Journal of Biostatistics and Epidemiology

J Biostat Epidemiol. 2021;7(4):321-343

Review Article

Gastrointestinal Manifestations of the COVID-19: A Systematic Review and Meta-Analysis with 111 studies

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ARTICLE INFO

Received 17.06.2021
Revised 28.08.2021
Accepted 13.10.2021
Published 15.12.2021

Key words:
COVID-19;
SARS-CoV-2;
Gastrointestinal Tract;
Systematic Review;
Meta-Analysis.

ABSTRACT

Introduction: Since the start of a pandemic from Wuhan, China in 2019, there is tremendous attention on the COVID-19 manifestation. One of the most important COVID-19 clinical presentations is gastrointestinal symptoms. The current systematic review study aims to focus on the implication of the gastrointestinal tract in patients infected with SARS-CoV-2.

Methods: We searched literature in MEDLINE, Scopus, Web of Science, and Embase to find related article by using the following keywords "COVID-19", "SARS-CoV-2 infection", "Gastrointestinal Tract", "digestive system". The heterogeneity of included studies was quantified with the I^2 statistic. A random-effects model was used to estimate the pooled prevalence and a meta-regression method was utilized to investigate the factors affecting heterogeneity between studies.

Results: Of 3028 retrieved documents, 111 studies with 21126 COVID-19 cases were included. The prevalence of any Gastrointestinal symptoms was 17.22% (14.48 to 20.13). The prevalence of diarrhea was 13.75% (12.07 to 15.44), anorexia 27.41% (21.53 to 33.29) and Nausea/vomiting 8.11% (6.87 to 9.35). Furthermore, the prevalence of other symptoms in current study was fever 76.70% (73.42 to 79.83), cough 58.07% (54.59 to 61.52) and dyspnea/shortness of breath 24.63% (20.06 to 29.48). According to meta-regression results, age (p: 0.027) and fever (p<0.001) had significant effect on prevalence of any Gastrointestinal symptoms.

Conclusion: The anorexia, diarrhea, nausea, and vomiting are the most common Gastrointestinal presentations.

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Introduction

The coronaviruses (CoVs) belong to the order Nidovirales, coronaviridae family. CoVs are a great group of viruses with positive-sense stranded RNA that contain a large genome size in length and enveloped virions. The viral genome is protected inside the nucleocapsid.[1] These viruses often lead to respiratory and infections in animals and humans.[2,3]

The 21-century is faced with the new member of coronaviruses that cause severe viral pneumonia in humans and named SARS-CoV-2 and the disease named COVID-19 in December 2019.[4] From mid-December 2019, SARS-CoV-2, a beta-coronavirus that originated from Wuhan, China, which about 80% similarity to the SARS-CoV in 2002(5). Other Human coronaviruses such as HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 are the low-risk and the reason for some common colds.[6-8] COVID-19 detection is confirmed by chest computed tomography (CT) and real-time Reverse transcription-polymerase Chain Reaction (RT-PCR). The SARS-CoV-2 has highly potential infectious that can survive in the environment for hours. However, all age groups of people prone to infection by SARS-CoV-2, but elderly people or those with underlying medical comorbidities are at higher risk. The average age of COVID-19 patients has determined to be in the 5th decade of life.[9, 10] The incubation period in most cases ranges from 2 to 14 days with a median of 5-6 days, it is may even as long as 24 days.[11] Although the outbreak is initiate from the zoonotic transmission but, the respiratory droplets and direct contact are considered as human to human transmission of SARS-CoV-2. However, the fecal-oral route is another transmission mode that can spread of viruses.[12, 13] The most common symptoms of COVID19 are fever, cough, fatigue, myalgia, shortness of breath, and dyspnea. Gastrointestinal (GI) symptoms such as anorexia, vomiting, diarrhea, and abdominal pain have also been observed in some cases.[14,15]

Apart from gastrointestinal symptoms, COVID19 patients show signs of liver injury with an abnormal level of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and elevated bilirubin levels in the blood test .[16,17] It should be noted that medication used for treat and management of COVID19 such as chloroquine or Lopinavir-Ritonavir may have an adverse effect on Gastrointestinal tract and liver dysfunction.[18]

studies show that SARS-CoV-2 RNA can be detected in anal or rectal swab and stool specimens of COVID19 patients, for this reason, more attention has been paid to the Gastrointestinal tract by SARS-CoV-2.[19, 20] The goal of present study is implement a systematic review and meta-analysis to estimation of the gastrointestinal manifestations prevlance in COVID-19 patients.

Materials and Methods

Search strategy for literature review

All steps in this systematic review and meta-analysis study were registered in the International Prospective Register of Systemic Reviews with CRD42021236766 code and the results were reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guideline. After consulting a professional librarian, a complete and comprehensive search without any language and time restrictions was conducted

in international data bases, including Pubmed, Scopus, Web Of Science and Embase to identify the articles on SARS-COV2- Related Gastrointestinal symptoms prevalence. Other sites including medrxiv, social science research network, were also searched to identify the unofficially published researches. To conduct the search, the text words and MESH Terms of SARS-COV2 and Gastrointestinal symptoms were used. The PICO in our study was:
Population: Covid 19 patient
Intervention: -
Comparison: -
Outcome: digestive disorder syndrome/sign

Detailed search strategy is mentioned in Box1 that developed based on MEDLINE and then used in other databases. Additionally, the Google Scholar was used to access gray literature in addition a COVID-19 expert was consulted to identify important articles. Then, all studies were imported to endnote X6, and after removing the duplicated articles, the remaining studies has been screened in three steps. In the first step, the titles were reviewed, and as step 2, if the article was relevant, the abstract and in step 3, the full text of the article was reviewed. The three steps were followed independently by two raters (RR, SS) and discrepancies were resolved based on the third person's opinion (IP). Blinding and task separation were applied in study procedure selection.

Box 1. search strategy based on PICO for MEDLINE (MeSH, Medical Subject Headings)

1. Covid-19 [text word] OR Covid-19 [Mesh term]
2. Coronavirus [text word] OR Coronavirus [Mesh term]
3. SARS-CoV-2 infection [text word] OR SARS-CoV-2 infection [Mesh term]
4. 1 OR 2 OR 3
5. Feature [text word] OR Feature [Mesh term]
6. manifestation [text word] OR manifestation [Mesh term]
7. characteristic [text word] OR characteristic [Mesh term]
8. Symptoms [text word] OR Symptoms [Mesh term]
9. Sign [text word] OR Sign [Mesh term]
10. 5 OR 6 OR 7 OR 8 OR 9
11. Gastrointestinal [text word] OR Gastrointestinal [Mesh term]
12. Gastrointestinal Tract [text word] OR Gastrointestinal Tract [Mesh term]
13. digestive system [text word] OR digestive system [Mesh term]
14. 11 OR 12 OR 13 OR 14
15: 4 AND 10 AND 14

Eligibility Criteria

The observational study such as cross-sectional, case series and cohort studies have criteria to include in present study. The Case reports and case series with less than 5 sample size were excluded.

Data Extraction and Quality Assessment

In all studies in addition to related COVID-19 symptoms including fever shortness of breath dyspnea, dyspnea cough and related-gastrointestinal symptoms (such as nausea/ vomiting, diarrhea, anorexia abdominal pain), name of authors, year, country, study design, sample size and age were extracted. In present study any Gastrointestinal symptom was considered for covid-19 patient with any single of Gastrointestinal symptoms.

Quality assessment

The Newcastle-Ottawa Scale (NOS) for cross-sectional studies was used for assessing the quality of included studies.[21] This scale has three sections: 1-selection (3 items, maximum score: 5 points), 2-comparability (1 item, maximum score: 2 points), and 3-outcome (2 items, maximum score: 3 points). The studies were evaluated by two raters (RP and MKH) independently, and a total score was calculated for each study. The studies were then assigned to one of the following categories accordingly: very good studies: 7-8 scores; good studies: 5-6 scores; satisfactory studies: 3-2 scores; unsatisfactory studies: 0-1 score.[22]

Statistical Analysis

All analysis was conducted with STATA software 14.0 (college station, texas). As previous suggestion,[23-25] the number of cases, the prevalence of gastrointestinal symptoms in COVID-19 and its different types were extracted. Heterogeneity was determined using Cochran's Q test of heterogeneity and the I^2 index was used to quantify heterogeneity. In accordance with Higgins classification approach, I^2 values above 0.7 were considered as high heterogeneity. The pooled prevalence was calculated using "metaprop" command and to estimate the pooled prevalence we used random-effects model. The meta-regression analysis was used to examine the effect of age, gender, sample size, publication date, study quality, and geographical area as factors affecting heterogeneity among the studies. The metabias command was used to check the publication bias, and if there was any publication bias, the prevalence rate was adjusted with the metatrim command using trim-and-fill method. In all analysis significance level was considered as 0.05.

Results

From 3028 articles found in the initial search, 1450 remained after removing duplications. Then 931 by the title, 202 by the abstract and 206 were removed by full text. At last 111 articles with 21126 sample size were analyzed. The flow chart of the study is shown in Figure 1 and details are shown in Table 1.

According to pooled prevalence (CI: 95%), prevalence of any Gastrointestinal symptoms was 17.22% (14.48 to 20.13) (Figure 2). The pooled prevalence of Gastrointestinal and Respiratory symptoms is shown in Figure3 and Table2. The most common reported symptom among all studies was diarrhea (was reported in 98 studies). The pooled prevalence of diarrhea was 13.75% (12.07 to 15.44). However; anorexia was the most common Gastrointestinal symptom with 27.41% (21.53 to 3.29). The pooled prevalence of Dysphagia and bloody stool were 18.15% (16.34 to 19.96) and 3.57% (1.22 to 9.98) and were only reported in 2 and 1 study, respectively. The 65 studies had reported Nausea/vomiting, corresponding to pooled prevalence of 8.11% (6.87 to 9.35). According to table 2, the pooled prevalence of fever, cough and dyspnea/shortness of breath was 76.70% (73.42 to 79.83), 58.07% (54.59 to 61.52) and 24.63% (20.06 to 29.48); respectively.

Heterogeneity and meta regression

According to table 2 and Cochran's Q-test of heterogeneity, heterogeneity was significant among all symptoms except dysphagia and blood stool (due to lesser data). Except for nausea/vomiting with I^2 equal to 55% and dysphagia with I^2 equal to 10%, for the other

Table 1. characteristic of studies in The Worldwide Prevalence of Gastrointestinal and clinical symptom in patient with COVID-19

First Author	Country	Year	Design	Mean Age [Range]	SS	Any Gastrointestinal symptoms	diarrhea	Nausea/vomiting	dysphagia	Abdominal pain/ discomfort	Blood stool	anorexia	Fever	cough	Dyspnea/ breath shortness	References
Zheng et al.	China	2020	Case Series	(3*)	25	3	3	2	---	2	---	-	13	11	2	(26)
Xu et al.	China	2020	Case Series	41*	62	3	3	---	---	---	---	-	48	50	2	(27)
Xiong et al.	China	2020	Case Series	6.33*	244	34	15	23	---	4	---	-	99	-	-	(28)
Sun et al.	China	2020	Case Series	47 (3-85)*	63	17	5	---	---	---	---	17	53	34	11	(29)
Ma et al.	China	2020	Case Series	7.3*	76	3	3	---	---	2	---	---	53	41	-	(30)
Kobayashi et al.	Japan	2020	Case Series	62 (40-80)	6	2	1	---	---	1	---	---	5	2	-	(31)
Klopfenstein et al.	France	2020	Case Series	56*	114	55	55	25	---	19	---	---	90	92	-	(32)
Cao et al.	China	2020	Cohort	54 (37-67)*	102	11	11	---	---	---	---	---	83	50	-	(33)
Chen et al.	China	2020	Case Series	62*	274	77	77	24	---	19	---	66	249	185	120	(34)
Kujawski et al.	USA	2020	Case Series	53 (21-68)*	12	1	1	1	---	---	---	---	7	8	1	(35)
Chen et al.	China	2020	Case Series	47.5	145	62	39	24	---	8	---	62	109	118	3	(36)
Du et al.	China	2020	Case Series	34.1 (0-65)*	67	8	2	3	---	---	---	8	37	32	3	(37)
Galván Casas et al.	Spain	2020	Case Series	42.26	234	107		---	---	---	---	---	280	259	171	(38)
Lian et al.	China	2020	Case Series	45 (5-88)*	465	36	36	22	---	---	---	---	399	312	22	(39)
Lin et al.	China	2020	Case Series	45.3±18.3	95	58	23	17	---	---	---	17	---	---	---	(40)
Liu et al.	China	2020	Case Series	48 ± 15 (15–80)	122	4	4	3	---	---	---		90	77	12	(41)
Wang et al.	China	2020	Case Series	71 (65–76)	339	94	43	13	---	---	---	94	311	179	138	(42)
Jin et al.	China	2020	Case Series	46.14±14.19	651	74	53	11	---	---	---	---	545	435	27	(43)
Kim et al.	Korea	2020	Cohort	40 (20–73)*	28	3	3	---	---	1	---	---	7	8	1	(44)
Lei et al.	China	2020	Case Series	47 (12-80)	14	3	3	---	---	---	---	---	7	7	---	(45)
Li et al.	China	2020	Case Series	47 ± 15 (20-90)	131	1	1	---	---	---	---	---	85	85	5	(46)
Liu et al.	China	2020	Case Series	57 (20-83)*	137	11	11	---	---	---	---	---	112	66	26	(47)
Meng et al.	China	2020	Case Series	56.7*	168	44	44	18	---	7	---	15	156	121	59	(48)
Shen et al.	China	2020	Case Series	8 (1-12)*	9	2	2	---	---	---	---	---	3	1	---	(49)
Sun et al.	China	2020	Case Series	48 (37-56)	337	12	12	---	---	---	---	---	206	111	---	(50)
Wang et al.	China	2020	Case Series	7.1 (1 -17)	31	3	3	2	---	---	---	---	20	14	---	(51)
Wang et al.	China	2020	Case Series	68.6 (53-82)	28	16	12	6	---	---	---	16	26	23	16	(52)
Du et al.	China	2020	Case Series	65.8*	85	16	16	4	---	3	---	48	78	19	60	(53)
Chen et al.	China	2020	Case Series	51 (42.75-62)*	42	8	7	4	---	5	---	---	36	22	9	(54)
Huang et al.	China	2020	Case Series	56.24 ± 17.14	34	5	5	---	---	---	---	---	32	17	5	(55)
Guan et al.	China	2020	Case Series	47	1099	55	42	55	---	---	---	---	473	745	205	(56)
Zhang et al.	China	2020	Case Series	73 (38–91)*	19	1	1	---	---	---	---	---	13	8	2	(57)
Chen et al.	USA	2020	Case-Control	48.32	101	75	51	30	---	26	---	54	66	75	---	(58)
Chang et al.	China	2020	Case Series	34 (34-48)*	13	1	1	---	---	---	---	---	---	6	---	(59)
Wan et al.	China	2020	Case Series	47(36-55)*	135	18	18	---	---	---	---	---	120	102	18	(60)
Lechien et al.	European countries	2020	Case Series	39.17	1420	437	473	272	274	270	---	---	645	897	697	(61)
Lo et al.	China	2020	Case Series	54 (27 – 64)*	10	8	8	5	---	2	---	---	8	5	5	(62)
Liu et al.	China	2020	Case Series	53.67(10-72)	12	2	2	2	---		---	---	10	11	---	(63)
Zhao et al.	China	2020	Case Series	46*	91	19	14	19	---	2	---	11	75	59	---	(64)
Wang et al.	China	2020	Case Series	51 (19–92)*	107	33	7	6	---	2	---	33	104	67	35	(65)
Garg et al.	USA	2020	Case Series	>=18	180	48	48	44	---	15	---	---	153	155	144	(66)
Li et al.	China	2020	Cohort	60 (48-69)*	548	179	179	45	---	16	---	---	476	415	310	(67)
Lian et al.	China	2020	Case Series	43.47±13.12	788	88	---	---	---	---	---	---	636	506	37	(68)
Sun et al.	Singapore	2020	Case-Control	42 (7–98)*	54	20	---	---	---	---	---	---	---	36	7	(69)
Wang et al.	China	2020	Case Series	44 (18-75)	66	3	3	3	---	---	---	---	60	37	14	(70)
Wang et al.	China	2020	Case Series	50 (16 - 89)*	1012	152	152	36	---	37	---	---	761	531	231	(71)

Wu et al.	China	2020	Case Series	46.10±15.42	80	1	1	1	---	---	---	---	63	51	30	(72)
Young et al.	Singapore	2020	Case Series	47(31-73)*	18	3	3	---	---	---	---	---	13	15	2	(73)
Zhang et al.	China	2020	Case Series	46.65 ± 13.82	645	53	53	22	---	---	---	---	540	425	26	(74)
Chen et al.	China	2020	Case Series	14.50 (9.25-15.75)*	12	4	4	---	---	---	---	---	7	9	---	(75)
Buscarini et al.	Italy	2020	Case Series	68.2±14.2	411	42	15	18	---	5	---	---	---	151	---	(76)
Dai et al.	China	2020	Case Series	44.6 ± 14.8	234	9	9	5	---	---	---	---	170	150	5	(77)
Huang et al.	China	2020	Case Series	41 (31–51)*	54	13	2	3	---	---	---	13	41	32	5	(78)
Huang et al.	China	2020	Case Series	44 (33.0-54.0)*	202	13	13	4	---	---	---	---	156	120	19	(79)
Lei et al.	China	2020	Case Series	43.2 (14.0)	20	5	5	3	---	---	---	---	16	11	2	(80)
Ma et al.	China	2020	Case Series	7.99*	115	3	---	---	---	---	---	---	29	47	---	(81)
Poggiali et al.	Italy	2020	Case Series	50± 18	10	10	6	3	---	1	---	---	9	---	4	(82)
Redd et al.	USA	2020	Case Series	63.4±16.6	318	195	107	84	1	46	---	110	258	247	191	(83)
Sun et al.	China	2020	Case Series	67 (64-72)*	244	81	72	---	---	10	---	---	211	179	---	(84)
Tan et al.	China	2020	Case Series	7 (1-12)	10	1	---	1	---	1	---	---	4	3	---	(85)
Tschopp et al.	Switzerland	2020	Cohort	56 (49-65)*	21	7	7	7	---		---	---	16	12	6	(86)
Chen et al.	China	2020	Case Series	70(65.81)*	50	12	---	---	---	---	---	---	37	25	28	(87)
Chen et al.	China	2020	Case Series	70 (65-81)*	38	1	1	---	---	---	---	---	25	16	23	(88)
Mo et al.	China	2020	Case Series	54 (42-66)*	155	26	7	3	---	3	---	26	126	97	50	(89)
Sun et al.	China	2020	Case Series	(2-15)	8	4	3	4	---		---	---	6	6	---	(90)
Tan et al.	China	2020	Case Series	(1-17)	13	4	2	1	---	1	---	---	6	6	---	(91)
Tomlins et al.	UK	2020	Cohort	59.82	95	13	11	13	---	5	---	---	68	70	41	(92)
Yin et al.	China	2020	Case Series	46 (31.5-65)*	33	5	5	---	---	---	---	---	23	13	6	(93)
Zheng et al.	China	2020	Case Series	49.40 ± 18.45	99	2	---	---	---	---	---	---	85	84	35	(94)
Zhao et al.	China	2020	Case Series	48 (27-56)*	19	1	1	---	---	---	---	---	15	9	---	(95)
Chen et al.	China	2020	Case Series	51 (36-64)*	249	8	8	---	---	---	---	---	217	91	19	(96)
Escalera-Antezana et al.	Bolivia	2020	Case Series	39 (25.3–43.4)*	12	2	2	1	---	2	---	---	9	9	---	(97)
Hajifathalian et al.	USA	2020	Cohort	61.1*	1059	234	234	168	---	72	---	240	717	682	625	(98)
Huang et al.	China	2020	Cohort	49 (41–58)*	41	1	1	---	---		---	---	40	31	22	(9)
Wang et al.	China	2020	Case Series	37 (25 – 88)*	35	9	9	3	---	---	---	---	30	19	---	(99)
Buenen et al.	Netherland	2020	Case Series	71 (27-94)*	107	36	36	---	---	14	---	---	83	---	---	(100)
Liang et al.	China	2020	Cohort	48.9±16.3	1590	80	57	80	---	---	---	---	1351	1052	331	(101)
Zhou et al.	China	2020	Case Series	50.6 (15–87)	254	66	46	21	---	3	---	---	213	98	10	(102)
Chen et al.	China	2020	Case Series	54 (20–91)*	203	10	10	3		4	---	6	181	122	59	(103)
Han et al.	China	2020	Case Series	45 (21-90)	108	15	15	---	---	---	---	---	94	65	---	(104)
Li et al.	China	2020	Case Series	52.8 ± 20.2	13	---	---	---	---	---	---	---	10	9	---	(105)
Lian et al.	China	2020	Case Series	55.28 ± 9.31	788	88	---	---	---	---	---	---	636	506	37	(106)
Pan et al.	China	2020	Case Series	52.9±16	204	103	35	4	---	2	---	---	95	---	---	(14)
Shekerdemian et al.	USA and Canada	2020	Cohort	13 (4.2-16.6)*	48	1	---	---	---	1	---	---	31	14	17	(107)
Sun et al.	China	2020	Case Series	45±16 (3 - 98)	150	20	2	1	---	---	---	20	142	108	15	(108)
Tang et al.	China	2020	Case-Control	67*	73	27	---	---	---	---	---	---	72	58	52	(109)
Wei et al.	China	2020	Case Series	37 (24-74)*	84	26	26	16	---	2	3	---	72	48	32	(110)
Yu et al.	China	2020	Case Series	64 (57–70)	226	7	---	---	---	---	---	---	45	---	---	(111)
Nicoletti et al.	Italy	2020	Case Series	6.2*	42	6	2	5	---	6	---	---	30	13	10	(112)
Aghemo et al.	Italy	2020	Case Series	65.0± 14.1	292	69	69	11	---	---	---	---	---	---	---	(113)
Cheng et al.	China	2020	Case Series	48.00 ± 11.38	30	2	2	1	---	---	---	---	23	20	1	(114)
Zhang et al.	China	2020	Case Series	48.3 (33-56)*	194	36	36	---	---	---	---	---	146	86	71	(115)
Hossain et al.	USA	2020	Case Series	65 ±16.1 (23-98)	119	60	---	---	---	---	---	---	41	46	---	(116)
Han et al.	China	2020	Case Series	62.5 (27–92)	206	117	67	24	---	9		102	138	53	30	(117)
Zheng et al.	China	2020	Case Series	21–76	73	1	1	---	---	---	---	---	62	16	---	(118)
Deng et al.	China	2020	Case Series	55 (33-74)*	225	33	33	---	---	---	---	---	189	85	99	(119)
Liu et al.	China	2020	Case Series	51.42	221	12	12	---	---	---	---	---	176	106	---	(120)
Liu et al.	China	2020	Case Series	53.95 ± 16.90	245	18	18	17	---	3	---	56	198	140	45	(121)

Chen et al.	China	2020	Case Series	55.5 (21-82)	99	2	2	1	---	---	---	---	82	81	31	(10)
Zhou et al.	China	2020	Case Series	66.10 ± 13.94	21	5	5	---	---	---	---	---	17	19	13	(122)
Zhang et al.	China	2020	Case Series	55.0 (39.0–66.5)*	221	80	25	---	---	5	---	80	200	136	64	(123)
Zhang et al.	China	2020	Case Series	57 (25-87)*	140	55	18	24	---	8	---	17	110	90	44	(124)
Liu et al.	China	2020	Cohort	65.5(23–96)*	140	5	5	3	---	3	---	---	90	63	9	(125)
Li et al.	China	2020	Case-Control	54 ± 13	31	---	3	5	---	---	---	---	25	25	---	(126)
Han et al.	China	2020	Case Series	32.1	32	6	6	6	---	---	---	---	29	24	13	(127)
Garazzino et al.	Italy	2020	Case Series	5 (0.3–9.6)	168	22	22	9	---	---	---	---	138	82	16	(128)
Feng et al.	China	2020	Case Series	53(40-64)*	476	49		---	---	---	---	---	390	269	109	(129)
Easom et al.	UK	2020	Cohort	42.5	68	9	9	2	---	---	---	---	27	53	17	(130)
Duanmu et al.	USA	2020	Case Series	45(1-91)*	100	10	10	15	---	---	---	---	71	87	38	(131)
Zhang et al.	China	2020	Case-Control	43.4±15.9	22	10	10	---	---	---	---	---	---	---	---	(132)
Fernández-Ruiz et al.	Spain	2020	Case Series	71*	18	5	4	---	---	---	---	---	15	12	11	(133)

*: Median; SS: sample size

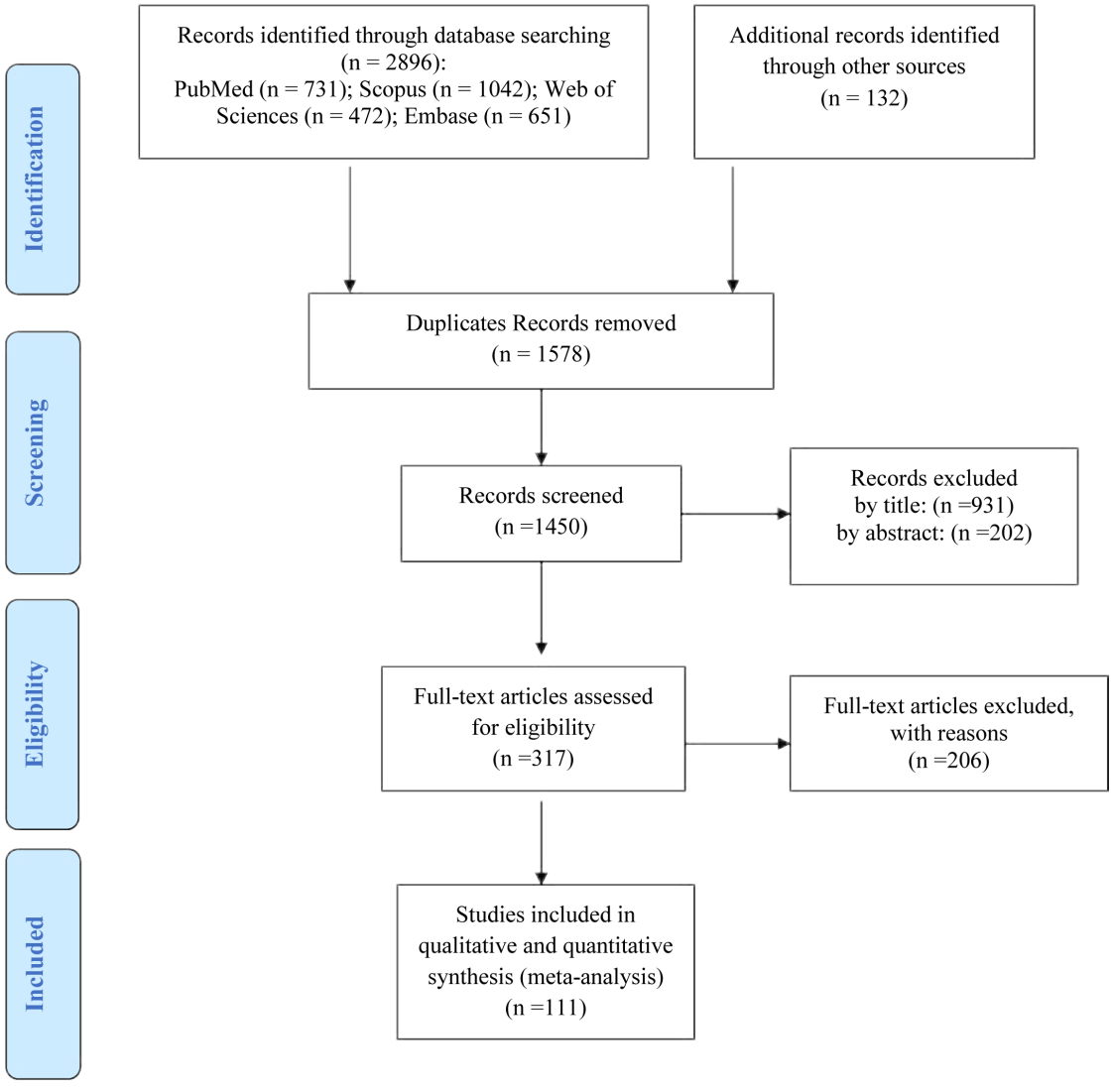

Figure 1. PRISMA flow diagram of the process of study selection for analysis.

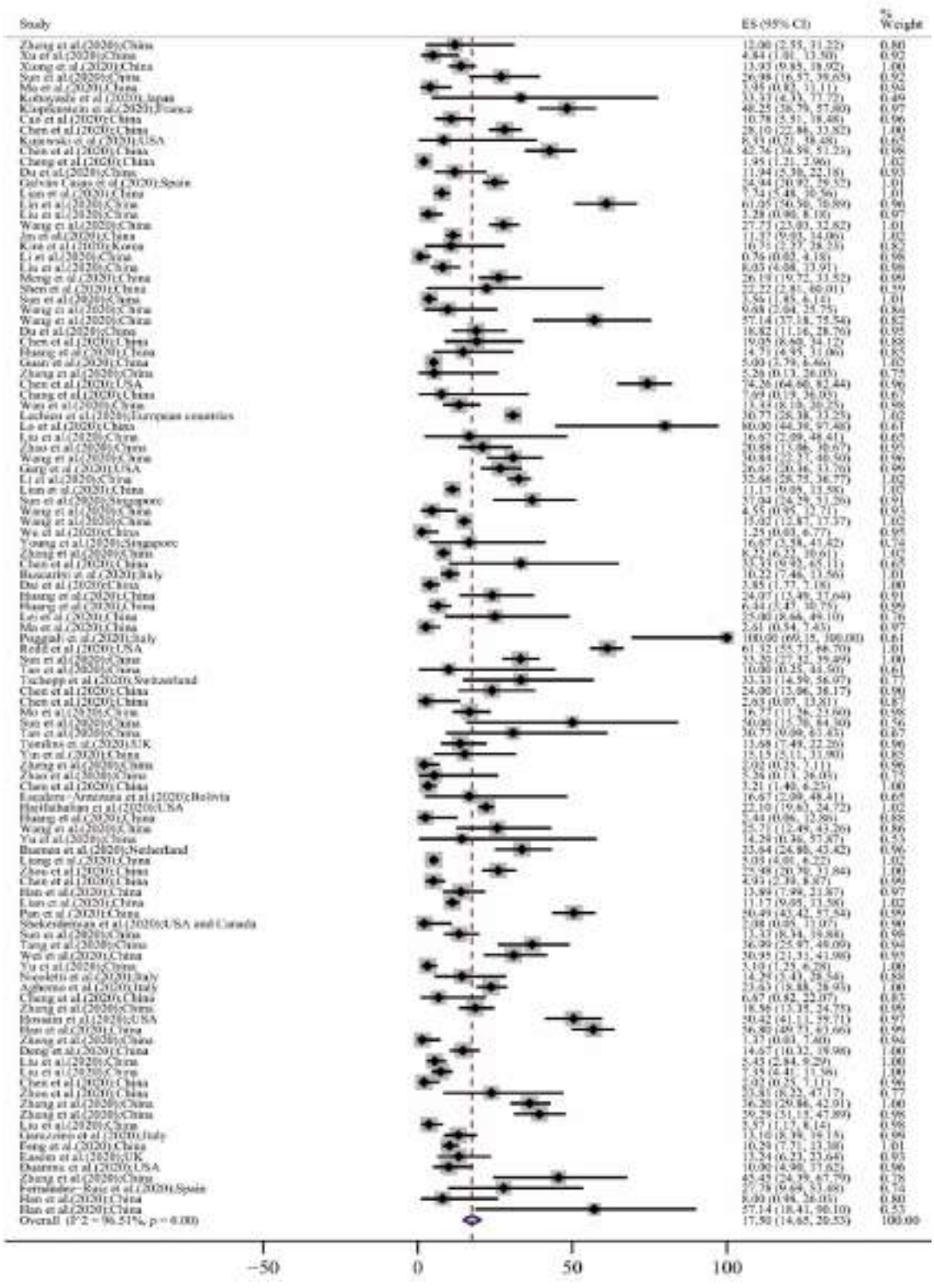

Figure 2. forest plot for prevalence of Any GI Symptoms in patients with COVID-19 based on a random-effects model. Each study identifies by the first author (year) and country. Each line segment's midpoint shows the prevalence estimate, length of line segment indicates 95% confidence interval (CI) in each study, and diamond mark illustrates the pooled estimate.

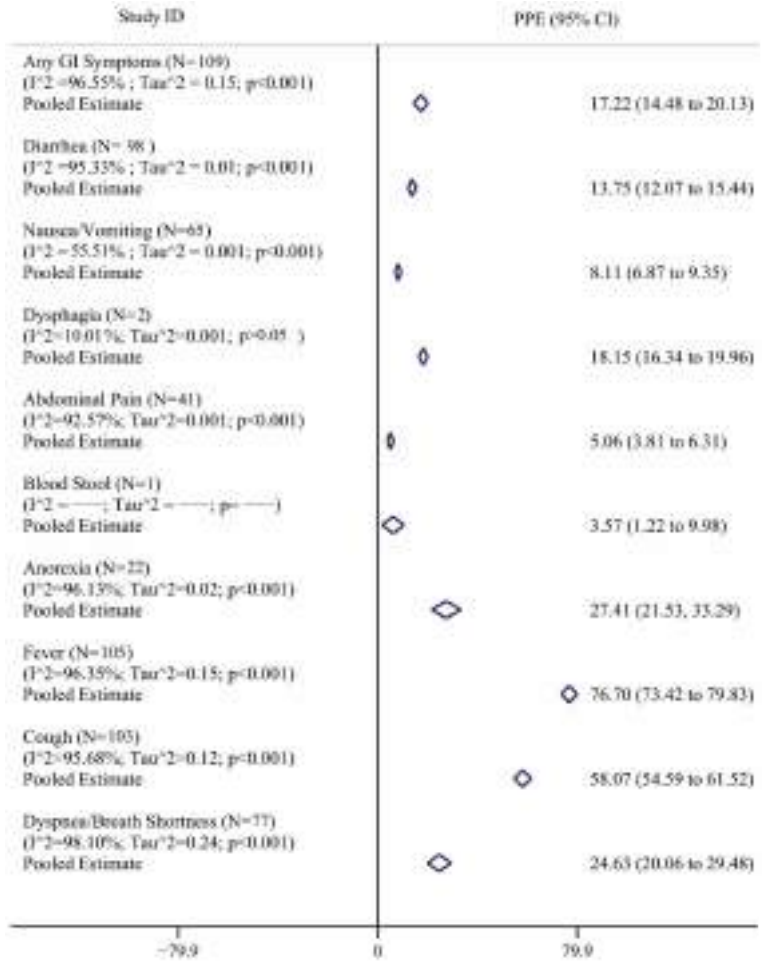

Figure 3. Pooled prevalence estimate of Gastrointestinal and clinical symptom in patient with covid-19 based on random effects model. The diamond mark illustrates the pooled prevalence estimate and length of diamond indicates 95% confidence interval.

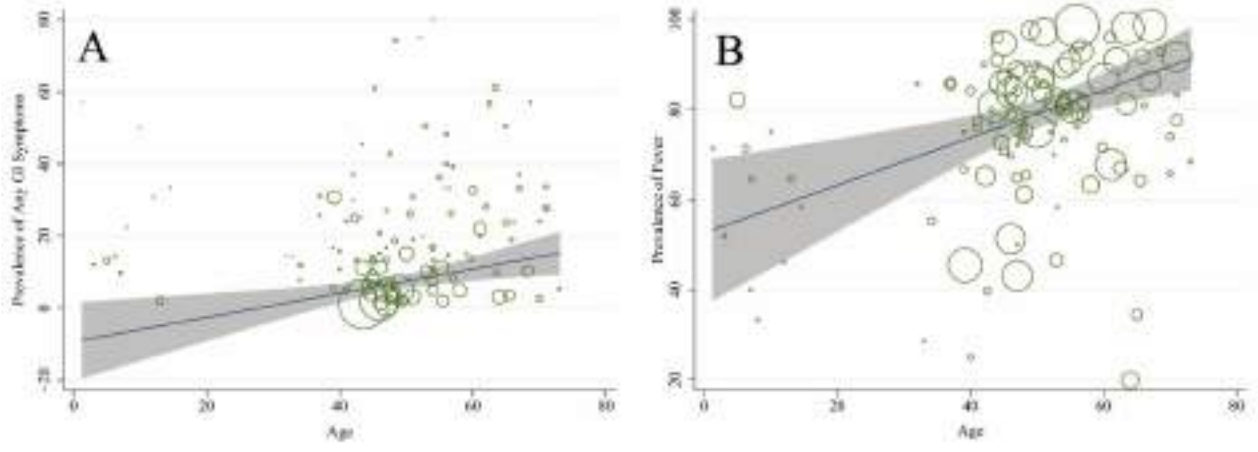

Figure 4. The association among prevalence of Any GI Symptoms (A) and Fever (B) with age by means of meta-regression. Size of circles indicates the precision of each study. There is significant association with respect to prevalence of Any GI Symptoms and fever with age. The prevalence of Any GI Symptoms and fever has been significantly increased with increases of age in this survey.

Table 2. Pooled Prevalence estimate and 95% Confidence Interval of Gastrointestinal and clinical symptom in patient with COVID-19

Systems	Symptom	Heterogeneity	Number of study	PPE %	95% CI
Digestive Symptoms					
	Any GI Symptoms	I2 =96.55%; Tau2 = 0.15; p<0.001	109	17.22	(14.48 to 20.13)
	Diarrhea	I2 =95.33%; Tau2 = 0.01; p<0.001	98	13.75	(12.07 to 15.44)
	Nausea/Vomiting	I2 =55.51%; Tau2 = 0.001; p<0.001	65	8.11	(6.87 to 9.35)
	Dysphagia	I2 =10.01%; Tau2 = 0.001; p>0.05	2	18.15	(16.34 to 19.96)
	Abdominal Pain	I2 =92.57%; Tau2 = 0.001; p<0.001	41	5.06	(3.81 to 6.31)
	Blood Stool	I2 = -; Tau2 = -; p= -	1	3.57	(1.22 to 9.98)
	Anorexia	I2 =93.16%; Tau2 = 0.02; p<0.001	22	27.41	(21.53 to 33.29)
Respiratory Symptoms					
	Fever	I2 =96.35%; Tau2 = 0.15; p<0.001	105	76.70	(73.42 to 79.83)
	Cough	I2 =95.68%; Tau2 = 0.12; p<0.001	103	58.07	(54.59 to 61.52)
	Dyspnea/Breath Shortness	I2 =98.10%; Tau2 = 0.24; p<0.001	77	24.63	(20.06 to 29.48)

CI, Confidence Interval; PPE, Pooled Prevalence estimate

Table 3. Result of publication bias and Fill and Trim method

		Egger's test		Fill and Trim	
Systems	Symptom	Coefficient	P-value	PPE %	95% CI
Digestive Symptoms					
	Any GI Symptoms	4.80	<0.001	20.3	(18.3 to 22.2)
	Diarrhea	4.12	<0.001	5.4	(3.5 to 7.3)
	Nausea/Vomiting	1.67	<0.001	0.60	(0.3 to 0.8)
	Dysphagia	---	---	---	---
	Abdominal Pain	2.79	<0.001	1.6	(0.04 to 2.9)
	Blood Stool	---	---	---	---
	Anorexia	5.41	<0.001	16.9	(11.3 to 22.5)
Respiratory Symptoms					
	Fever	-2.15	0.021	75.1	(72.1 to 78.1)
	Cough	7.53	<0.001	24.7	(18.2 to 31.2)
	Dyspnea/Breath Shortness	6.52	<0.001	7.5	(3.7 to 11.3)

CI, Confidence Interval; PPE, Pooled Prevalence estimate

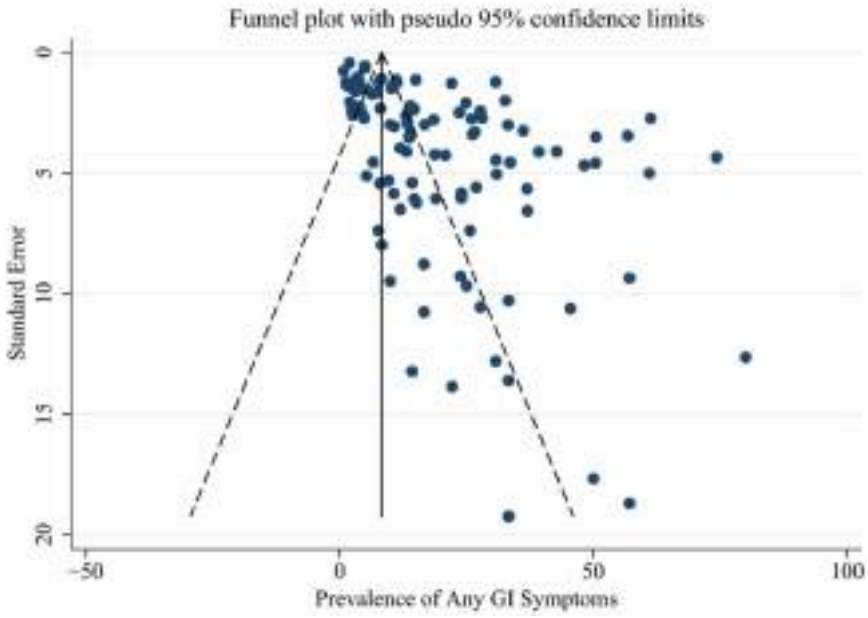

Figure 5. The funnel plot for assessing publication bias. The vertical and horizontal axis showed the prevalence of Any GI Symptoms and standard error of prevalence.

symptoms I^2 was over 90%. According to meta-regression results, age had significant effect on prevalence of any Gastrointestinal symptoms (coefficient 0.002; p: 0.027) and fever (coefficient 0.004; p<0.001). (Fig 4A & 4B).

Publication bias

According to Egger's test result which is shown in Table 3, a significant publication bias was observed for all symptoms (P<0.05). The Fill & Trim approach was used to adjust publication bias and also to correct pooled prevalence (based on table 3 and Fig 5).

Discussion

An increasing number of gastrointestinal symptoms were reported in some COVID-19 patients and it seems GI system is involved in SARS-CoV-2 pathophysiology.[9, 61] Shanbehzadeh et al. showed the GI system was a usefull criteria for diagnostic of COVID-19.[134-136] Alessio Aghemo et al. demonstrated the association of gastrointestinal symptoms with prognosis in COVID-19 patients.[113] In our study gastrointestinal symptoms in admitted COVID-19 patients might be due to drug adversity. Because, majority of these patients are on antiviral/antibacterial administration schedule.[113] Diarrhea (7 to 28%), vomiting (2 - 7%) in adults, nausea (5-16%) and abdominal pain (1-11%) were reported in COVID-19 patients treated with Lopinavir or Ritonavir.[137] Our results exhibited that diarrhea is the most common Gastrointestinal symptom among patiens. We found that prevalence of Nausea/vomiting among the patienes was 8.11%. Our result is different from mohammadi et al. study. They showed 79.13% of the patients had nausea or/and vomiting as one of the common symptoms among the patients.[137] Our results showed that anorexia (27.41%) was one of the common

symptom among patients. Mohammadi et al. systematics review study was in accordance with our results. They showed anorexia (91.3%) is the most common symptom among the patients.[137] A study conducted by Chen evaluating the specificity of gastrointestinal symptoms, showed 53% anorexia prevalence among COVID-19 patients.[58] Among the infected individuals evaluated in our study, 18.15% had Dysphagia. Fever, dry cough and dyspnea are the most common symptomes in different types of studies regarding COVID-19 patients.[47,138,101] We demonstrated that the prevalence of fever, cough and dyspnea/ shortness of breath were 76.7%,58.07% and 24.63% respectively, as fever and cough were the most reported signs and symptoms in the Lian J et al. study.[39] Similar to other studies, our research had some limitations. 1: we couldn't perform gender-specific estimation, beacuase of insufficient data in primary studies; 2: we estimated symptomes prevalence based on WHO data and we waned to conduct spatial analysis in different area,[139-142] but there were not enough studies to reach a robust analysis. performing a comprehensive review and estimating the pooled prevalence based on different gastrointestinal sypmtoms among COVID-19 patients were the current study's strengths.

Conclusion

Our systematic review study exhibit that a significant part of COVID-19 patients could symptoms like gastrointestinal symptoms which may delay the identification of the virus and increse the disese pathogenecity. However; a major proportion of COVID-19 patients are under treatment of antiviral/ bacterial medication which may be a cause of gastrointestinal symptoms.

Conflict of interest statement

The authors declare no conflicts of interest regarding this article

Acknowledgement

The authors are grateful to Tehran University of Medical Sciences, Tehran, Iran. (Grant no: 48741).

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