Epidemiological approximation of the enteric manifestation and possible fecal-oral transmission in COVID-19: A preliminary systematic review

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Systematic Review

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Abstract

Objectives: to conduct a systematic review to describe the epidemiological scientific evidence on gastrointestinal symptoms (GIS), enteric involvement and fecal excretion of SARS-CoV-2 viral RNA and to discuss the possible fecal-oral transmission pathway of COVID-19.

Methods: We have reviewed GIS, enteric involvement, and fecal test results of SARS CoV-2 from case reports and retrospective observational studies related to the digestive system published about the outbreak.

Results: The prevalence of GIS in patients infected with SARS CoV-2 ranges from 1.7% (1/56)-100% (10/10), GIS included diarrhea 1/99(1%)-8/10(80%), nausea/vomiting 1/28(3.6%)-5/10 (50%), abdominal pain 2/103(1.9%)-1/3(33.3%). A total of 3% of infected patients may experience GIS in the absence of respiratory symptoms. A pooled analysis of the results showed 16.1% GIS, 8.3% diarrhea and 12% nausea-vomiting. A higher percentage of diarrhea in patients with severe disease (5.8%) than in non-severe disease (3.5%), and a more severe course in patients with GIS (22.97%) than in those without GIS (8.12%) was found. Histological studies demonstrated the presence of ACE2 receptors and the nucleocapsid of the virus in gastrointestinal. The RNA of the virus has been detected in 27-53% of patients with COVID-19 in whom respiratory and stool samples have been analyzed, and it may persist in stool for up to an average of 11.2 days after negativization of the respiratory samples.

Conclusions: GIS are common in SARS CoV-2 infection at the time of patient admission, sometimes represent the only clinical manifestation. Infection of the GI tract is possible due to the presence of ACE2 receptors, and there may be viral replication with fecal elimination.

Introduction

In early December 2019, a set of cases of pneumonia of an unknown cause was identified in Wuhan (China) [1, 2]. China notified the WHO office on 31 December 2019. On 7 January 2020, the Chinese Health Authorities confirmed the identification of a novel betacoronavirus (SARS-CoV-2) from the same family that caused SARS (severe acute respiratory syndrome) or MERS (Middle East Respiratory Syndrome). On 30 January 2020, the Director-General of the World Health Organization (WHO) declared a Public Health Emergency of International Concern. On 11 March 2020, the World Health Organization made an address that declared the outbreak caused by the novel betacoronavirus 2 (2019-nCoV) a pandemic [3, 4].

There is evidence of the similarity of SARS-CoV-2 with the genetic sequences of different coronaviruses (CoV) present in at least 5 species of bats, according to surveillance studies conducted [5, 6]. At least three of these species were found in Wuhan, Hubei province, in the center of the People's Republic of China (source: www.iucnredlist.org), but the bat CoV with which SARS-CoV-2 has greatest genomic similarity was isolated from *Rhinolophus sinicus* (genetic sequence MG772933, described in [7], which could indicate that this species could also have been the original source of 2019_nCoV and probably

reached humans after passing from an intermediate host, the civet *Paguma larvata* or the pangolin *Manis pentadactyla* [8, 9]. Although said genetic similarity has been studied, the epidemiological link must be proven [10]. The way in which the virus could be transmitted from the animal source to the first human cases is unknown.

As of 22 April 2020, when this article was written, the virus had spread, according to cases reported, to 215 countries, territories or reporting areas around the world, as reflected in the WHO SARS-CoV-2 Disease (COVID-19) Situation Report-98 published on 27 April 2020. More than 2878196 cases and at least 198668 deaths have been confirmed [11].

It is important to note that the basic reproduction number (R0), the indicator of transmissibility of SARS-CoV-2, has been estimated at 2.30 from reservoir to person and that person-to-person transmission and the expected number of secondary infections resulting from introducing a single infected individual into an otherwise susceptible population was 3.58 [12]. Two reviews recorded a total of 32 studies of different methodologies estimating R0 values ranging from 1.5 to 6.5 during the epidemic in Wuhan [13].

In the absence of specific clinical manifestations, the identification of transmission chains and follow-up of subsequent contacts would be much more complicated, especially if many infected individuals remain asymptomatic, presymptomatic, or mildly symptomatic carriers [14].

The clinical manifestations such as dry cough, fever and dyspnea are well known and described. In the first series in Wuhan, 2% to 10% of patients with COVID-19 had GIS such as diarrhea, abdominal pain and vomiting [15, 16]. Gastrointestinal (GI) infection is possible, and the mechanism for SARS-CoV infection in the GI tract is already known to be the cellular receptor of angiotensin-converting enzyme 2 (ACE2) [17].

To date, several studies have been published that refer to the viral excretion of SARS-CoV-2 in stool and investigate whether fecal SARS-CoV-2 RNA levels correlate with disease severity and/or the presence or absence of GIS, and, on the other hand, analyzing whether SARS-CoV-2 RNA in stool can also be detected in the incubation or convalescent phases of COVID-19 [18], which could imply possible fecal-oral transmission.

The identification of the main routes of transmission of SARS-CoV-2 infection should be a priority in health research, as it may make it possible to define preventive strategies to further reduce its burden of morbidity and mortality. Since different occupations, migratory and mobility activities of communities and populations may represent different pathways for acquiring infection, our objective was to describe the epidemiological scientific evidence on the possible fecal-oral transmission route of SARS-CoV-2 infection from recent outbreaks of COVID-19 through a systematic review of published studies.

Methods

Search strategy and inclusion criteria

We conducted a systematic search of electronic medical databases (PubMed®, Embase® and Google Scholar®) from 31 January until 12 April 2020 (date of last search) to retrieve published scientific articles assessing or making references to the GIS, GI infection, detection of viral RNA in stool and possible enteric or fecal-oral transmission of the SARS-CoV-2 during the COVID-19 global pandemic. Each reference retrieved was independently examined, following predefined criteria for determining eligibility for the systematic review (Figure 1). The descriptors were used to recruit studies that included information on the presence or absence of GIS during COVID-19, studies on enteric involvement, excretion of the virus and its relationship to disease severity, fecal concentrations of SARS-CoV-2 viral RNA in biological samples and their possible detection in the incubation or convalescent phases, and on the possibility of fecal-oral transmission of COVID-19.

Inclusion and exclusion criteria

Eligibility criteria included original and editorial articles, comments, letters to the editor, guidelines and case reports in which original results were presented. Research not involving humans (for example, in vitro or animal research; experimental studies with an evaluation of SARS-CoV-2 infection in GI biological samples recovered from laboratory databases) was included. Eligible study designs included randomized, cohort, case-control, cross-sectional, ecological studies, and modelling studies.

Exclusion criteria were: documents written in a language other than English, Portuguese, Spanish, French, Italian; publications on systematic reviews; previous systematic reviews were not eligible; studies that do not assess or provide the prevalence of GIS in confirmed cases of COVID-19 or about the elimination of viral RNA in stool.

Study selection and data extraction

Decisions were made independently by two reviewers using the search strategy for eligible studies, which were compared, and discrepancies were resolved by consensus or consultation after discussion with another independent investigator. The retrieved study references were stored in an electronic bibliographic data repository to identify additional relevant publications that were missed in the initial search strategy.

For the extraction of data from the selected articles, a pre-designed data collection form was prepared to extract relevant information from the full texts included; including the study design; year of publication; period of data collection.

Quality Assessment

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was used as an instrument used for the critical reading and evaluation of cross-sectional epidemiological studies and case series, and those with a focus on prevalence (cohort, case-control and cross-sectional), according to a 22-point checklist related to the different sections of an article: title, summary, introduction, methodology, results and discussion. Of these, 18 points are common to the three study designs: cohort,

case-control, and cross-sectional; the other four are specific to cohort, case-control or cross-sectional studies [19, 20]. The quality of the study was considered HIGH (H) if most summary statements were answered as “excellent” or “good”; MEDIUM (M) if internal validity was rated as “MEDIUM”, or most summary statements were rated as “good” or “fair”; and LOW (L) if internal validity was rated as “LOW”, or most summary statements were rated as “fair” or “poor” [21].

Statistical methods

Considering the heterogeneity in the studies identified through the systematic review and the options for presenting the results in each article, a quantitative synthesis of the main findings could not be made. We performed a pooled analysis to show an estimate of GIS reported in the studies included in our analysis.

Results

Study characteristics

In total, we identified 350 references addressing potentially relevant descriptors of the review (Figure 1). Of these, 35 (10%) articles met our eligibility criteria and were therefore included in the analysis (Table 1). All articles selected according to the review objective were published in 2020 due to the recent emergence of the COVID-19 pandemic, and data collection or surveillance periods of these studies took place between December 2019 and 24 March 2020, mainly in the following regions: Asia (88.8%), Europe (12.1%) and the Americas (9.1%). Studies spanned a wide age range, from pediatric subjects one day of age to 92 years, in those studies in which information was provided, including experimental studies. Most studies analyzed were observational 26/35 (72.2%), 8/35 (23%) cohort, and 1/35 (3%) case-control studies. According to the external quality assessment of the studies, 17/35 (48.5%) had medium quality and 12/35 (34.2%) were of high quality according to STROBE (Table 1).

General characteristics of the included studies

Due to the novelty in the occurrence of the COVID-19 pandemic, no broad geographical distribution was observed in the studies reviewed, we included 2/35 (5.7%) types of articles sent to journals as correspondence articles, letter to editor or brief review, as they provided data from an original study. Table 1 shows the list of studies according to the inclusion criteria and descriptors used.

The PubMed bibliographic repository was the most widely used for the retrieval through open access to available articles. The articles identified were mainly designed as cross-sectional descriptive studies and some observational studies (cohort, cases and controls) with a retrospective or longitudinal design. One case-control study was found, and no ecological or modelling studies or RCT studies were found (Table 1).

As regards sex and age, as another of the sociodemographic variables collected in the different studies included, we found the distribution by sex to be relatively homogeneous in the different studies and varied in a range from pediatric patients aged 1 day to adult patients aged 92 years.

Histological samples from the stomach, small intestine, and colon were screened for the detection and/or localization of ACE2 receptor cells, and the nucleocapsid of the coronavirus using staining techniques in 2/35 (5.7%) articles showing abundant ACE2 in the cytoplasm of glandular cells of gastric, duodenal, and rectal epithelia (Table 3).

Discussion

COVID-19 GIS

During the 2002 SARS epidemic, diarrhea was reported in 16.7% of cases [56]. In the MERS epidemic, 26% of cases were reported with diarrhea, 21% with nausea-vomiting and 17% with abdominal pain [57].

In the first studies published on COVID-19, conducted in hospital centers in Wuhan (epicenter of the pandemic), nausea or vomiting was observed in 5% and diarrhea in 3.7% of the cases studied [32, 50].

Subsequently, many studies have analyzed the occurrence of GIS, showing great variability coinciding with the pooled analysis. Our analysis showed GIS in 16%, diarrhea in 8.1%, nausea-vomiting in 12%, and abdominal pain in 4%.

It is well known that the dominant clinical signs of COVID-19 are respiratory symptoms (cough, dyspnea and fever), but, as has been seen in this review, there is a significant percentage of cases with GIS from the time of patient admission (before starting treatment) and that, sometimes, may precede the respiratory symptoms [16, 30]. One study showed that up to 3% of cases may have exclusively presented with GIS [38]. The presence of these GIS has not been related to the positivity of viral RNA in stool [41].

On the other hand, there are studies showing that the presence of GIS may indicate a higher probability of a severe course [37, 42]. A higher percentage of diarrhea was observed in patients with severe disease (5.8%) than in non-severe disease (3.5%). Guan *et al* [42] and a significant serious course was found in patients with gastrointestinal symptoms (22.97%) than in those without gastrointestinal symptoms (8.12%) $p<0.001$ [37]. In another study, this difference with the presence of GIS was not observed in 37.8% of patients with non-severe disease and 42% of patients with severe disease [44].

Enteric involvement

The finding of an angiotensin-converting enzyme receptor as the entry for SARS-CoV-2 to the cell suggests that human organs with a high level of ACE2 expression, such as pulmonary alveolar epithelial cells and small intestinal enterocytes, are potentially vulnerable and a target for SARS-CoV-2 infection [28, 29, 58, 59].

The binding of SARS-CoV-2 to ACE2 has been shown to have approximately 10-20 times greater affinity than SARS-CoV via S protein, which may provide an explanation of why SARS-CoV-2 has more person-to-person spread compared with SARS-CoV [60, 61]. COVID-19 disease can affect, in addition to the

respiratory and GI tract, various organs such as the kidneys, liver, musculoskeletal, cardiovascular and neurological systems. [62, 63].

In this review, we found [28, 29] articles supporting the above statement that human ACE2 is a receptor for SARS-CoV-2 expressed in gastric, intestinal and colonic cells [64, 65].

The possible infection of the GI cells was studied in tissue samples from the esophagus, stomach, duodenum and rectum, and although no significant histological alteration was observed, through staining, the presence in the cytoplasm of the cells of the ACE2 receptors and the nucleocapsid of the SARS-CoV-2 was determined. This indicates the possibility of enteric infection [29]. This enteric infection could release virions and cause possible fecal-oral transmission.

Other reports have suggested that if SARS-CoV-2 can actually infect the human intestinal epithelia, it would have significant implications for fecal-oral transmission and the containment of viral propagation [32, 42].

Infection of intestinal cells can be expressed with GIS, such as abdominal pain, vomiting and diarrhea, as demonstrated in some studies [66, 67].

One study showed that the extension in days of viral RNA elimination in stools has not been related to disease severity [41].

This reinforces the need for future studies on enteric participation and viral excretion of SARS-CoV-2 in stool and for research on whether fecal SARS-CoV-2 RNA levels correlate with disease severity and the presence or absence of GIS [18].

Fecal levels of SARS-CoV-2 viral RNA and possible fecal-oral transmission of infection

The primary transmission pathway is by inhalation of respiratory microdroplets, but there may be other mechanisms such as**: conjunctival**: one study showed the presence of RNA in conjunctiva [68]; **fecal**: another study in Singapore showed the presence of virus RNA in samples from an infected patient's toilet and on **fomites**: the same study detected the virus on many surfaces of the room [70].

In this regard, it has been postulated that the dynamics of SARS-CoV-2 must be determined to study possible fecal transmission, and it is therefore important to take simultaneous respiratory and fecal samples to study the kinetics and viral load of SARS-CoV-2. The Ct values reflect, in an inversely related manner, the viral load and are suggested by some authors for expression [24, 71].

Viral kinetics in infected patients have not yet been fully determined. Viral RNA in COVID-19 has been found in stool in the early and late phase of the disease at a rate, in the most numerous series, of between one-third and one-half of the cases [22, 40, 41]. Viral RNA may remain positive in stool samples, up to an average of 11.2 days and up to a maximum of 33 days after being negative in respiratory

samples, suggesting that the virus could actively replicate in the GI tract of the infected patient and that fecal-oral transmission could occur after viral clearance in the respiratory tract. [40, 41].

One German study found high viral loads in stool and the presence of subgenomic RNA sgRNA in some patients, indicating the possible viability of the virus, though it could not be cultured in stool [54].

In contrast, another study found no significant value of viral RNA in stool [37] . A study of the pediatric population showed persistent excretion of SARS-CoV-2 in the stool of children between 8-20 days after negativization in respiratory samples. This would increase the possibility of the virus being transmitted through contaminated fomites, so there is a need for massive efforts at all levels to prevent the spread of infection between children after reopening daycare centers and schools, as noted in one of the articles discussed in this review [39].

It has been suggested that the prolonged RNA presence of SARS-CoV-2 after negativization in respiratory specimens may be an infectious source of COVID-19 in the community and may represent a threat to public health, if eligibility for discharge is based on the current version of the COVID-19 Diagnosis and Treatment Plan [39, 72]. Therefore, SARS-CoV-2 RT-PCR measurement in stool would be recommended following the clearance of viral RNA in respiratory specimens from hospitalized or quarantined patients [39, 41].

High viral load in elderly patients has been associated not only with the low immunity of the elderly but also with high expression of the ACE2 receptor (the cellular entry receptor for SARS-CoV-2) in older adults, and further studies with a larger sample size are needed to clarify and understand the relationship between viral load and disease severity [73, 74].

In histological studies, some authors have suggested that if SARS-CoV-2 can actually infect the human intestinal epithelium, it would have significant implications for fecal-oral transmission and the containment of viral propagation [32, 42].

It has also been suggested that further studies are needed to elucidate the exact role of fecal-oral transmission in the spread of SARS-CoV-2 through environmental studies, and studies on viability and infectivity [18, 75].

Strengths And Limitations

To our knowledge, this is the first systematic review on the prevalence of GIS and enteric involvement of COVID-19 infection, and also includes studies on the excretion and concentration of SARS-CoV-2 virus in biological GI samples and on the possibility of fecal-oral transmission of COVID-19. This is possibly the first study conducted in Spain, where the pandemic is having a severe impact. Several electronic databases were searched for our systematic review, the vast majority of references were retrieved, and a large number of studies related to the subject matter at hand were included. Furthermore, since the data analysis was essentially descriptive, no significant bias is expected from our methodological option.

However, we found substantial methodological limitations. The heterogeneity between studies and the novelty of the pandemic health event constituted an established limitation of systematic reviews, and, in this case, the majority of studies being conducted at this time are ongoing and have not yet been published. To minimize potential bias, we attempted to select all studies published to date globally, regardless of sample size.

Despite the limitations of the data in the reviewed articles, the estimates reported here show the frequency of the GIS and that the presence of SARS-CoV-2 viral RNA in stool could represent a significant burden for the probable fecal-oral transmission of the infection. Further work is needed to update the case definition, studying enteric involvement through the design of prospective observational studies using a sample size representative of the population that allows results to be outsourced.

Conclusions

Gastrointestinal symptoms are common in SARS CoV-2 infection at the time of patient admission, sometimes preceding respiratory symptoms, and sometimes represent the only clinical manifestation. The case definition evolves rapidly as knowledge accumulates, and the definition could be revised including these considerations. The presence of GIS could predict a poorer course of the disease. In the context of the current pandemic, adequate clinical suspicion may lead to an early diagnosis and treatment of the disease and may hypothetically reduce the frequency of progression to more severe disease.

Infection of the GI tract is possible due to the presence of ACE2 receptors, and there may be viral replication with fecal elimination. Studies are required to assess viability and transmissibility. Viral RNA is detected in stool for a longer time than in the respiratory system. As has been suggested, its detection in fecal samples should be considered as one of the routine diagnostic tests to guide decision making on hospital discharge and the lifting of isolation measures.

It is advisable to design and conduct prospective epidemiological studies at the community level or using a sample size representative of different populations and to substantiate the preliminary findings made in some case studies reported in this systematic literature review. Such studies will make it possible to determine the actual prevalence of GIS and its potential correlation with severity.

Declarations

Conflict of interest: The authors declare that they have no conflict of interest.

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Tables

Table 1 Demographic characteristics and comparison of quality of the studies included in the review

of n	Country/Region	Sex n (%) M: male F: female	Age m: months y: years	Monitoring period	Design	STROBE
al.	Wuhan, China/Asia	NK	NK	12 December 2019- 3 February 2020	Descriptive	M
2020	South Korea/Asia	Patient 1: Chinese F (primary case) Patient 2: Korean M	35-55y	December 2019-February 2020	Descriptive	M
2020	Guangzhou, China/Asia	6/10 (60) M 4/10 (40) F	pediatric	22 January-20 February 2020	Prospective observational, 1 site	H
t al.	Rome, Italy/Europe	Asymptomatic Italian M1 from Wuhan	20y	3-22 February 2020	Descriptive, one case	M
2020	Wuhan, Hubei, China/Asia	6 M 2 F	R: 2m-15y	24 January-24 February 2020	Description of a case series	M
2020	Macau, China/Asia	3/10 (30) M 7/10 (70) F	$\bar{x}$: 54y R: 27-64y	21 January-16 February 2020	Descriptive	M
2020	Shandong, China/Asia	Children 6/8 (75) Adults 2/8 (25)	R: 11m-39y	NK	Descriptive	M
2020	Guangdong, China/Asia	NK	NK	1-14 February 2020	Descriptive	H
et	Washington, USA/America	1 M returning from Wuhan on 15 January	35y	19-20 January 2020	Descriptive 1 case	M
al.	Seoul, South Korea/Asia	15/28 (53.6) M 13/28 (46.4) F	$\bar{x}$: 40y R: 20-73y	19 January-17 February 2020	Cohort	H
al.	Wuhan, China/Asia	75/138 (54.3) M 63/138 (45.7) F	$\bar{x}$: 56y R: 22-92y	1 January-3 February 2020	Retrospective cohort	H
al.	Wuhan, China/Asia	2 M (father and child) 1 F	65y (primary case) 27y (secondary case) Mother NK	17-20 Jan	Cohort (3-family member cluster)	H
al.	Seoul, South Korea/Asia	1/5 Girl, contact with mother and uncle (traveled to Wuhan) confirmed	Girl 10y	29 January-18 February 2020	Description of a case, NK for the *cluster*	M
al.	Taichung, Taiwan/Asia	17 (40) M 26 (60) F	$\bar{x}$: 34.0y R: 3-68y	20 January- 19February 2020	Cohort	H
al.	Wuhan, China/Asia	35 (67) M 17 (33) F	$\bar{x}$: 51.9y	24 December 2019-26 January 2020	Retrospective observational of an outbreak	H
2020	Zhejiang, China/Asia	37/74 (50) M 37/74 (50) F	$\bar{x}$: 46.1±14.1y	17 January 2020-8 February 2020	Retrospective cohort	H

2020	Hubei, China/Asia	97/204 (47.5) M 107/204 (52.4) F	x̄: 52.9y (SD±16)	18-January- 18 March 2020	Multicenter cross-sectional descriptive	H
al.	Qingdao, Shandong, China/Asia	NK	Pediatric <10y R: 1-6y	17 January- 10 March 2020	Retrospective Descriptive	H
2020	Beijing, China/Asia	17 NK	NK	NK	Descriptive	L
2020	Zhuhai, China/Asia	NK	NK	16 January-15 March 2020	Descriptive	M
al.	China/Asia	58.1 M 41.9 F	x̄: 47y R: 35-58y	11 December 2019-31 January 2020	Multicenter cohort	H
2020	Wuhan, China/Asia	104/171 (60.8) M 67/171 (39.2) F	Pediatric <10y x̄: 6.7y R: 1 day-15y	28 January-26 February 2020	Cross-sectional descriptive	M
al.	Wuhan, China/Asia	71/140 (50.7) M 69/140 (49.3) F	x̄: 57y	16 January-3 February 2020	Retrospective cohort	H

Age=may be the mean/median (x̄) and/or range (R) of ages, NK=data not reflected or is not known; STROBE checklist guidelines (observational and descriptive cross-sectional studies), H= high; M= medium; L= low

Table 1, Continued

of n	Country/Region	Sex n (%)	Age m: months y: years	Monitoring period	Design	STROBE
2020	Hubei, Wuhan, China/Asia	61/137 (44.5) M 76/137 (55.5) F	x̄: 57y R: 20-83y	30 December 2019-24 January 2020	Retrospective cross-sectional descriptive	M
t al.	New York-Presbyterian-Columbia, USA/America	145/278 (52) M 133/272 (48) F	R: 18y- >70y	10 March-21 March 2020	Case-controls	H
G et	California, USA/America	62 (53.4) M	x̄: 50y R: 35-67y	4-24 March 2020	Retrospective cross-sectional descriptive	M
2020	Wuhan, China/Asia	102/183 (56) M 81/183 (44) F	x̄: 53.8y	1 January-20 February 2020	Retrospective cross-sectional descriptive	M
t al.	Paris, France/Europe	3/5 (60) M 2/5 (40) F	R: 30-80y	24 January-19 February 2020	Cohort	H
al.	Wuhan, China/Asia	30/41 (73) M 11/41 (27) F	x̄: 49y R: 41-58y	31 December 2019-2 January 2020	Cross-sectional descriptive	M
al.	Huanan, China/Asia	67/99 (67.8) M 32/99 (32.3) F	55.5y (SD:±13.1)	1-25 January 2020	Retrospective cross-sectional descriptive	M
al.	Singapore/Asia	9/18 (50) M 9/18 (50) F	x̄: 47y	23 January-3 February 2020	Descriptive of an outbreak	M
2020	Zhejiang, China/Asia	(35, 5) M	x̄: 41 R: 32-52y	10-26 January 2020	Descriptive	L
al.	Munich, Germany/Europe	NK	NK	23-27 January 2020	Descriptive of a cluster	M

Age=may be the mean/median (x̄) and/or range (R) of ages, NK=data not reflected or is not known; STROBE checklist guidelines (observational and descriptive cross-sectional studies), H= high; M= medium; L= low

Table 2 Gastrointestinal symptoms and enteric involvement according to studies included in the review

rimary or/Year of olication	Sample (N)	GIS frequency (%)	Diarrhea n (%)	Nausea/Vomiting n (%)	Abdominal pain n (%)	Several GIS or other n (%)	Positive GI Samples
JY et al. [23]	2	2/2 (100)	NK	NK	NK	NK	SS*
Y et al. [24]	10	3/10 (30)	3/10 (30)	NK	NK	NK	SS*
stri E et 020 [25]	56	1/56 (1.7)	NK	NK	NK	NK	SS*
D et al. [26]	8	8/8 (100)	3/8 (37.5)	NK	NK	5/8 (62.5)	NK*
L et al. [27]	10	10/10 (100)	8/10 (80)	5/10 (50)	NK	NK	SS*
X et al. [28]	27	8/27 (29.6)	NK	NK	NK	NK	SS*
nue ML et 020 [30]	1	1/1 (100)	1/1	1/1	1/1	NK	SS*
ES et al. [31]	28	5/28 (18)	3/28 (39)	1/28 (3.6)	1/28 (3.6)	NK	SS*
g D et al. [32]	138	36/138 (26.1)	14/138 (10.1)	14/138 (10.1) 5/138 (3.6)	3/138 (2.2)	NK	NK*
LT et al. [33]	28	3/28 (10.7)	1/3 (33.3)	1/3 (33.3)	NK	NK	NK*
WH et al. [35]	43	2/43 (4.6)	5/43 (11.6)	3/43 (7)	3/43 (7)	NK	NK*
X et al. [37]	651	74/651 (11.4)	53/651 (8.1)	10/651 (1.5) 11/651(1.6)	NK	3/74 (4)	NK*
L et al. [38]	204	103/204 (50.5)	35/103 (34)	4/103 (3.9)	2/103 (1.9)	81 (78.6)	SS*
YH et al. [39]	60	3/60 (5)	1/3 (33.3)	NK	1/3 (33.3)	NK	SS*
Y et al. [41]	74	23/74 (31)	NK	NK	NK	NK	SS*
W et al. [42]	1099	96/1099 (8.7)	41/1099 (3.8)	55/1099 (5)	NK	NK	NK*
X et al. [43]	1391	171/1391 (12.3)	15/171 (8.8)	11/171 (6.4)	NK	NK	NK*
g JJ et al. [44]	140	55/139 (39.6)	18/139 (12.9)	24/139 (17.3)	8/139 (5.8)	NK	NK*
K et al. [45]	137	11/137 (8)	11/137 (8)	NK	NK	NK	NK*
l YR et al. [46]	278	97/278 (34.8)	56/278 (20.1)	63/278 (22.6)	NK	NK	NK*
ankeril G 2020 [47]	116	37/116 (31.9)	12/116 (10.3)	12/116 (10.3)	NK	5/116 (4.3)	NK*
S et al. [48]	1141	183/1141 (16)	68/1141 (5.9)	134/1141 (11.7) 119/1141 (10.4)	45/1141 (3.9)	16/1141 (9)	NK*

ıg C et al. [50]	41	1/40 (3)	1/40 (3)	NK	NK	NK	NK*
ı N et al. [51]	99	2/99 (2)	1/99 (1)	NK	NK	NK	NK*
g BE et al. [52]	18	4/18 (22.2)	3/18 (16.6)	3/18 (16.6)	NK	NK	SS*
ŁW et al. [53]	62	3/62	3 /62 (4.8)	NK	NK	NK	NK*
el R et al. [54]	9	2/9 (22.2)	2/9 (22.2)	NK	NK	NK	SS*

Frequency of gastrointestinal infection by SARS-CoV-2; GI symptomatology or enteric involvement (GIS); GI sampling that usually included: *stool swab (SS)* or histological samples (H); *Respiratory samples could include nasal and pharyngeal swabs, bronchoalveolar lavage fluid, sputum or bronchial aspirates (URT and LRT), other serological samples, but in this review we focused on studies of intestinal samples; NK=not known or datum not reflected

Table 3 Fecal excretion of viral RNA of SARS-CoV-2 and the possible fecal-oral transmission pathway based on viral load and intestinal cytology according to the experimental studies included in the review

r of on	Laboratory technique (genes tested)	VLAS (log_{10} copies/µL, log_{10} cop/swab, qPCR Ct values)	Positive fecal samples n (%)	Positive fecal samples after negativization respiratory samples n (%)	Fecal RNA detection range (days)	Infer fecal-oral transmission
t al.	qRT-PCR by HiScript® II One Step qRT-PCR	n_1= 4/15 (27%) qPCR Ct: 30.9-31.2 n_2= Day 1: 5/16 (31 %) Day 5: 6/16 (38 %) Ct: 17.8-33.8 qPCR	n:1 = 4/15 (27) n:2 Day 0: 5/16 (31) Day 5: 6/16 (38)	NK	NK	NK
2020	qRT-PCR; histological NK	ACE2 abundantly present in the epithelia of the small intestine	NK	8/23 (34,7)	R: 1-35	Family Cluster person-person
2020	rRT-PCR; Duodenal-rectal histology by endoscopyhistological staining (H&E) and viral staining of the ACE2 receptor, by confocal laser scanning microscopy (Viral nucleocapsid protein staining)	ACE2 stained positive in the cytoplasm of glandular cells of gastric, duodenal and rectal epithelia R: image 20mm-100mm	39/73 (53,4)	17/73 (23,3)	R: 3-10	Propagation of infected cells to uninfected cells
t al.	rRT-PCR (RdRp/E)	NK	1/1 (100)	1/1 (100)	R: 5-17	Family Cluster person-person
t al.	RT-PCR (ORFab/N)	3/3 (100) Ct value <40	3/3 (100)	3/3 (100)	R: 4-30	Fecal-oral Possible contaminated fomites
2020	rRT-PCR (N)	9/17 (53%) R: 500 - 1.21 x 10	9/17 (53)	NK	R: 3-15	Family Cluster person-person
2020	RT-PCR	41/74 (55 %) Ct: 28,26 ±11 R: 8-47	41/74 (55)	32/41 (78)	after first symptom $\bar{x}$: 27.9 (SD: ±10.7) R:0-42 After respiratory negativization $\bar{x}$: 11.2 (SD: ±9.2) R: 0-33	Possible fecal-oral
et al.	rtRT-PCR (RdRp-	6.8 – 7.4 x 10 g	2/5 (40)	NK	R: 2-18	Family Cluster

	IP1/E)	stool				person-person
t al.	RT-PCR (ORFab/N) virus cellular isolation	<106; R: 6.76 x 10^5 - 7.11 X 10^8	8/9 (89)	5/8 (62,5)	R: 5-12	Family Cluster
2020	rRT-PCR (RdRp/E)	500-700 R: 1/27-1/37 x 10^5	0/2 (0)	NK	R: 4-19	NK

VLAS=Viral load in stool or anal swab: value of viral load detected in stool samples or rectal swabs; R: range of days; M: mean number of days; CS= cytological staining of tissue samples; day of detection=day of infection on which SARS-CoV-2 virus is detected in GI samples; Ct= for viral RNA measurements, some authors used cycle threshold (Ct) values of serial rectal and nasopharyngeal swab tests to approximately indicate viral load (inversely related to the Ct value) to show their change over time in sampled patients with a positive value of 40 for SARS-CoV-2

Figures

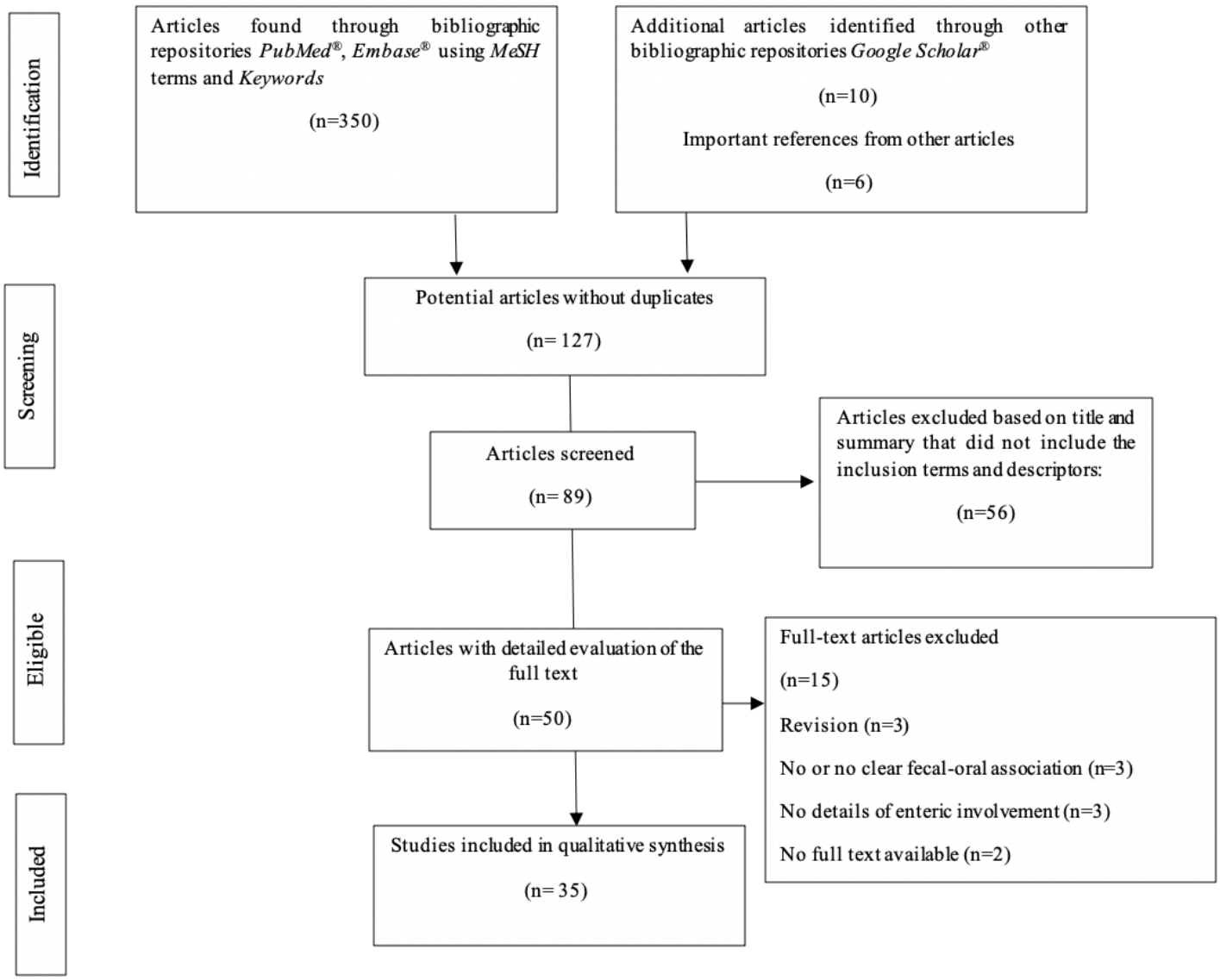

Figure 1

Four-level flow chart of studies on epidemiological scientific evidence on the possible fecal-oral transmission pathway of SARS-CoV-2 infection (COVID-19)