	Luo et al,[4] 2020	China	1/1/20-2/20/20	Case series	1141	53.8	44	B	All	( )
34	Nobel et al,[44] 2020	US	3/10/20-3/21/20	Case control	278	( )	48	B	207	8
35	Pan et al,[45] 2020	China	1/12/20-2/6/20	Retrospective cohort	21	35 (21-59)	71.4	NS	All	26
36	Pan et al,[46] 2020	China	1/18/20-2/28/20	Retrospective cohort	103	52	47.5	B	All	20-61
37	Pung et al,[47] 2020	Singapore	( )-2/15/20	Case series	17	40 (36-51)	59	( )	All	≥22
38	Redd et al,[48] 2020	US	Until 4/2/20	Retrospective cohort	318	63.4±16.6	45.3	B	All	( )
39	Ren et al,[49] 2020	China	12/18/19-12/29/19	Case series	5	53.6 (41-65)	40	S	All	17
40	Shi et al,[50] 2020	China	12/20/19-1/23/20	Retrospective cohort	81	49.5 (25-81)	48	NS	All	( )
41	Shi et al,[51] 2020	China	1/20/20-2/10/20	Retrospective cohort	416	64 (21-95)	50.7	( )	All	( )
42	Shu et al,[52] 2020	China	2/13/20-2/29/20	Retrospective cohort	545	50 (38-58)	51.6	NS	All	( )
43	Siegel et al,[53] 2020	US	2/20	Case series	3	38.6 (26-50)	0	( )	All	9
44	Song et al,[54] 2020	China	1/20/20-1/27/20	Case series	51	49±16	50.9	( )	All	5
45	Spiteri et al,[55] 2020	Italy	1/24/20-2/21/20	Case series	38	42 (2-81)	34.2	( )	35	Up to 20
46	Tabata et al,[56] 2020	Japan	2/11/20-2/25/20	Case series	104	68 (25-93)	53.3	B	10	3-15 (median, 10)
47	Wan et al,[57] 2020	China	2/12/20-3/6/20	Case series	230	47.5 (7-90)	44	B	All	( )
48	Wang et al,[58] 2020	China	1/1/20-1/28/20	Case series	138	56 (22-92)	45.7	B	All	( )
49	Wang et al,[59] 2020	China	1/21/20-2/5/20	Case series	18	39 (29-55)	5.5	B	All	3-18
50	Wang et al,[60] 2020	China	1/31/20-2/12/20	Case series	26	42.0 (33.5-53.3)	57	( )	All	( )
51	Wang et al,[61] 2020	China	1/1/20-2/6/20	Case series	339	69 (65-76)	49.8	B	All	28

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TABLE. Continued

Serial No.	Reference, year	Country	Study Period	Type of Study	N	Age (y)[b]	Female (%)	Severity of Infection	Hospitalization	Follow-up (d)
52	Wang et al,[62] 2020	China	2/7/20-2/12/20	Case series	1012	50 (16-89)	48.2	( )	All	24
53	Wang et al,[63] 2020	China	1/21/20-1/24/20	Case series	4	47.5 (19-63)	25	( )	All	( )
54	Wei et al,[64] 2020	China	1/19/20-2/7/20	Case series	84	37 (24-74)	66.6	( )	All	13-32
55	Wolfel et al,[65] 2020	Germany	1/23/20-( )	Case series	17	40 (36-51)	58.8	( )	All	( )
56	Wu et al,[66] 2020	China	1/22/20-2/14/20	Retrospective cohort	80	46.1 (30.7-61.5)[c]	51.3	( )	All	24
57	Wu et al,[67] 2020	China	1/20-2/20	Case series	80	44±11	47.5	( )	All	( )
58	Wu et al,[68] 2020	China	1/16/20-3/15/20	Case series	74	( )	24.3	( )	All	( )
59	Xia et al,[69] 2020	China	( )	Case series	10	56.5±11.16	40	( )	All	( )
60	Xiao et al,[70] 2020	China	2/1/20-2/14/20	Case series	73	43 (10 mo-78 y)	65.7	B	All	26
61	Xie et al,[71] 2020	China	2/2/20-2/23/20	Case series	79	60.0 (48.0-66.0)	44.3	B	All	11.9
62	Xiong et al,[72] 2020	China	1/11/20-2/5/20	Case series	42	49.5 (26-75)	40.5	NS	All	22
63	Xu et al,[73] 2020	China	1/23/20-2/4/20	Case series	90	50 (18-86)	56.6	B	All	( )
64	Xu et al,[74] 2020	China	1/10/20-1/26/20	Case series	62	41 (32-52)	44	NS	All	17
65	Yang F et al,[75] 2020	China	1/1/20-4/15/20	Case series	52	63 (34-98)	46.2	B	All	41
66	Yang et al,[76] 2020	China	12/24/19-1/26/20	Case series	52	59.7±13.3	33	S	All	15-48
67	Young et al,[77] 2020	Singapore	1/23/20-2/3/20	Case series	18	47 (31-73)	50	NS	All	23-34
68	Yu et al,[78] 2020	China	1/20/20-1/23/20	Case series	4	74.5 (65-88)	50	B	( )	18
69	Zhang et al,[79] 2020	China	1/2/20-2/10/20	Case series	221	55.0 (39.0-66.5)	51	B	All	6-45
70	Zhang et al,[80] 2020	China	12/19-2/16/20	Case series	140	57 (25-87)	50	B	All	( )
71	Zhang et al,[81] 2020	China	1/27/20-2/10/20	Case series	14	41 (18-87)	50	( )	All	1-14
72	Zhao et al,[82] 2020	China	1/2/20-2/5/20	Retrospective cohort	19	48 (27-56)	42.1	( )	All	( )
73	Zhao et al,[83] 2020	China	( )	Case series	101	44.4 (17-75)	44.5	B	All	( )
74	Zhao et al,[84] 2020	China	1/16/20-2/10/20	Case series	91	46 ()	46.2	B	All	1-26
75	Zhou et al,[85] 2020	China	12/29/19-1/31/20	Retrospective cohort	191	56 (46-67)	38	S	All	( )
76	Zhou et al,[86] 2020	China	1/16/20-1/30/20	Case series	62	52.8 (30-77)	37.1	( )	All	14
77	Zhou et al,[87] 2020	China	12/20/19-2/9/20	Case series	254	50.6 (15-87)	54.7	( )	All	( )
78	Zou et al,[88] 2020	China	1/7/20-1/26/20	Case series	18	59 (26-76)	50	B	All	( )

[a]( ) = missing; All = if all were hospitalized, number represents patients who were hospitalized; B = both; C-NERC = COVID-19 National Emergency Response Center; C-NIRST = COVID-19 National Incident Room Surveillance Team; NA = not available; NS = nonsevere; S = severe.

[b]Represented as median (range) or mean ± SD, unless otherwise specified.

[c]Represented as median (interquartile range).

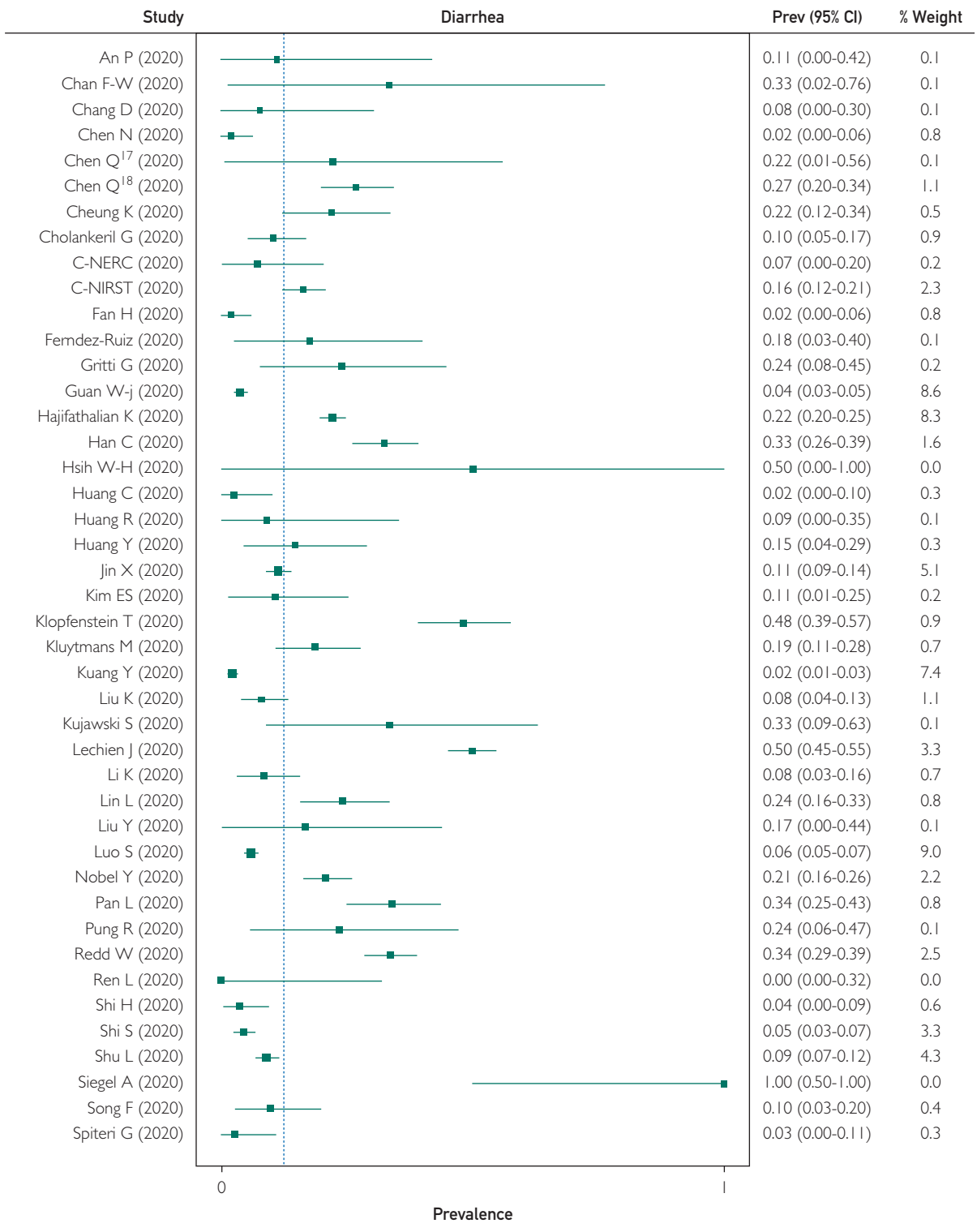

FIGURE 2. Forest plot shows weighted pooled prevalence (Prev) of diarrhea in patients with coronavirus disease 2019 infection. C-NERC = COVID National Emergency Response Center; C-NIRST = Coronavirus Disease 2019 National Incident Room Surveillance Team; Q = Cochrane's Q test.

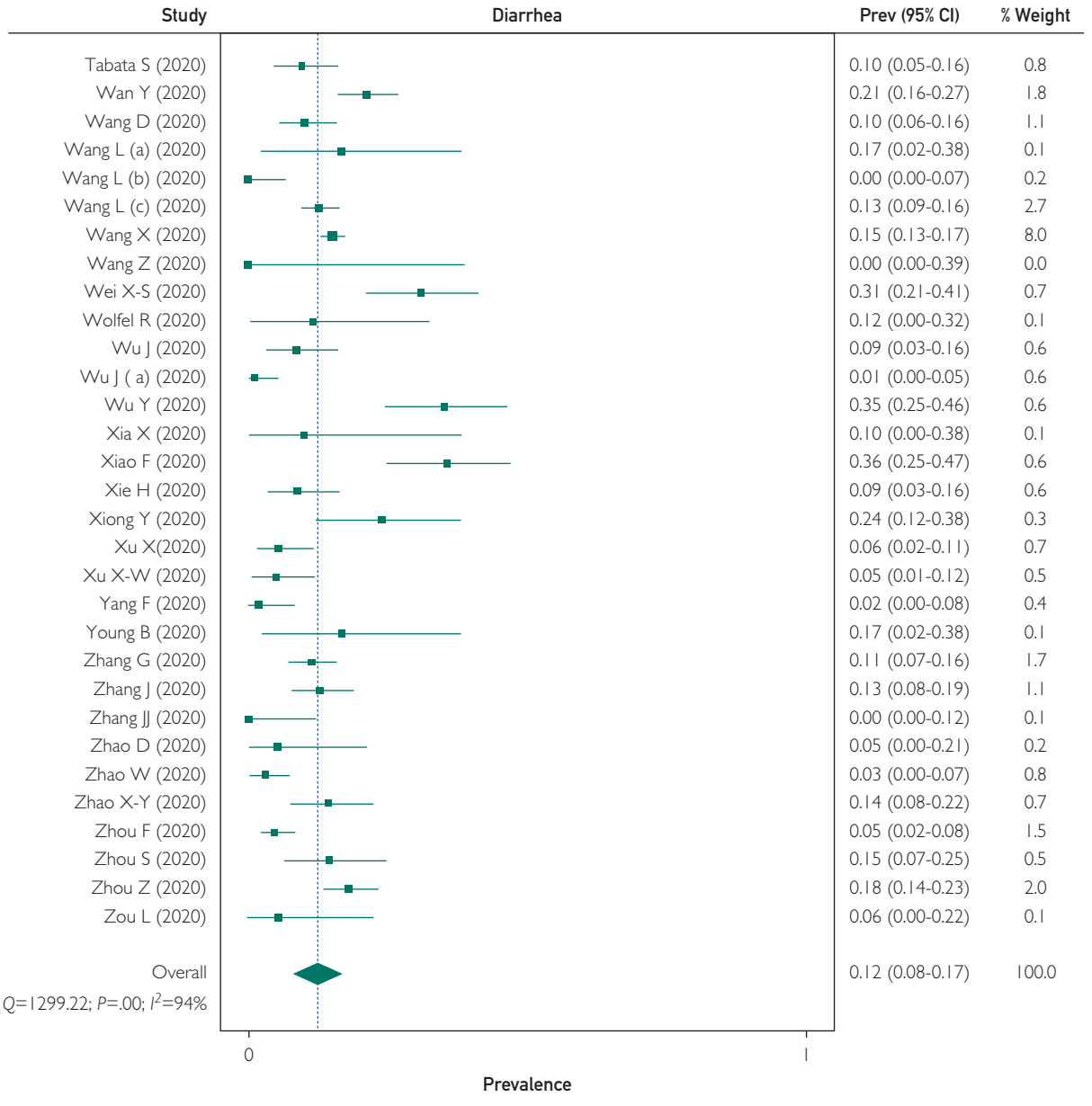

FIGURE 2. (*continued*).

The prevalence of nausea and/or vomiting with COVID-19 infection was reported in 42 studies. Among a total of 9696 patients, 988 reported nausea and/or vomiting with a WPP of 9.0% (95% CI, 5.5% to 12.9%). There was significant heterogeneity among the studies with I^2=93% (Supplemental Figure 2, available online at http://www.mayoclinicproceedings.org). Removing the outlier study, the WPP was unchanged (9.0%; 95% CI, 5.5% to 12.9%; I^2=93%).

Other GI symptoms reported were loss of appetite and abdominal pain, reported in 20 and 27 studies, respectively. Among the 20 studies reporting loss of appetite, prevalence ranged from 1% to 100%; overall, 744 of 3201 patients with COVID-19 infection reported loss of appetite with a WPP of

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22.3% (95% CI, 11.2% to 34.6%; I^2=94%; Supplemental Figure 3, available online at http://www.mayoclinicproceedings.org).

Among the 27 studies reporting on abdominal pain, prevalence ranged from 0% to 50%; overall, 418 of 5896 patients with COVID-19 infection reported abdominal pain, with a WPP of 6.2% (95% CI, 2.6% to 10.3%; I^2=92%; Supplemental Figure 4, available online at http://www.mayoclinicproceedings.org).

Subgroup and Sensitivity Analyses

For diarrhea, 9 studies reported symptoms at onset of illness, with a WPP of 8.1% (95% CI, 1.3% to 16.6%; I^2=95%). This was similar to the WPP from 19 studies that reported diarrhea at hospital admission (10.2%; 95% CI, 4.0% to 17.4%; I^2=95%; P=.68). For nausea/vomiting, 5 studies reported symptoms at illness onset with a WPP of 12.1% (95% CI, 9.4% to 14.9%; I^2=26%). This was similar to the estimate from 10 studies reporting symptoms at admission (WPP=8.3%; 95% CI, 0.3% to 19.2%; I^2=96%; P=.45).

Loss of appetite at illness onset was reported in 4 studies (WPP=28.9%; 95% CI, 11.5% to 48.1%; I^2=84%), which was similar to the estimate from the 3 studies reporting it at admission (WPP=16.3%; 95% CI, 0% to 39.8%; I^2=80%; P=.36). Four studies each reported abdominal pain at illness onset (WPP=4.1%; 95% CI, 1.5% to 7.3%; I^2=50%) and at admission (WPP=7.3%; 95% CI, 0% to 18.6%; I^2=67%), with the estimates being statistically similar (P=.53).

For diarrhea, 53 studies were from China, while 21 studies were from outside China. The WPP of diarrhea was higher in the non-China subgroup (25.3%; 95% CI, 14.8% to 36.5%; I^2=92% vs 9.2%; 95% CI, 5.8% to 12.9%; I^2=91%; P=.01). For nausea/vomiting, the WPP from the 12 studies in the non-China subgroup (17.4%; 95% CI, 11.3% to 24%; I^2=96%) was higher than that from the 30 studies in the China subgroup (6.4%; 95% CI, 3.4% to 9.8%; I^2=90%; P<.001]. The WPP of loss of appetite was similar in both subgroups (non-China: 4 studies; WPP=27.3%; 95% CI, 13.9% to 41.7%; I^2=85% vs China: 16 studies; WPP=21.4%; 95% CI, 7.7% to 36.9%; I^2=95%; P=0.57). The WPP of abdominal pain was higher in the non-China subgroup (13 studies; WPP=12%; 95% CI, 3.4% to 22.3%; I^2=91% vs China subgroup: 14 studies; WPP=3.5%; 95% CI, 2.3% to 4.8%; I^2=53%), though this was not statistically significant (P=.08).

On performing sensitivity analyses by removing studies with high risk of bias, estimates did not change and heterogeneity did not decrease for any symptom (all P>.05).

Mortality Among Patients With COVID-19 Infection

A total of 42 studies reported overall mortality among patients with COVID-19 infection, which ranged from 0% to 100%. One study included only patients who had died of COVID-19 infection and hence was excluded from this analysis. Of the 8122 patients in the remaining 41 studies, 320 died with a WPP for overall mortality of 2.1% (95% CI, 0.2% to 4.7%). There was significant heterogeneity among the studies with an I^2=94% (Figure 3). Cause of death (regardless of whether attributable to COVID-19 infection) was not specified in any of the studies. Publication bias was seen on visual inspection of a funnel plot (Supplemental Figure 5, available online at http://www.mayoclinicproceedings.org).

Twenty-one studies reported mortality as an outcome among patients with GI symptoms. Of a total of 4983 patients, 34 died with a WPP of 0.4% (95% CI, 0% to 1.1%). There was significant heterogeneity among the studies with I^2=74% (Figure 4). Mortality among patients with GI symptoms was similar to the overall mortality (P=.15).

Subgroup analyses by study location provided similar estimates of overall mortality (non-China subgroup: 13 studies; WPP=5.8%; 95% CI, 0.9% to 11.9%; I^2=88% vs China subgroup: 28 studies; WPP=1.2%; 95% CI, 0% to 3.5%; I^2=94%; P=.12). Mortality estimates were similar in patients presenting with GI symptoms (non-China subgroup: 5 studies;

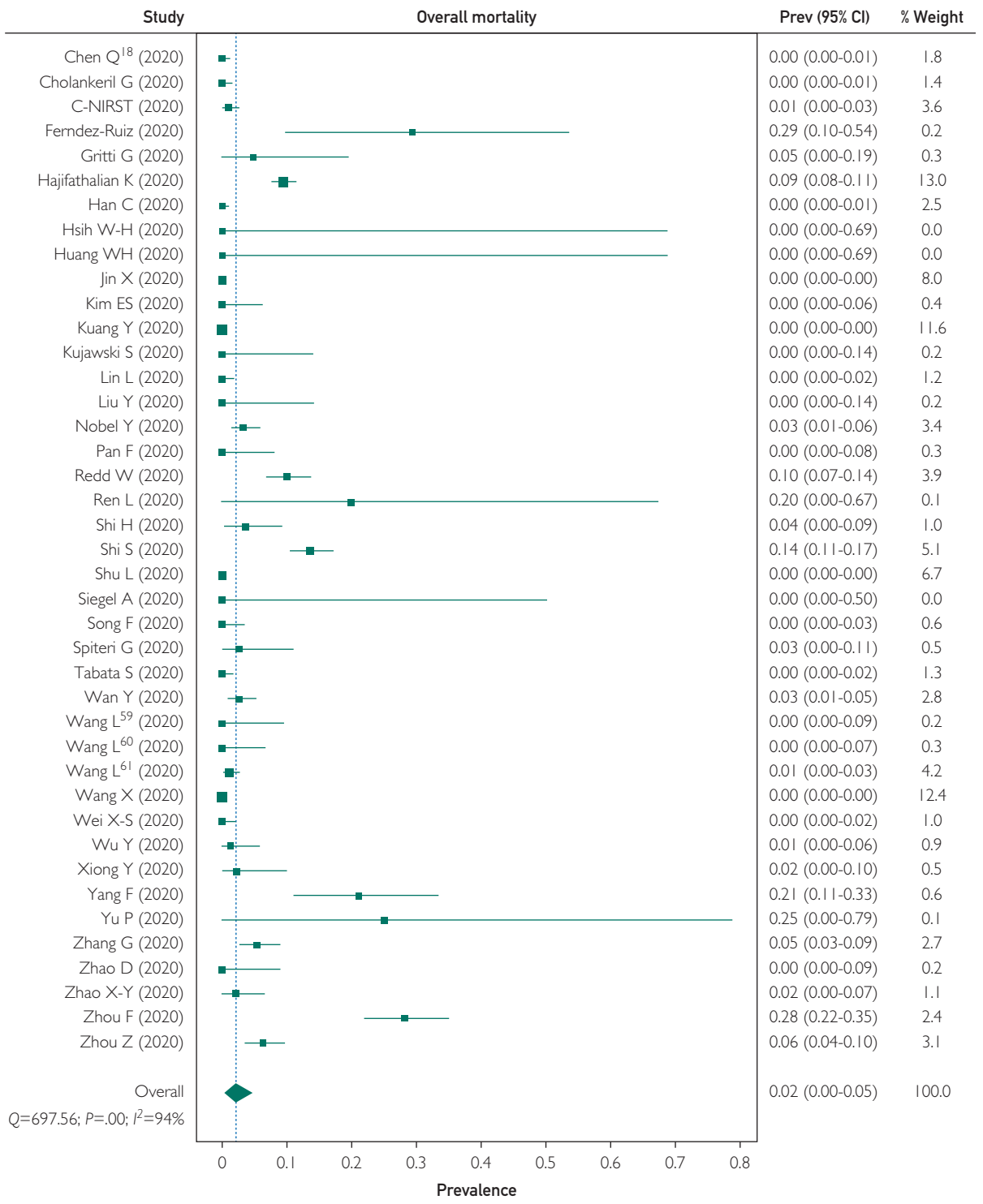

FIGURE 3. Forest plot shows weighted pooled rate of overall mortality in coronavirus disease 2019 infection. C-NIRST = Coronavirus Disease 2019 National Incident Room Surveillance Team; Prev = prevalence; Q = Cochrane's Q test.

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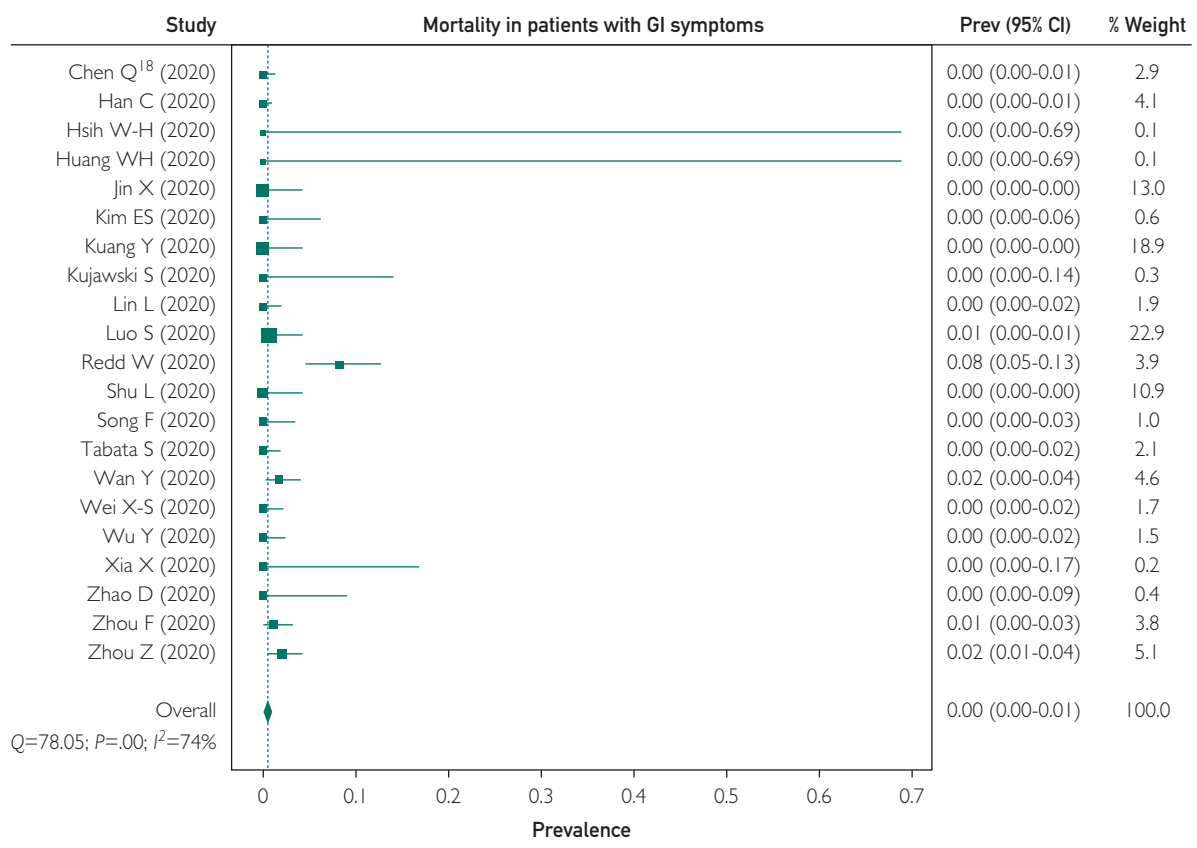

FIGURE 4. Forest plot shows weighted pooled rate of mortality in coronavirus disease 2019 infection with gastrointestinal (GI) symptoms. Prev = prevalence; Q = Cochrane's Q test.

WPP=3.8%; 95% CI, 0% to 12.3%; I^2=78% vs China subgroup: 16 studies; WPP=0.3%; 95% CI, 0% to 0.7%; I^2=56%; *P*=.27).

On performing sensitivity analyses by removing studies with high risk of bias, estimates and between-study heterogeneity did not decrease for either mortality in patients with GI symptoms or overall mortality.

Quality of Evidence

Per the GRADE framework, the quality of evidence for the prevalance of GI symptom outcome was low because of study design (observational studies only), lack of consistency of methodology, presence of publication bias, and significant heterogeneity in all effect estimates. The quality of evidence was considered very low for mortality outcome because of study design (observational studies only), lack of consistency of methodology, presence of publication bias, significant heterogeneity, and inconsistency among reported results. Additionally, none of the studies had adjusted for any potential confounding factors for mortality outcome (Supplemental Table 4, available online at http://www.mayoclinicproceedings.org).

DISCUSSION

In this systematic review and meta-analysis, we found that GI symptoms were present in up to 1 in 5 patients with COVID-19 infection. The highest prevalence was for loss of appetite (approximately one-fifth of patients), whereas the other symptoms occurred in up to 10% of patients. Mortality among patients with GI symptoms was similar to overall mortality. This must be interepreted with caution because variable follow-up, lack of uniform criteria for

COVID-19—attributable mortality, and lack of adjustment for cofounders would affect estimates of mortality. The WPPs of diarrhea and nausea/vomiting were higher in the subgroup of studies conducted outside China compared with studies from China, likely due to increasing awareness and reporting of GI manifestations as the pandemic progressed. There was substantial heterogeneity for all estimates, and publication bias was present. Overall, the quality of evidence was low for outcomes of prevelance of GI symptoms and very low for mortality outcomes.

Several reports have described the occurrence of GI symptoms and possible feco-oral transmission in patients with COVID-19 infection.[4,29,68] A previous systematic review of 6 studies reported diarrhea, nausea, vomiting, and abdominal pain in less than 10% of patients, which is similar to our results.[89] One recent meta-analysis of 47 studies with 10,890 patients estimated a pooled prevelance of diarrhea to be 7.7%; nausea/vomiting, 7.8%; and abdominal pain, 2.7%. The study also pooled the prevalence of diarrhea among studies from countries other than China only and found the prevelance of diarrhea in non-China studies to be higher, with a pooled prevelance of 18.3%.[6] Another meta-analysis of 29 studies reported a pooled prevalence of digestive symptoms of 15%, with nausea or vomiting, diarrhea, and loss of appetite being the 3 most common symptoms.[90] The prevalence of most GI symptoms in our study and the subgroup analyses by study location are similar to prior meta-analyses. Among all GI symptoms, the prevalance of loss of appetite in our study was higher than the other GI symptoms. Loss of appetite is commonly seen with febrile illness, which could contribute to the higher rates. However, fewer included studies reported this symptom, which could affect our estimates.

Several important factors should be considered while interpreting results from our study. Until the date of this review, we are still in the mid-phase of the pandemic, with data reported predominantly being from China. Only a quarter of the included studies are from reports outside China. Additionally, the quality of data collection during pandemics is not robust due to the possibility of inadequate documentation of symptoms. The studies included in this meta-analysis primarily included hospitalized patients. Patients with mild disease who were not admitted to the hospital were not included. Patients with mild to moderate symptoms constitute a majority (81%) of those infected with SARS-CoV-2.[3] Exclusion of these patients is likely to affect estimates of symptom prevalence. In the absence of published reports of symptom analyses in this cohort of patients, it is difficult to assess the direction in which our estimates would change and therefore our results are not necessarily generalizable to outpatients.

Another important factor is that GI symptoms may be underreported. Increasing awareness, comprehensive symptom questionnaires, and prospective study design would likely provide more reliable estimates of GI symptoms in future studies. In the studies included, there was also limited information for GI-specific laboratory tests, endoscopy reports, histopathology reports, and imaging. Angiotensin-converting enzyme 2 is one of the receptors to which coronaviruses bind. Angiotensin-converting enzyme 2 is expressed in the lung, and within the GI tract, it is expressed in the small intestine, large intestine, and cholangiocytes.[91] This may facilitate the spread of the virus through the GI tract and could explain the occurrence of GI symptoms in COVID-19 infection. Future studies should explore these aspects, which would shed light on the pathophysiology of GI involvement in COVID-19 infections.

We found mortality in patients with GI symptoms to be similar to overall mortality. Of note, mortality reported here is all-cause mortality. Deaths in patients with COVID-19 could be due to the infection itself or to underlying comorbid conditions. A uniform definition for COVID-19—attributable mortality and a standardized time frame (eg, within 30 days) would be essential in assessing the impact of the infection and its

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differing presentations on mortality. Studies included in the systematic review did not assess the effect of different factors such as age and comorbid conditions on mortality. Moreover, several studies did not report or had limited follow-up, which would affect mortality estimates. By doing a sensitivity analysis based on risk of bias (which incorporates follow-up duration as a quality indicator), we could partly adjust for limited follow-up.

Strengths of this study include a comprehensive search strategy with studies from different countries and assessment of several GI symptoms. However, the study has several limitations. Most of the included studies are retrospective and thus at high risk of bias. There is also evidence of significant heterogeneity and publication bias. Several included studies are from Wuhan, China, making it difficult to exclude the possibility of overlapping patients in different studies. As mentioned, several factors affect mortality estimates. Only 12 included studies had information regarding comorbid GI conditions, which precluded assessment of whether symptoms were attributable to the infection or underlying disease. Only 1 study mentioned whether patients had GI symptoms only or if they had GI symptoms with respiratory symptoms. Hence, we could not assess whether GI symptoms present alone or with other symptoms. Finally, most studies were in the hospital setting. Thus, there was underrepresentation of mild to moderate cases and cases within the community.

CONCLUSION

Up to 1 in 5 patients with COVID-19 infection have GI symptoms. Clinicians should be aware of the possibility that patients with COVID-19 infection can have GI symptoms and keep a low threshold for testing for the infection. Our study highlights the need for high-quality prospectively collected data, with inclusion of patients in the community setting and exploration of the causes underlying mortality.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **C-NERC** = COVID National Emergency Response Center; **C-NIRST** = Coronavirus Disease 2019 National Incident Room Surveillance Team; **COVID-19** = coronavirus disease 2019; **GI** = gastrointestinal; **GRADE** = Grading of Recommendations, Assessment, Development and Evaluations; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **WPP** = weighted pooled prevalence

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