EDITORIAL

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ЖЕЛУДОЧНО-КИШЕЧНЫЕ ПРОЯВЛЕНИЯ ПРИ НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИИ. ОБЗОР ЛИТЕРАТУРЫ И МЕТААНАЛИЗ

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РЕЗЮМЕ. Новая коронавирусная инфекция, вызванная тяжелым острым респираторным синдромом, коронавирусом 2 (SARS-CoV-2), возникла в Ухане, провинция Хубэй, в начале декабря 2019 года, далее быстро распространилась по всему Китаю, а затем и по всему миру, переросла в пандемию и продолжает угрожать здоровью людей. Во многих странах были зарегистрированы клинические случаи новой коронавирусной инфекции с проявлениями симптомов со стороны желудочно-кишечного тракта (такие симптомы, как потеря аппетита, тошнота, рвота, диарея, потеря вкуса, боли в животе) при отсутствии симптомов поражения со стороны дыхательных путей, а в фекалиях при этом идентифицирована РНК SARS-CoV-2. По данным разных авторов, частота болей в животе составляет 10–29%, тошноты и рвоты — 10–29%, диареи — от 30 до 50% случаев. Симптомы могут быть связаны с непосредственным действием вируса на кишечный эпителий, ткань поджелудочной железы и связанной с этим ферментативной недостаточностью, развитием дисбиоза. В некоторых исследованиях были описаны многократные случаи обнаружения РНК SARS-CoV-2 в кале пациентов длительно с гастроинтестинальными проявлениями, одновременно у этих же пациентов ПЦР-мазки из зева и носа на SARS-CoV-2 при многократном заборе становились отрицательными, то есть возможна передача инфекции SARS-CoV-2 не только воздушно-капельным путем, но и фекально-оральным. В связи с чем анализ желудочно-кишечных симптомов (их частота и клинические особенности), предшествующих респираторным проявлениям во время COVID-19 или при отсутствии респираторных проявлений, может быть диагностически и эпидемиологически значим для улучшения раннего выявления и лечения новой коронавирусной инфекции. В данной статье представлен метаанализ желудочно-кишечных проявлений при COVID-19. В метаанализе рассматривается вопрос о степени вовлечения желудочно-кишечного тракта при SARS-CoV-2. Эти результаты могут помочь врачам-клиницистам своевременно установить и дифференцировать новую коронавирусную инфекцию. Клинические врачи могут недооценивать значимость проявлений желудочно-кишечных симптомов в практике, что может повлиять на точность постановки диагноза.

КЛЮЧЕВЫЕ СЛОВА: COVID; COVID-19; коронавирус; SARS-CoV-2; желудочно-кишечный тракт; поражение.

GASTROINTESTINAL MANIFESTATIONS OF NOVEL CORONAVIRUS INFECTION. REVIEW AND META-ANALYSIS

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SUMMARY. Novel coronavirus infection causing a severe acute respiratory syndrome originated in Wuhan, Hubei province, at the beginning of December 2019. Clinical cases of novel coronavirus infection associated with gastro-intestinal symptoms (like loss of appetite, nausea, vomiting, diarrhea, loss of taste and abdominal pains), but without any symptoms of a respiratory disorder were registered in many countries. However, the fecal test showed RNA of coronavirus. The findings of different investigations show prevalence of abdominal pains being registered in 10–29% cases, nausea and vomiting in 10–29%, and diarrhea from 30 to 50% cases. The symptoms can be due to direct action of the virus to the intestinal epithelial lining, pancreas tissue resulting in enzymatic insufficiency and development of dysbiosis. Some investigations note multiple cases of revealing RNA of coronavirus in fecal test of patients with prolonged gastrointestinal manifestations, at the same time the PCR swab tests from the nasopharynx, which were taken several times, showed negative results to coronavirus in these patients, i.e. coronavirus can be transmitted not only by air, but also by the fecal oral way. The analysis of gastro-intestinal symptoms (their prevalence and clinical peculiarities) followed by respiratory manifestations of COVID-19, or in a case of absence of respiratory symptoms, turn to be diagnostically and epidemiologically significant for early detection and treatment of novel coronavirus infection. Meta-analysis of gastrointestinal manifestations of novel coronavirus infection is presented in this article. The results may help the practitioners to diagnose and differentiate the novel coronavirus infection in due time.

KEY WORDS: COVID; COVID-19; coronavirus; SARS-CoV-2; gastrointestinal tract; involvement.

BACKGROUND

Coronaviruses are positive-stranded RNA viruses family comprising 43 types and affecting human beings, birds and amphibian [1–4]. Their spike glycoproteins resemble the solar crown. SARS-CoV-2 is a beta coronavirus resulting in pandemic COVID-19. The disease caused by novel coronavirus (SARS-CoV-2) mainly affects respiratory system, however gastrointestinal tract can also be affected. The prevalence of abdominal pains is 10–29%, according to different investigations, vomiting and nausea rates are 10–29%, diarrhea varies from 30 to 50% of cases [10]. Despite the pandemic prevalence of severe respiratory syndrome caused by SARS-CoV-2, features of clinical manifestations, non-standard course of the disease and routes of its transmission seem still unclear. Huge retrospective epidemiological studies in Wuhan have shown that most of novel coronavirus infection cases were accompanied by fever, weakness, dry cough and other symptoms characteristic of pulmonary system involvement [12].

To penetrate a cell angiotensin-converting enzyme 2 (ACE 2) receptors are used by SARS-CoV-2 [36, 49]. Angiotensin-converting enzyme 2 receptors are known to be expressed by kidneys, gastrointestinal tract and other tissues as well [18]. Moreover, angiotensin-converting enzyme 2 not only transports neutral amino acids and maintains homeostasis of the intestine but also has other functions besides renin-angiotensin system. The conditions of angiotensin-converting enzyme 2 disturbance in its expression and function potentially activate intestinal dysbacteriosis [2, 6, 9]. Most investigations evidently demonstrate that high expression of (ACE2) in the intestinal tract make small and large intestines highly susceptible to infections by SARS-CoV-2 [14, 17]. This theory has been proved clinically by the biologically informative analysis of COVID-19 case, based on a single-cell transcriptomics which was aimed at revealing ACE2 expressing cell distribution. The recent investigation has shown ACE2 expression is more common in the ileum and the large intestine rather than in the lungs. ACE2 is better absorbed by the ileum and the large intestine enterocytes thus explaining diarrhea in most of COVID-19 patients [19, 44]. Furthermore, ACE2 is revealed in stratified epithelial cells of the esophagus [44]. According to the Human Protein Atlas database the matrix expression of RNA and ACE2 protein

in the intestine is 100 times higher than it is in the lungs [7, 33–35].

Many countries have recorded clinical cases of novel coronavirus infection with the symptoms of gastrointestinal tract (like loss of appetite, nausea, vomiting, diarrhea, loss of taste, abdominal pains) with no symptoms of the respiratory tract involvement [20, 23, 29]. Several COVID-19 cases were revealed SARS-CoV-2 RNA by clinical tests of stool after PCR-negative results taken from the nasopharynx, these cases were registered in China and the USA [11, 32, 39]. Furthermore, positive stool tests in COVID-19 patients are confirmed in 53.42% cases of the hospitalized patients. [41, 43]. Thus, we may conclude gastrointestinal tropism of SARS-CoV-2 [15, 22, 26]. It requires scientific data analysis concerning prevalence of gastrointestinal manifestations of this infectious disease.

MATERIALS AND METHODS

A systematic survey and meta-analysis were carried out according to PRISMA recommendations [27]. The databases from the main publications systems like PubMed and e-Library for the period from 2011 to 2020 were collected. The data were assessed according to the theme, by their title and abstract correspondence by two authors independently. The total search was performed without any limitation, by the language, date, publication status limitations and other characteristic features of the investigation. The articles and/or abstracts contained such terms as “COVID”, “COVID19”, “coronavirus”, “SARS-COV2”, “gastro-intestinal” and “digestive”. The selection criteria were limited to studies of COVID-19 patients showing the symptoms of the gastro-intestinal tract (nausea, vomiting, diarrhea, abdominal pain) and with those having no symptoms of the gastro-intestinal tract as a comparison group.

As a result, we found 170 articles, each of which was analyzed. Meta-analysis included 30 articles, as each of them corresponded to the requirements of the investigation; representing detailed quantitative data about gastrointestinal symptoms. Meta-analysis included the studies describing individual gastro-intestinal symptoms if they reported the share of cases with the symptom (Table 1).

Statistically the data were processed with MS Excel software and MedCalc programs. All the data were collected in one database and divided into groups. Signs percentage and confidence interval (CI) for the share were calculated afterwards.

RESULTS

60 investigations with 4243 cases were analyzed in a recent meta-analysis of the Chinese groups of scientists. Total prevalence of gastrointestinal symptoms was in 17.6% (CI 95%, 12.3–24.5); 11.8% cases with non-severe form of COVID-19 showed gastrointestinal symptoms (CI 95%, 4.1–29.1), 17.1% cases with severe form of COVID-19 had gastrointestinal symptoms (95%, 6.9–36.7). This meta-analysis showed prevalence of positive RNA SARC-CoV-2 stool results in 48.1% (CI 95%, 38.3257.9); 70.3% of them were with positive virus results (CI 95%, 49.6–85.1), these tests were collected right after negative PCR tests from nasopharynx [5].

The American investigation, included in the current meta-analysis, surveyed 150 COVID-19 hospitalized patients, among them 31 patients (20.6%) had at least one or more gastrointestinal symptoms. These patients were compared with the rest 119 COVID-19 patients having no gastrointestinal symptoms (control group). The average age of the patients was 57.6, and 63.3 in the control group. Statistically significant difference in the concomitant diseases and laboratory data were not noticed. Mortality rate between the study group and control group did not differ (41.9 vs 37.8% $p=0.68$). Statistically significant difference in the secondary outcomes, including the duration of the hospitalized days (7.8 days vs 7.9 days, $p=0.87$) and the artificial ventilation requirement were not noticed (29% vs 26.9%, $p=0.82$). The analysis of the laboratory findings had no statistically significant difference in both study and control groups: average hemoglobin level, leukocytes, lymphocytes and thrombocytes count. Ferritin level was lower in the study group with gastrointestinal symptoms than in the control group, but the result was statistically insignificant ($p=0.61$). The average levels of CRP, creatinine and lactic acid were higher but they were not statistically significant in both groups [31].

In retrospective investigation headed by Chaoqun Han, the clinical picture of the COVID-19 patients was most commonly the following: 67 patients were hospitalized with diarrhea, 13 of them (19.4%) developed diarrhea as a first symptom before respiratory disorders; the others developed diarrhea within 10 days after respiratory symptoms. Females developed diarrhea most commonly (44/67, 65.7% vs 71/139, 51.1%, $p=0.048$). Diarrhea lasted from 1 to 14 days,

Table 1

Clinical manifestations of gastrointestinal symptoms in COVID-19 patients

Authors of investigations	Research date	Country	COVID-19 patients, total	COVID-19 patients with gastrointestinal manifestations	Decrease of appetite	Nausea	Vomiting	Diarrhea	Abdominal pains
Lei Zhang and others [46]	2020	China		80	43	17	17	33	
Preethi Ramachandran and others [30]	2020	USA	150	31		6	6	15	3
Tharwat Sulaiman and others [32]	2020	China	254	66		21	15	46	3
Hu Zhang and others [44]	2020	China	505	164	93	27	13	62	17
Xi Jin and others [15]	2020	China	651	74		10	11	53	
Jin-Wei Ai and others [3]	2020	China	142	7	7	4	2	6	6
Valeri Velev and others [34]	2020	Bulgaria	31	14		5	5	4	
Yaru Xiao and others [41]	2020	China	912	90	22	22	15	90	6
Jerome R. Lechien and others [18]	2020	Italy		188	92		39	71	40
Ting Zheng and others [47]	2020	China	1320	192	62		57	107	11
Jitian Li and others [20]	2020	China	655			22	19	33	
Jiangshan Lian and others [21]	2020	China	465				22	36	
Chien-Hsiang Weng and others [39]	2020	USA	105				39	39	
George Cholankeril and others [5]	2020	USA	207	70			22	22	14
Samson Ferm and others [8]	2020	USA	892	219	105	148	91	177	70
Nirmaljot Kaur and others [16]	2020	China, USA, Germany, Italy, Vietnam, Thailand, Canada, Nepal, Korea	6635		132		343	627	
AntonioVena and others [36]	2020	Italy	317				14	18	
Fei Xiao and others [40]	2020	China	74					26	
Kui Liu and others [23]	2020	China	137					11	
WenjieYang and others [42]	2020	China	149				1	11	
M Liu and others [24]	2020	China	30				9	9	
Wei-Jie Guan and others [37]	2020	China	1099				55	42	
Dawei Wang and others [27]	2020	China	138			14	5	14	3
Lei Pan and others [27]	2020	China	204	103	81		4	35	2
Shihua Luo and others [25]	2020	China	1141	183	180	134	119	68	45

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G-Q Qian and others [29]	2020	China	91		23	11	6	21	
Zhenyu Fan and others [7]	2020	China	148				3	6	
Chaoqun Han and others (Digestive only) [13]	2020	China	206	48	31		7	23	2
Chaoqun Han and others. (Digestive + respiratory) [13]	2020	China	206	69	39		17	44	7
Jin-Jin Zhang and others [45]	2020	China	139	55	17	24	7	18	8

Table 2

Number of COVID-19 patients with gastrointestinal symptoms

Gastrointestinal manifestations	COVID-19 patients with gastrointestinal symptoms			COVID-19 patients without gastrointestinal symptoms		
	Percentage	CI 95%	Number of investigations	Percentage	CI 95%	Number of investigations
Decrease of appetite	0.5514 815/1478	0.5142–0.5906	13	0.0639 792/12393	0.0595–0.0685	12
Nausea	0.4230 434/1026	0.3841–0.4647	12	0.0792 464/5862	0.0721–0.0867	14
Vomiting	0.2691 478/1776	0.2456–0.2944	19	0.0543 921/16956	0.0509–0.0579	27
Diarrhea	0.5259 934/1776	0.4927–0.5607	19	0.0985 1690/17163	0.0938–0.1033	29
Abdominal pain	0.1551 237/1528	0.1360–0.1762	15	0.0304 200/6577	0.0263–0.0349	15

most commonly 5.4±3.1 days. The average daily bowel emptying was 4.3±2.2 (18 was maximum). The COVID-19 patients with gastrointestinal symptoms rarely complained of the pains and discomfort in the abdomen [14].

204 COVID-19 patients with confirmed diagnosis were investigated by multi-center study. 41.6% patients with gastrointestinal symptoms developed nausea and vomiting, 17.2% COVID-19 patients had diarrhea [28]. One should not neglect that the patients with moderate COVID-19 more commonly developed diarrhea, nausea and vomiting, then the patients with mild case of COVID-19 [45]. The fact that the digestive symptoms are closely associated with the severity of the condition was also confirmed by another investigation carried out in Wuhan [38]. Diarrhea, nausea, vomiting and anorexia were common for the intensive care patients than in those not being admitted to the intensive care unit. Anorexia became a predictor of the severity of the COVID-19 patients condition and a statistically significant symptom.

RESULTS OF META-ANALYSIS

In 30 chosen investigations that we have analyzed clinical manifestations are expressed by such gastrointestinal symptoms as decrease of appetite, nausea, vomiting, diarrhea and abdominal pains in the study group as compared with those having no gastrointestinal symptoms (Table 1, Table 2).

As a result, diarrhea seems to be most common symptom of the gastrointestinal tract. This symptom was noticed in 19 investigations with the total percentage of 0.5259 (CI 95% 0.4927–0.5607). The next symptom is vomiting, which is mentioned in 19 investigations, with 0.2691 percentage (CI 95% 0.4927–0.5607). Abdominal pain was registered in 15 investigations with the percentage of 0.1551 (CI 95% 0.1360–0.1762). Decrease of appetite was mentioned in 13 investigations with percentage of 0.5514 (CI 95% 0.5142–0.5906).

CONCLUSION

The meta-analysis was based on retrospective survey of the currently published research works. It took into account data and material limitations, contradictory results of the investigations concerning the involvement of the gastrointestinal tract involvement accompanying COVID-19 patients. The results of the investigation dealing with the degree of gastrointestinal tract involvement in SARS-CoV-2 cases can help the clinicians make a correct diagnosis and differentiate novel coronavirus infection in due time.

It is necessary to carry out further prospective research work to reveal total involvement of the gastrointestinal tract in novel coronavirus infection, to assess the degree of gastrointestinal influence on the clinical course and clinical outcome of the infectious disease.

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