Prevalence of gastrointestinal symptoms in coronavirus disease 2019 : a meta-analysis

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Abstract

***Background and study aims* :** The coronavirus disease 2019 (COVID-19) is a pandemic infection spreading worldwide at an unprecedented rate. Our aim was to assess the frequency of gastrointestinal (GI) involvement in COVID-19.

***Patients and methods* :** We performed a systematic review and meta-analysis of all studies reporting clinical data about COVID-19 patients, published until 25th March 2020. The primary endpoint was the pooled prevalence of COVID-19 patients complaining of GI symptoms. Secondary endpoints were the pooled prevalence of cases with COVID-19 positive stool samples, and of asymptomatic COVID-19 patients. We used random-effects model for meta-analysis.

***Results* :** Thirty-three studies were included in the meta-analysis. Out of 4434 COVID-19 patients, the pooled prevalence of GI manifestations was 11.51% (95% CI : 8.16 to 15.35). The most frequent GI symptom was diarrhea (7.78% of cases ; 95% CI : 5.05 to 11.04), followed by nausea/vomiting (3.57% ; 95% CI : 1.87 to 5.80), poor appetite (2.39% ; 95%CI : 0.55 ; 5.46) and abdominal pain (0.78% ; 95% CI : 0.26 to 1.57). Positivity for COVID-19 in stool samples was observed in 41.50% (95% CI : 17.70 to 67.65) of cases. 11.85% (95% CI : 3.53 to 24.17) of COVID-19 patients remained asymptomatic.

***Conclusions* :** The present meta-analysis shows that a significant proportion of COVID-19 patients suffer from GI manifestations, as well as COVID-19 positivity in stool samples. Asymptomatic patients need to be considered a further potential route of viral transmission. (Acta gastroenterol. belg., **2020**, 83, **603-615**).

Key words : COVID-19, gastrointestinal symptoms, fecal-oral viral transmission, asymptomatic patients.

Introduction

The coronavirus disease 2019 (COVID-19) is a pandemic infection spreading worldwide at an unprecedented rate (1). The most frequent COVID-19 manifestation is represented by pneumonia, characterized by fever, dyspnea and cough. However, other organs may be involved by the infection, with several possible clinical scenarios (2). Gastrointestinal (GI) symptoms have also been reported in some series, but the correct estimate of their occurrence risks to be underestimated (3,4).

As far as human-to-human viral spread concerns, respiratory droplets represent the main certain route of transmission. However, fecal excretion of the virus has also been proved by several studies to be another possible source, with a duration of transmission lasting after the resolution of the respiratory symptoms (5). It has indeed been proved that COVID-19 exploits Angiotensin-converting enzyme 2 (ACE2) as receptor for entry process, and ACE2-mRNA is highly expressed in the GI system (3).

Asymptomatic COVID-19 patients also make their role in the process of viral spread, but their correct rate needs to be systematically defined (2).

The aims of this paper are to assess, through a systematic review and a meta-analysis, the pooled prevalence of GI symptoms in COVID-19 patients, as well as to investigate the viral fecal-oral transmission and the pooled prevalence of asymptomatic patients.

Methods

Inclusion Criteria and Outcomes

We considered all publications reporting clinical data of COVID-19 adult patients, or about COVID-19 positivity in stool samples. Exclusion criteria were : study population including only pregnant patients or cases with age < 18 years ; publications not reporting clinical data ; study design as reviews, meta-analyses, recommendations/guidelines, editorials, case series/reports.

The primary outcome of this review was to estimate the pooled prevalence of GI manifestations in adult COVID-19 patients. The secondary outcomes were to describe the reported frequency of COVID-19 positivity in fecal samples, and to measure the pooled prevalence of asymptomatic adult patients.

Search Method

A computerized search, with last update on 25th March 2020, was performed using these databases : Medline, Cochrane Database of Systematic Reviews, Scopus and ISI web of knowledge. For "disease condition", the following terms were adopted : COVID-19, "Novel coronavirus 2019", "2019 nCoV", "SARS-CoV-2", "coronavirus disease 2019". No language or date filters were applied.

Reference management were led by the Endnote program (Endnote X4, Bld 6695). Study selection was performed according to the PRISMA Guidelines (6). Titles and abstracts were initially checked in order to assess whether the publications dealt with COVID-infection. Complete full texts were then evaluated, and papers eligible for qualitative and quantitative analyses were included. We also screened the reference lists of all the selected papers.

Data Extraction and Risk of Bias

Two independent reviewers (E.M., F.A.) carried out the search, study selection and data extraction. In case of disagreement, the opinion of a third reviewer (G.d.P.) was requested. Excluded publications were recorded, as well as the reasons for exclusion. In order to avoid duplicate publications, a careful check of all the hospitals involved in the studies was performed, and when data derived from the same hospital we only considered the paper with the largest population and with more details about GI symptoms.

The following data were recorded for each study :
– first author
– type of publication
– Nation where diagnosis was performed
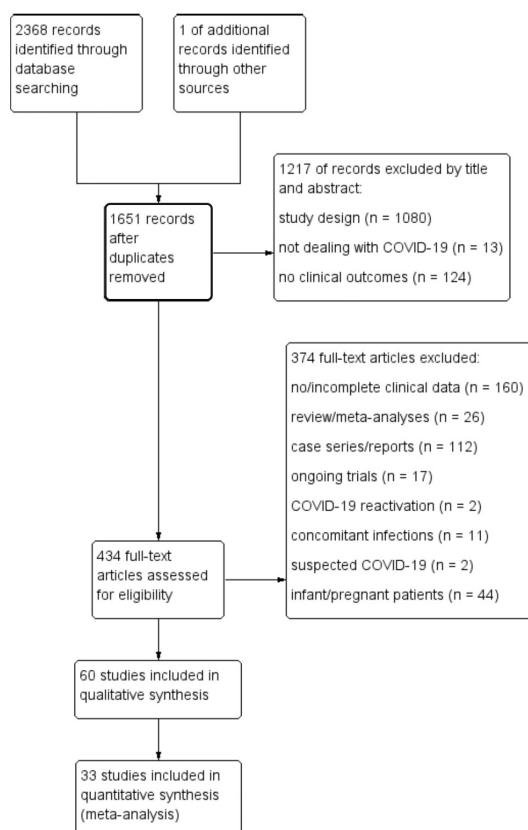– total number of patients included
– number of patients with GI symptoms
– type of symptom
– number of patients with COVID-19 positive stool sample
– number of asymptomatic patients.

Data about the outcomes were recorded as dichotomous variables (presence or absence of the outcome). When the total amount of patients with GI manifestations was not clearly stated in the publication, we considered for this outcome the rate of the most frequent GI symptom reported in the study population.

Study quality was evaluated by two authors (E.M. and F.A.) independently, according to the MINORS criteria (7). Disagreements were resolved by a third author (G.d.P.).

Statistical Method

Single-arm meta-analyses were performed using the software program Medcalc 15.6.1 (www.medcalc. be), adopting the random-effects model. Heterogeneity was assessed by Cochran Q test, with significance set at P value < 0.10. We considered an I^2 of $\geq 50\%$ as representative of heterogeneity.

For sensitivity analysis, we investigated the influence of different patients' recruitment (unicenter or multicenter study), and potential bias due to inclusion in some studies of children and pregnant patients (3,8-18).

Results

Search Results and Risk of Bias

Database searches provided a total amount of 2368 references. In details, 1532 were retrieved by Medline, 570 by Scopus, 249 by Isi web of science, and 17 by the Cochrane Library (Figure 1). Two "special collection" documents suggested by the Cochrane Library (including 37 systematic reviews) were excluded because they dealt with critical care in general. Screening the references of included publications, one additional publication was evaluated (19).

After excluding title duplicates, 1651 references were screened, and 1217 of these did not respond to inclusion criteria. Full texts of 434 publications were evaluated, and 60 were included in qualitative analysis (studies description detailed in Supplementary Table 1). After excluding further 27 papers due to risk of data duplication, 33 studies were considered eligible for the meta-analyses (3,5,8-16,18, 20-40). Clinical data are reported in Table 1 and in Supplementary Table 1, while the evaluation of the risk of bias is described in Supplementary **Table** 2.

Prevalence of GI symptoms

Fifty-six references reported data about GI symptoms in COVID-19 patients (Supplementary Table 1). Exclu-

Figure 1. — Study selection sequence to perform the meta-analysis.
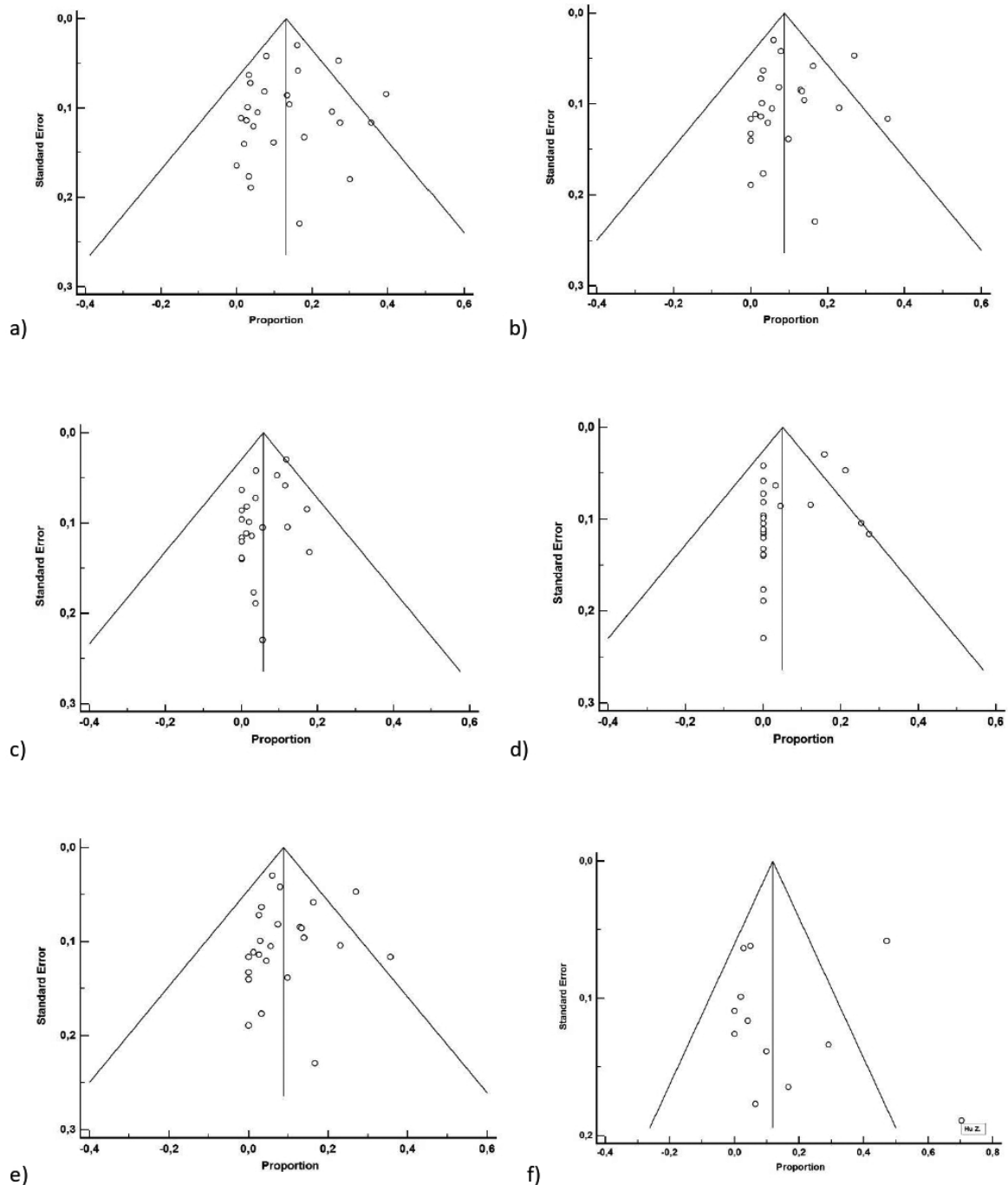
Supplementary Figure 1. — Funnel plots of meta-analyses for : a) GI symptoms ; b) diarrhea ; c) nausea/vomiting d) poor appetite ; e) abdominal pain/discomfort ; f) asymptomatic patients

ding data derived from the same Chinese hospitals, 27 references (3,8-16,18,20,22,23,25,27-32, 34,36-40) were considered for quantitative analysis. The total population amounted for 4434 patients, and meta-analysis showed a pooled prevalence of GI symptoms of 11.51% (95%CI : 8.16 ; 15.35) (Figure 2). Heterogeneity was however significantly high (I^2 = 92.09%, p < 0.01). Funnel plot is shown in Supplementary Figure 1a.

We performed sensitivity analysis, investigating the influence of different patients' recruitment (unicenter or multicenter study), and potential bias due to inclusion in some studies of children and pregnant patients (3, 8-18). Removing these studies from the meta-analysis did not significantly affect the results or reduce heterogeneity.

Focusing on the different GI symptoms, the most frequent was diarrhea (7.78% ; 95%CI : 5.05 ; 11.04 ; I^2 = 91.85%, p < 0.01). Nausea/vomiting affected 3.57% (95%CI : 1.87 ; 5.80 ; I^2 = 90.82%, p < 0.01) of patients, while 2.39% (95%CI : 0.55 ; 5.46 ; I^2 = 96.22, p < 0.01) had poor appetite and 0.78% (95%CI : 026 ; 1.57 ; I^2 = 80.10%, p < 0.01) had abdominal pain/discomfort. Figure 3 reports the forest plots according to different symptoms,

Table 1. — **Q**ualitative analysis of the studies : demographics and clinical presentation

First author	N	Asymptomatics, *n* (%)	GI symptoms, *n* (%)	+ stools, *n* (%)
Gautret P.	36	6 (16.7)	0 (0)	Not reported
Spiteri G.	31	2 (6.4)	≥ 1 (3.2) [a]	Not reported
7. Australian Report	295	139 (47.1)	≥ 48 (16.3)	Not reported
Wang Y.	55	16 (29.1)	Not reported	Not reported
Xu X.	90	Not reported	≥ 5 (5.5) [a]	Not reported
Xiao F.	73	Not reported	≥ 26 (35.6) [a]	39 (53.4)
Wu Y.	74	Not reported	33 (44.6)	41 (56.2)
Liu Y	76	Not reported	≥ 2 (2.6) [a]	Not reported
Wang W.	205	Not reported	Not reported	44/153 (28.7)
Qin C.	452	Not reported	≥ 122 (26.7) [a]	Not reported
Zhou S.	62	0 (0)	9 (14.5)	Not reported
Liu M.	30	Not reported	9 (30.0)	Not reported
Zhang J.J.	140	Not reported	55/139 (39.6)	Not reported
Zhou F.	191	Not reported	≥ 7 (3.6) [a]	Not reported
Luo S.	1141	Not reported	183 (16.0)	Not reported
Han R.	108	Not reported	15 (13.9)	Not reported
Zhang X.	573	Not reported	≥ 45 (7.9) [a]	Not reported
Yang W.	149	Not reported	≥ 11 (7.4) [a]	Not reported
Qian G.Q.	91	Not reported	≥ 23 (25.3) [a]	Not reported
Chen J.	249	7 (2.8)	≥ 8 (3.2) [a]	Not reported
Zhao W.	101	2 (1.9)	≥ 3 (2.9) [a]	Not reported
Tian S.	262	13 (4.9)	0 (0)	Not reported
Xu, Y.H.	50	Not reported	1 (2.0)	Not reported
Wan S.	135	Not reported	≥ 18 (13.3) [a]	Not reported
Li K.	83	0 (0)	7 (8.4)	Not reported
Wu J.	80	Not reported	≥ 1 (1.2) [a]	Not reported
Xu T.	51	Not reported	5 (9.8)	Not reported
Hu Z.	27	19 (70.4)	1 (3.7)	Not reported
Liu K.	56	Not reported	10 (17.8)	Not reported
Liu K.	51	5 (9.8)	5 (9.8)	Not reported
Liu K.C.	73	3 (4.1)	20 (27.4)	Not reported
Zheng M.	68	Not reported	3 (4.4)	Not reported
Wang L.	18	Not reported	≥ 3 (16.7) [a]	Not reported

[a] Total number of patients with GI symptoms not indicated in the publication. GI : gastrointestinal.

while funnel plots are shown in Supplementary Figure 1b-e.

Available data did not allow to calculate the rate of COVID-19 patients complaining only of GI symptoms.

COVID-19 positive stool samples

A total of 4 publications (Supplementary Table 1) clearly reported data about fecal test positivity for COVID-19. After excluding possible data duplicates (2 studies from The Fifth Affiliated Hospital of Sun Yat-Sen University, Zhuhai, Guangdong), only Wu Y. and Wang W. (5, 24) were included in the meta-analysis, with 227 patients.

The results of the randomized effects model meta-analysis showed that rate of positive stool samples for COVID-19 was 41.50% (95%CI : 17.70 ; 67.65) (Figure 4). A funnel plot was not drawn, as only 2 studies were included. Significant heterogeneity was however observed (I^2 = 93.27%, p < 0.01).

Rate of asymptomatic patients

Seventeen references (Supplementary Table 1) clearly reported the proportion of asymptomatic patients in the included population. Excluding data derived from the same hospitals, only 12 references (8,9,13,16,20,21,26,32,33,35,37,39) were eligible for meta-analysis. Out of 1332 COVID-19 patients, asymptomatic cases accounted for 11.85% (95%CI : 3.53 ; 24.17) (Figure 5). Heterogeneity was high (I^2 = 97.04%, p < 0.01), a funnel plot was drawn to assess publication bias (Supplementary Figure 1f).

Discussion

The present study investigates the GI involvement in COVID-19 patients, estimating a pooled prevalence of 11.51% of infected patients. The most frequent of GI manifestations was diarrhea (7.78%), followed by nausea/vomiting (3.57%), poor appetite (2.39%) and abdominal pain/discomfort (0.78%).

Supplementary Table 1. — **Qualitative analysis of the studies: demographics and clinical presentation**

First author	Type of study	Nation (City, Province)	Patients, n	Gender (male), n (%)	Age [years; mean (range)]	Asymptomatic, n (%)	GI symptoms, n (%)	Type of GI symptoms, n (%)	COVID-19 + fecal specimen, n (%)
Gautret P.	Ongoing single-arm trial (preliminary results)	France (Marseille, Nice, Avignon, Briançon)	36	15 (41.7)	Not reported	6 (16.7)	0 (0)	-	Not reported
Spiteri G.	Retrospective, multicenter	Europe	31	25 (80.7)	Not reported	2 (6.4)	≥ 1 (3.2) [a]	Diarrhea (1), nausea (1)	Not reported
Australian Report	Epidemiology Report 7	Australia	295 [b]	Not reported	- (0-94)	139 (47.1)	≥ 48 (16.3) [a]	Diarrhea (48), nausea/vomiting (34), abdominal pain (6)	Not reported
Guan W.J. [c]	Retrospective, multicenter	China	1099 [b]	637 (57.9)	47	Not reported	≥ 55 (5.0) [a]	Nausea/vomiting (55), diarrhea (42)	Not reported
Wu Z. [c]	Retrospective, multicenter	China	72314	Not reported	Not reported	889 (1.2)	Not reported	-	Not reported
Wang Y.	Retrospective, unicenter	China (Shenzhen, Guangdong)	55 [b]	22 (40.0)	- (2-69)	16 (29.1)	Not reported	-	Not reported
Xu X.	Retrospective, unicenter	China (Guangzhou, Guangdong)	90	39 (43.3)	- (18-86)	Not reported	≥ 5 (5.5) [a]	Diarrhea (5), nausea (5), vomiting (2)	Not reported
Deng L.	Retrospective, unicenter	China (Zhuhai, Guangdong)	33	17 (51.5)	44.5	Not reported	Not reported	-	18 (54.5)
Xiao F.	Retrospective (?), unicenter	China (Zhuhai, Guangdong)	73 [b]	41 (56.2)	43 (1-78)	Not reported	≥ 26 (35.6) [a]	Diarrhea (26), GI bleeding (10)	39 (53.4)
Wu Y.	Retrospective (?), unicenter	China (Zhuhai, Guangdong)	74	39 (52.7)	Not reported	Not reported	33 (44.6)	Not reported	41 (56.2)
Chung M. [c]	Retrospective, multicenter	China (Zhuhai, Guangdong; Nanchang, Jiangxi; Qingdao, Shandong)	21	13 (61.9)	51 (29-77)	Not reported	1 (4.7)	Nausea	Not reported
Liu Y	Retrospective, unicenter	China (Nanchang, Jiangxi)	76	48 (63.1)	Not reported	Not reported	≥ 2 (2.6) [a]	Diarrhea (2), vomiting (2)	Not reported
Wang W. [c]	Retrospective, multicenter	China (Hubei; Shandong; Beijing)	205 [b]	Not reported	44 (5-67)	Not reported	Not reported	-	44/153 (28.7)
Qin C.	Retrospective, unicenter	China (Wuhan, Hubei)	452	235 (52.0)	58 (22-95)	Not reported	≥ 122 (26.7) [a]	Diarrhea (122), poor appetite (96), nausea/vomiting (42), abdominal pain (23)	Not reported
Li Y.	Retrospective, unicenter	China (Wuhan, Hubei)	54	24 (44.4)	Not reported	Not reported	≥ 11 (20.4) [a]	Diarrhea (7), nausea/vomiting (11)	Not reported
Zhou S.	Retrospective, unicenter	China (Wuhan, Hubei)	62	39 (62.9)	52.8 (30-77)	0 (0)	9 (14.5)	Abdominal pain/diarrhea	Not reported
Liu M.	Retrospective, unicenter	China (Wuhan, Hubei)	30	10 (33.3)	Not reported	Not reported	9 (30.0)	Not reported	Not reported
Wang Y.	Prospective, unicenter	China (Wuhan, Hubei)	90	33 (36.7)	45	Not reported	≥ 6 (6.7) [a]	Diarrhea (6), poor appetite (6), abdominal pain (2)	Not reported
Zhang J.J.	Retrospective, unicenter	China (Wuhan, Hubei)	140	71 (50.7)	57 (25-87)	Not reported	55/139 (39.6)	Nausea (24), diarrhea (18), vomiting (7), poor appetite (17), abdominal pain (8)	Not reported

He X.W.	Retrospective, unicenter	China (Wuhan, Hubei)	54	34 (62.9)	68	0 (0)	2 (3.7)	Diarrhea	Not reported
Chen L.	Retrospective, unicenter	China (Wuhan, Hubei)	29	21 (72.4)	56 (26-79)	0 (0)	4 (13.8)	Diarrhea	Not reported
Wang D.	Retrospective, unicenter	China (Wuhan, Hubei)	138	75 (54.3)	56 (42-68)	Not reported	≥ 14 (10.1)[a]	Diarrhea (14), nausea (14), vomiting (5), abdominal pain (3)	Not reported
Liu W.	Retrospective (?), unicenter	China (Wuhan, Hubei)	78	39 (50.0)	38 (33-57)	0 (0)	0 (0)	-	Not reported
Xiong Y.	Retrospective, unicenter	China (Wuhan, Hubei)	42	25 (59.5)	49.5 (26-75)	Not reported	10 (23.8)	Diarrhea	Not reported
Yuan M.	Retrospective, unicenter	China (Wuhan, Hubei)	27	12 (44.4)	60	Not reported	0 (0)	-	Not reported
Zhou F.	**Retrospective, multicenter**	**China (Wuhan, Hubei)**	**191**	**119 (62.3)**	**56**	**Not reported**	**≥ 7 (3.6)[a]**	**Diarrhea (5), nausea/ vomiting (7)**	**Not reported**
Peng Y.D.	Retrospective, unicenter	China (Wuhan, Hubei)	112	53 (47.3)	62	Not reported	15 (13.4)	Diarrhea	Not reported
Luo S.	**Retrospective, unicenter**	**China (Wuhan, Hubei)**	**1141**	**Not reported**	**Not reported**	**Not reported**	**183 (16.0)**	**Nausea (134), vomiting (119), abdominal pain (45), diarrhea (68), poor appetite (180)**	**Not reported**
Huang C.	Prospective, unicenter	China (Wuhan, Hubei)	41	30 (73.2)	49 (41-58)	Not reported	1/38 (2.6)	Diarrhea	Not reported
Wang Z.	Retrospective, unicenter	China (Wuhan, Hubei)	69	32 (46.4)	Not reported	Not reported	≥ 10 (14.5)[a]	Diarrhea (10), vomiting (3), poor appetite (7)	Not reported
Shi H.	Retrospective, multicenter	China (Wuhan, Hubei)	81	42 (51.8)	Not reported	Not reported	≥ 4 (4.9)[a]	Vomiting (4), poor appetite (1), diarrhea (3)	Not reported
Han R.	**Retrospective, unicenter**	**China (Wuhan, Hubei)**	**108**	**38 (35.2)**	**45 (21-90)**	**Not reported**	**15 (13.9)**	**Diarrhea**	**Not reported**
Liu K.	Retrospective, multicenter	China (Hubei)	137	61 (44.5)	55 (20-83)	Not reported	11 (8.0)	Diarrhea	Not reported
Yang X.	Retrospective, unicenter	China (Wuhan, Hubei)	52	35 (67.3)	Not reported	Not reported	≥ 2 (3.8)[a]	Vomiting (2), GI bleeding (2)	Not reported
Zhou Z.	Retrospective, unicenter	China (Wuhan, Hubei)	254[b]	115 (45.3)	50.6 (15-87)	Not reported	66 (26.0)	Abdominal pain (3), vomiting (15), diarrhea (46), nausea (21)	Not reported
Huang Y.	Retrospective, unicenter	China (Wuhan, Hubei)	34	14 (41.2)	56.24	Not reported	5 (14.7)	Diarrhea	
Mo P.	Retrospective, unicenter	China (Wuhan, Hubei)	155	86 (55.5)	Not reported	Not reported	7 (4.5)	Diarrhea (7), abdominal pain (3), nausea (3), vomiting (3)	Not reported
Chen N.S.	Retrospective, unicenter	China (Wuhan, Hubei)	99	67 (67.7)	55.5 (21-82)	Not reported	≥ 2 (2.0)[a]	Diarrhea (2), nausea (1), vomiting (1)	Not reported
Zhang X.	**Retrospective, unicenter**	**China (Hangzhou, Zhejiang)**	**573**	**295 (51.5)**	**Not reported**	**Not reported**	**≥ 45 (7.9)[a]**	**Diarrhea (45), nausea/ vomiting (22)**	**Not reported**
Xu X.W.	Retrospective, multicenter	China (Zhejiang)	62	35 (56.4)	Not reported	Not reported	3 (4.9)	Diarrhea	Not reported

Yang W.[c]	Retrospective, multicenter	China (Zhejiang)	149	81 (54.4)	45.1	Not reported	≥ 11 (7.4)[a]	Diarrhea (11), nausea (2), vomiting (2)	Not reported
Qian G.Q.	Retrospective, multicenter	China (Zhejiang)	91	37 (40.7)	Not reported	Not reported	≥ 23 (25.3)[a]	Poor appetite (23), diarrhea (21), nausea (11), vomiting (6)	Not reported
Chen J.	Retrospective, unicenter	China (Shangai)	249	126 (50.6)	Not reported	7 (2.8)	≥ 8 (3.2)[a]	Diarrhea (8), poor appetite (8)	Not reported
Song F.	Retrospective, unicenter	China (Shangai)	51	25 (49.0)	49	Not reported	≥ 9 (17.6)[a]	Poor appetite (9), diarrhea (5), nausea/vomiting (3)	Not reported
Fan Z.	Retrospective, unicenter	China (Shangai)	148[b]	75 (50.7)	50 (15-88)	5 (3.4)	≥ 6 (4.0)[a]	Diarrhea (6), nausea (3), vomiting (3)	Not reported
Zhao W.	Retrospective, multicenter	China (Changsha, Hunan)	101[b]	56 (55.4)	44.4 (17-75)	2 (1.9)	≥ 3 (2.9)[a]	Diarrhea (3), nausea/vomiting (2)	Not reported
Tian S.	Retrospective, multicenter	China (Beijing)	262[b]	127 (48.5)	47.5 (1-94)	13 (4.9)	0 (0)	-	Not reported
Xu, Y.H.	Retrospective, unicenter	China (Beijing)	50[b]	29 (58.0)	- (3-85)	Not reported	1 (2.0)	Discomfort	Not reported
Wu J.	Retrospective, multicenter	China (Chongqing)	80	42 (52.5)	44	Not reported	7 (8.7)	Abdominal pain/diarrhea	Not reported
Wan S.	Retrospective, unicenter	China (Chongqing)	135	72 (53.3)	47	Not reported	≥ 18 (13.3)[a]	Diarrhea (18), poor appetite (6)	Not reported
Li K.	Retrospective, multicenter	China (Chongqing; Shandong)	83	44 (53.0)	45.5	0 (0)	7 (8.4)	Abdominal pain/diarrhea	Not reported
Wu J.	Retrospective, multicenter	China (Jiangsu)	80[b]	39 (48.7)	46.1	Not reported	≥ 1 (1.2)[a]	Diarrhea (1), nausea/vomiting (1)	Not reported
Xu T.	Retrospective, unicenter	China (Changzhou, Jiangsu)	51	25 (49.0)	Not reported	Not reported	5 (9.8)	Diarrhea	Not reported
Hu Z.	Retrospective, unicenter	China (Nanjing)	27	9 (33.3)	Not reported	19 (70.4)	1 (3.7)	Vomiting	Not reported
Liu K.	Retrospective, unicenter	China (Hainan)	56	31 (55.3)	Not reported	Not reported	10 (17.8)	Vomiting	Not reported
Liu K.	Randomized controlled trial	China (Haikou, Hainan)	51	28 (54.9)	Not reported	5 (9.8)	5 (9.8)	Diarrhea	Not reported
Liu K.C.	Retrospective, multicenter	China (Anhui)	73[b]	41 (56.2)	- (5-86)	3 (4.1)	20 (27.4)	Poor appetite	Not reported
Zheng M.	Retrospective (?), multicenter	China (Anhui)	68	36 (52.9)	- (11-84)	Not reported	3 (4.4)	Diarrhea	Not reported
Zhu W.	Retrospective, multicenter	China (Hefei, Anhui)	32	15 (46.9)	Not reported	Not reported	1 (3.1)	Diarrhea	Not reported
Wang L.	Retrospective, unicenter	China (Zhengzhou, Henan)	18[b]	10 (55.6)	39	Not reported	≥ 3 (16.7)[a]	Diarrhea (16.7%), nausea and vomiting (5.6%)	Not reported

References in bold have been also included in meta-analyses. [a] Total number of patients with GI. symptoms not indicated in the publication. [b] Including children and/or pregnant patients Supplementary Table 1. Qualitative analysis of the studies: demographics and clinical presentation. [c] Involving multiple Chinese Provinces. GI : gastrointestinal; COVID-19: 2019 novel coronavirus disease.

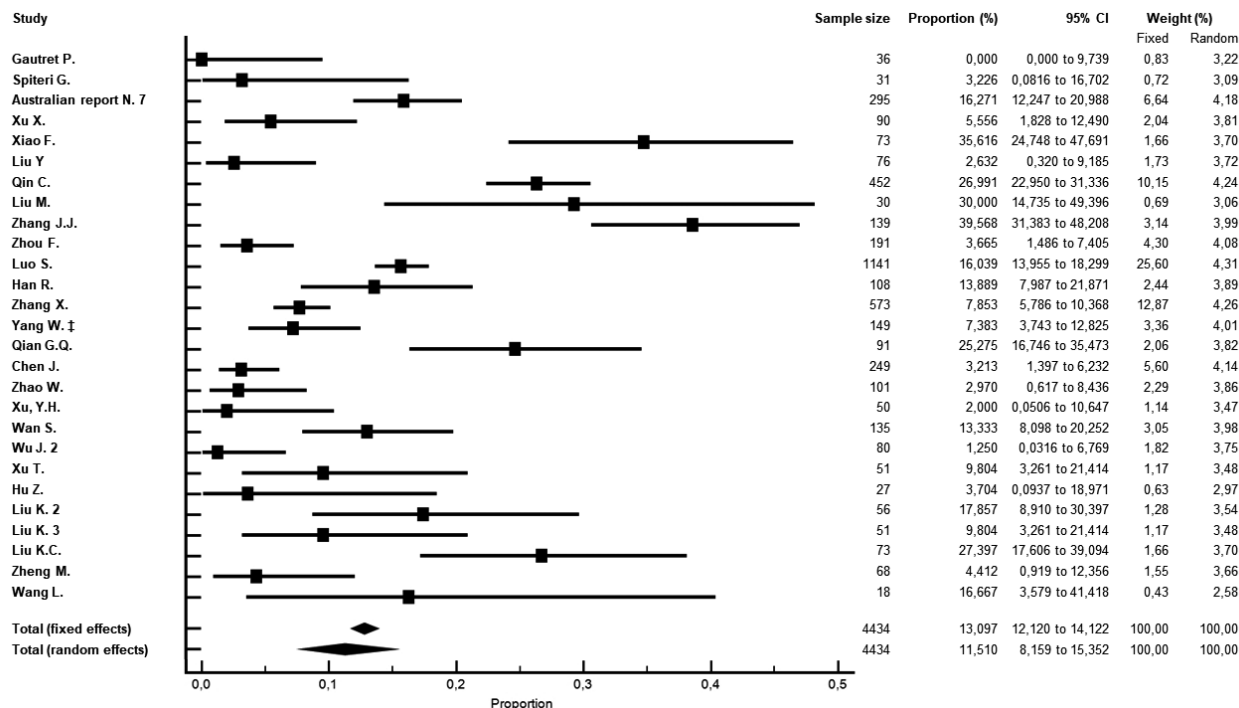| Study	Sample size	Proportion (%)	95% CI	Weight (%) Fixed	Weight (%) Random
Gautret P.	36	0,000	0,000 to 9,739	0,83	3,22
Spiteri G.	31	3,226	0,0816 to 16,702	0,72	3,09
Australian report N. 7	295	16,271	12,247 to 20,988	6,64	4,18
Xu X.	90	5,556	1,828 to 12,490	2,04	3,81
Xiao F.	73	35,616	24,748 to 47,691	1,66	3,70
Liu Y	76	2,632	0,320 to 9,185	1,73	3,72
Qin C.	452	26,991	22,950 to 31,336	10,15	4,24
Liu M.	30	30,000	14,735 to 49,396	0,69	3,06
Zhang J.J.	139	39,568	31,383 to 48,208	3,14	3,99
Zhou F.	191	3,665	1,486 to 7,405	4,30	4,08
Luo S.	1141	16,039	13,955 to 18,299	25,60	4,31
Han R.	108	13,889	7,987 to 21,871	2,44	3,89
Zhang X.	573	7,853	5,786 to 10,368	12,87	4,26
Yang W. ‡	149	7,383	3,743 to 12,825	3,36	4,01
Qian G.Q.	91	25,275	16,746 to 35,473	2,06	3,82
Chen J.	249	3,213	1,397 to 6,232	5,60	4,14
Zhao W.	101	2,970	0,617 to 8,436	2,29	3,86
Xu, Y.H.	50	2,000	0,0506 to 10,647	1,14	3,47
Wan S.	135	13,333	8,098 to 20,252	3,05	3,98
Wu J. 2	80	1,250	0,0316 to 6,769	1,82	3,75
Xu T.	51	9,804	3,261 to 21,414	1,17	3,48
Hu Z.	27	3,704	0,0937 to 18,971	0,63	2,97
Liu K. 2	56	17,857	8,910 to 30,397	1,28	3,54
Liu K. 3	51	9,804	3,261 to 21,414	1,17	3,48
Liu K.C.	73	27,397	17,606 to 39,094	1,66	3,70
Zheng M.	68	4,412	0,919 to 12,356	1,55	3,66
Wang L.	18	16,667	3,579 to 41,418	0,43	2,58
Total (fixed effects)	4434	13,097	12,120 to 14,122	100,00	100,00
Total (random effects)	4434	11,510	8,159 to 15,352	100,00	100,00

Figure 2. — Forest plot of GI symptoms in COVID-19.

The involvement of GI system during COVID-19 must be taken in consideration. In fact, GI symptoms might increase the rate of early diagnoses, indicating additional patients to be screened for this viral infection. Furthermore, fecal-oral transmission is another possible route of viral spread, and must be considered as well.

Our meta-analysis showed positive stool samples for COVID-19 in 41.50% of cases (Figure 4). Viral shedding in feces was described by Wu Y. (5) as independent from the presence of GI symptoms, and lasting for nearly 5 weeks after the patients' respiratory samples tested negative for COVID-19. This information must not be forgotten in hospitals, in particular in endoscopy service, where International Societies recommend strategies to reduce the risk of infection for patients and for healthcare professionals. These recommendations include en-hanced disinfection policy for endoscopy rooms and reprocessing of instruments, as well as wearing adequate personal protective equipment (PPE) also during lower endoscopies (41,42).

Our results also prove that 11.85% of COVID-19 patients remain asymptomatic. This data is important, as it means that about 1:10 infected persons may be unidentified, and continue to spread the virus. This result explains why policies of screening for the general population are being debated worldwide at the moment.

If we compare our results with a recently published paper (43), Cheung K.S. included 60 studies and 4243 patients in meta-analysis, reporting a rate of 17.6% GI symptoms during COVID-19. We suppose that this overestimation might be due to duplication of patients' data. Bauchner H. (44) have suggested this problem as a potential source of inaccurate scientific record, affecting the accuracy of estimates of prevalence of the disease or outcomes, as well as of meta-analyses. In order to limit this bias, we have performed a careful check of all the hospitals involved in the analyzed Chinese studies, and when data derived from the same institution we only considered the paper with the largest population and/or with more details about GI symptoms. For the same reason, differently from Cheung K.S. (43), we excluded data from Guan W.J. (2), derived from 552 hospitals across China, and we excluded case series/reports. These main methodological differences explain why, although our search was more updated (25th March vs. 11th March), we included in the meta-analysis only 27 out of 56 evaluated studies.

The same strict selection criteria were adopted considering the COVID-19 positivity in fecal samples, and this explains the different number of included studies and different results in comparison to Cheung K.S. (43).

Although the adopted selection criteria, high hetero-geneity was observed in all of our meta-analyses, and our attempt to perform a sensitivity analysis could not reduce it. Heterogeneity might be due to several reasons. We consider as the major responsible the different study designs of analyzed publications, together with the limited quality of included studies (Supplementary Table 1). The application of MINORS score (7) to assess risk of bias have not been feasible for some papers reporting epidemiological data. Furthermore, the validity of meta-analysis increases when only randomized controlled trials (RCTs) are included, but in some situations RCTs are few. As most of the available clinical data about COVID-19 patients are offered by observational studies, this limit is hard to be overcome at the moment.
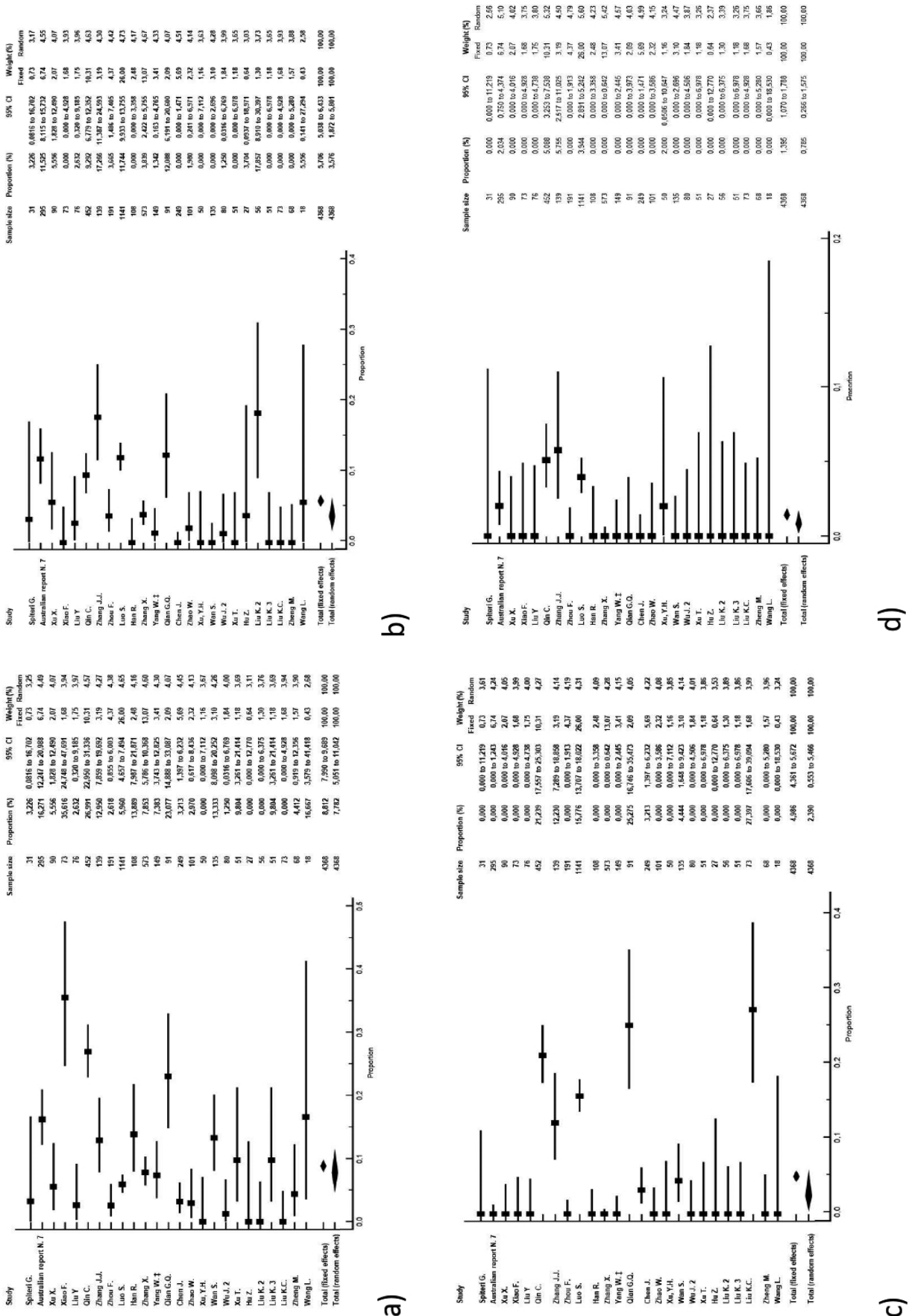
Figure 3. — Forest plot according to type of GI symptoms in COVID-19 Outcomes : a) diarrhea ; b) nausea/vomiting ; c) poor appetite ; d) abdominal pain/discomfort.

Supplementary Table 2. — **Quality evaluation according to MINORS criteria**

First author	1	2	3	4	5	6	7	8	9	10	11	12	Score
Gautret P.	2	1	2	2	0	1	2	2	0	2	1	2	17
Spiteri G.	-	-	-	-	-	-	-	-	-	-	-	-	NA
Australian Report	-	-	-	-	-	-	-	-	-	-	-	-	NA
Guan W.J.	2	2	1	2	2	2	2	0					13
Wu Z.	-	-	-	-	-	-	-	-	-	-	-	-	NA
Wang Y.	2	2	1	2	2	2	2	0					13
Xu X.	2	1	1	2	1	2	1	0					10
Deng L.	2	2	1	2	0	2	2	0	0	1	2	2	16
Xiao F.	2	1	0	2	0	2	2	0					9
Wu Y.	2	1	0	2	0	2	2	0					9
Chung M.	2	2	1	2	2	2	2	0					13
Liu Y	2	0	1	2	0	2	2	0					9
Wang W.	2	0	1	2	0	2	2	0					9
Qin C.	2	2	1	2	0	2	2	0					11
Li Y.	2	2	1	2	0	2	2	0					11
Zhou S.	2	1	1	2	1	2	2	0					11
Liu M.	2	2	1	2	0	2	2	0					11
Wang Y	2	2	2	2	2	2	2	0					14
Zhang J.J.	2	2	1	2	2	2	2	0					13
He X.W.	2	0	1	2	0	2	2	0					9
Chen L.	2	0	1	2	0	2	2	0					9
Wang D.	2	2	1	2	2	2	2	0					13
Liu W.	2	2	0	2	1	2	2	0					11
Xiong Y.	2	1	1	2	2	2	2	0					12
Yuan M.	2	2	1	2	2	2	2	0					13
Zhou F.	2	1	1	2	2	2	2	0					12
Peng Y.D.	2	2	1	2	0	2	2	0					11
Luo S.	2	2	1	2	0	2	2	0					11
Huang C.	2	2	2	2	2	2	2	0					14
Wang Z.	2	2	1	2	2	2	2	0					13
Shi H.	2	1	1	2	2	2	2	0					12
Han R.	2	1	1	2	1	2	2	0					11
Liu K.	2	1	1	2	1	2	2	0					11
Yang X.	2	1	1	2	1	2	2	0					11
Zhou Z.	2	1	1	2	2	2	2	0					12
Huang Y.	2	1	1	2	1	2	2	0					11
Mo P.	2	2	1	2	1	2	2	0					12
Chen N.S.	2	1	1	2	1	2	2	0					11
Zhang X.	2	2	1	2	2	2	2	0					13
Xu X.W.	2	2	1	2	1	2	2	0					12
Yang W.	2	2	1	2	2	2	2	0					13
Qian G.Q.	2	1	1	2	1	2	2	0					11
Chen J.	2	1	1	2	1	2	2	0					11
Song F.	2	1	1	2	2	2	2	0					12
Fan Z.	2	2	1	2	1	2	2	0					12
Zhao W.	2	1	1	2	2	2	2	0					12
Tian S.	2	1	1	2	2	2	2	0					12
Xu, Y.H.	2	1	1	2	1	2	2	0					11
Wu J.	2	2	1	2	1	2	2	0					12
Wan S.	2	1	1	2	1	2	2	0					11
Li K.	2	2	1	2	2	2	2	0					13
Wu J	2	2	1	2	1	2	2	0					12
Xu T.	2	1	1	2	0	2	2	0					10
Hu Z.	2	0	1	2	0	2	2	0					9
Liu K.	2	1	1	2	0	2	2	0					10
Liu K.	2	2	2	2	0	2	2	0	1	2	2	2	19
Liu K.C.	2	1	1	2	2	2	2	0					12
Zheng M.	2	1	0	2	0	2	2	0					9
Zhu W.	2	2	1	2	2	2	2	0					13
Wang L.	2	1	1	2	0	2	2	0					10

References in bold have been also included in meta-analyses. NA : not applicable.

Study	Sample size	Proportion (%)	95% CI	Weight (%) Fixed	Weight (%) Random	
Wu Y.	74	55,405	43,389 to 66,975	32,75	48,84	
Wang W. ‡	153	28,758	21,737 to 36,623	67,25	51,16	
Total (fixed effects)	227	37,241	30,963 to 43,854	100,00	100,00	
Total (random effects)	227	41,505	17,699 to 67,656	100,00	100,00	
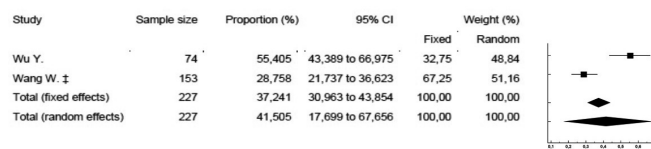
Figure 4. — Forest plot of positive fecal samples for COVID-19.

Study	Sample size	Proportion (%)	95% CI	Weight (%) Fixed	Weight (%) Random
Gautret P.	36	16,667	6,372 to 32,812	2,77	8,06
Spiteri G.	31	6,452	0,791 to 21,422	2,39	7,96
Australian report N. 7	295	47,119	41,307 to 52,989	22,14	8,66
Wang Y.	55	29,091	17,630 to 42,898	4,19	8,28
Zhou S.	62	0,000	0,000 to 5,776	4,71	8,33
Chen J.	249	2,811	1,138 to 5,706	18,70	8,64
Zhao W.	101	1,980	0,241 to 6,971	7,63	8,49
Tian S.	262	4,962	2,668 to 8,335	19,67	8,65
Li K.	83	0,000	0,000 to 4,347	6,28	8,43
Hu Z.	27	70,370	49,819 to 86,247	2,09	7,86
Liu K. 3	51	9,804	3,261 to 21,414	3,89	8,25
Liu K.C.	73	4,110	0,856 to 11,544	5,53	8,39
Total (fixed effects)	1325	11,870	10,184 to 13,726	100,00	100,00
Total (random effects)	1325	11,855	3,529 to 24,175	100,00	100,00

Figure 5 — Forest plot of asymptomatic COVID-19 patients.

Another limitation of the present meta-analysis is the inclusion of studies published before march 2020, offering a snapshot only of the first part of the pandemic disease. However, if we compare our results to more updated meta-analyses about the same topic, the pooled prevalence is not significantly different from our results, and ranges from 9% to 15% (45, 46). Furthermore, everyday many papers about COVID-19 are being published, making the chance to offer a complete overview of this disease impossible.

In conclusion, the present updated meta-analysis confirms that GI symptoms are present in a significant proportion of COVID-19-patients, and that fecal-oral transmission must be considered as a potential route of transmission. For this reason, adequate PPE must be available in all endoscopy services in order to limit the risk of infection among patients and healthcare professionals. Asymptomatic patients account for 11.70% of infected cases, and represent a significant source of further viral transmission. These results need to be updated when prospective studies will be available, in order to offer a complete overview of this topic.

Conflicts of interest

Authors have no conflicts of interest to declare.

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