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The outcomes of Gastrointestinal manifestations in Covid-19 infection on mortality, disease severity and hospitalization period. A mini-review

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Abstract: Introduction: Since the documentation of the first case of Covid-19 disease in Dec 2019 in China the world is suffering under the weight of this pandemic which applied a heavy burden on public health. Although covid-19 infection is dangerous for causing Acute respiratory distress syndrome and its sequelae however an important number of cases manifest with gastrointestinal symptoms whether before or during illness. We will try in this mini-review to highlight the prevalence of gastrointestinal symptoms in Covid-19 patients and its impact on disease prognosis.

Methods: We reviewed 43 research articles, 24 met selection criteria while the remaining articles were screened for information regarding any gastrointestinal manifestations.

Conclusion: Some cases were found to have GI manifestations without pulmonary disease. Most reports showed GI manifestations have no significant association with worse outcomes but are associated with longer hospitalization period. Further studies will help determine the impact of GI manifestations on disease course.

Keywords: COVID-19, Gastrointestinal symptoms, outcomes, Mortality, severe disease, hospitalization period.

نتائج التظاهرات الهضمية عند مرضى Covid-19 على الوفيات وشدة المرض وفترة الاستشفاء. مراجعة مصغرة

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المستخلص: تقدمة: منذ توثيق أول حالة إصابة بمرض كوفيد-19 في ديسمبر 2019 في الصين، يعاني العالم تحت وطأة هذا الوباء الذي شكل عبئًا ثقيلًا على الصحة العامة. على الرغم من أن عدوى كوفيد-19 خطيرة لتسببها في متلازمة الضائقة التنفسية الحادة وعقابيلها، إلا أن هناك عددًا كبيرًا من الحالات التي تتظاهر بأعراض هضمية سواء قبل المرض أو أثناءه. سنحاول في هذه المراجعة المصغرة تسليط الضوء على معدل انتشار أعراض الجهاز الهضمي لدى مرضى كوفيد-19 وتأثيرها على تشخيص المرض.

الطرق: قمنا بمراجعة 43 مقالة بحثية، 24 منها استوفت معايير الاختيار بينما تم فحص المقالات المتبقية للحصول على معلومات بخصوص أي مظاهر معدية معوية لعدوى كوفيد-19.

الخلاصة: وجدنا أن بعض المرضى لديهم تظاهرات معدية معوية بدون مرض رئوي. أظهرت معظم التقارير أن تظاهرات الجهاز الهضمي ليس لها ارتباط ذو قيمة بنتائج أسوأ ولكنها مرتبطة بفترة مكوث أطول في المستشفى.

ستساعد الدراسات الإضافية في تحديد تأثير مظاهر الجهاز الهضمي على مسار المرض.

الكلمات المفتاحية: كوفيد-19، أعراض الجهاز الهضمي، النتائج، الوفيات، المرض الشديد، فترة الاستشفاء.

INTRODUCTION.

Since the documentation of the first case of Covid-19 disease in Dec 2019 in China the world is suffering under the weight of this pandemic that applied a heavy burden on public health.

Although covid-19 infection is dangerous for causing Acute respiratory distress syndrome and its sequelae however an important number of cases manifest with gastrointestinal symptoms whether before or during illness.

We will try in this mini-review to highlight the prevalence of gastrointestinal symptoms in Covid-19 patients and its impact on disease prognosis.

METHODS.

Data sources and search strategy:

In this mini review, we conducted a search and review using PubMed, Science Direct and Google scholar for studies published between Jan 1, 2020, and June 17, 2021. The results of initial search strategy were first screened by title and abstract. The full texts of relevant articles were examined for inclusion and exclusion criteria.

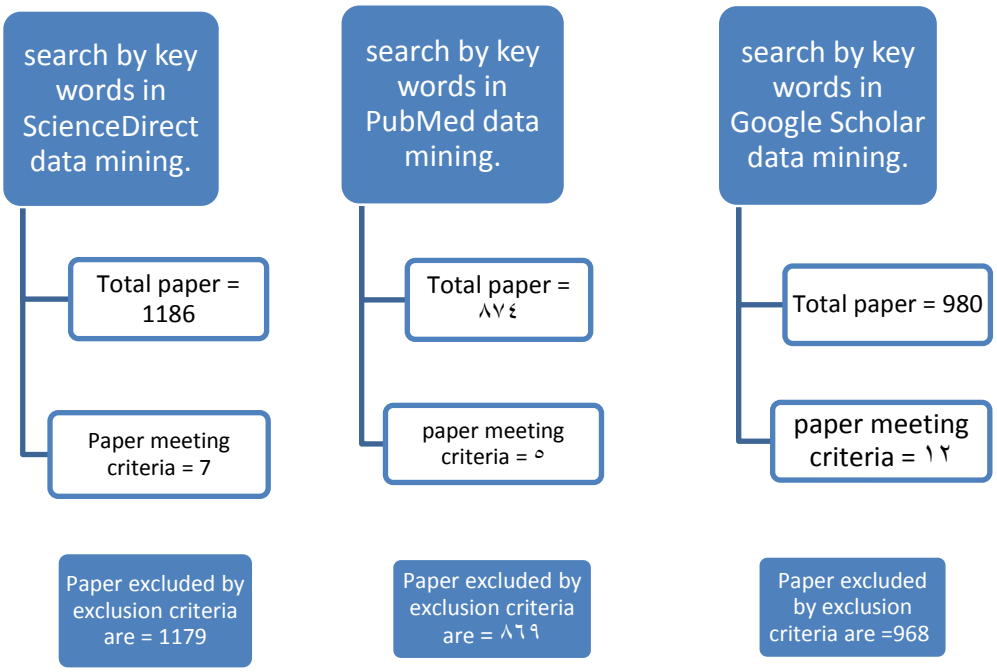
Selection criteria:

Eligibility criteria included studies looking at patients with COVID-19 having GI symptoms (diarrhea, anorexia, nausea, vomiting and abdominal pain) compared to those with COVID-19 infection but without any GI manifestations as a control group and studies that compared the prevalence of gastrointestinal symptoms according to the severity of COVID-19.

We included published peer-reviewed articles that reported the epidemiological, clinical features, prevalence of gastrointestinal findings, clinical outcomes and mortality in confirmed COVID-19 infected patients by positive RT-PCR. Additional articles were retrieved by screening the reference lists of included studies. Included study designs: case series, retrospective cohort studies, case control studies, cross-sectional studies, meta-analysis studies, review studies and observational studies for assessing outcomes, with no language restrictions. We excluded case reports, duplicate studies and studies that lack relevant information.

Data extraction and definitions:

Specific search terms used were "COVID-19" or "SARS-COV-2" or "CORONAVIRUS" and "GASTROINTESTINAL SYMPTOMS" or "DIGESTIVE SYMPTOMS" or "GASTROINTESTINAL MANIFESTATIONS" and "SEVERITY" and "MORTALITY" and "OUTCOMES" and" CLINICAL PROGRESSION" and "HOSPITALIZATION". Severe disease was defined according to the studies, mainly on patients with need of intensive care unit (ICU) care, or having acute respiratory distress syndrome (ARDS), or patients with pulse oxygen saturation (Spo2) less than 90%, patients needing mechanical ventilation were also classified as having severe disease.



RESULTS.

Table added in the bottom of this article demonstrates the prevalence of disease severity among patients with covid-19 having GI symptoms in comparison to those without GI symptoms.

DISCUSSION.

Examination of the articles included in this Mini-Review of medicinal literature revealed a significant presence of gastrointestinal symptoms in covid-19 infected individuals with variable prevalence ranging between 16% to 33%, [1] Among GI manifestations of covid-19 infection (excluding anorexia) diarrhea was the most common symptom [2,3]

The possible reason for GI manifestations is that SARS-CoV-2 spike protein binds Angiotensin-converting enzyme 2 (ACE2) receptors (abundantly expressed in pulmonary and intestinal epithelium) [4]

impairing its function to mediate host cell entry, [5, 6] Reports showed that the presence of diarrhea is associated with higher viral load and prolonged viral shedding for up to ≥ 33 days [3, 5, 7] abdominal pain, however, may be associated with increased viral replication in intestinal tract [5] for it was common among patients receiving intensive care unit (ICU) care [8, 9] Also, SARS-CoV-2 RNA can be detected in stool samples of infected individuals which indicates possible fecal-oral transmission [3, 10] and association with increased disease severity. [11] Studies also found that gastrointestinal (GI) manifestations may precede pulmonary manifestations [5, 12, 13, 14] and were present without pulmonary manifestations in some cases [12, 15, 16, 17, 18] causing delayed diagnosis of covid-19 infection and subsequent negative impact on patients and their contacts.

The presence of GI symptoms in covid-19 patients was associated with longer hospitalization period, [7, 13, 14, 15, 19, 20, 21] But mortality rate, however, was similar to overall mortality [22, 23] while other studies found that patients with GI manifestations have lower mortality rates. [19, 21, 24, 25]

Moreover, studies showed an increase in disease severity in Covid-19 patients with GI manifestations including clinical deterioration and ICU admission [12, 13, 14, 23, 26, 27, 28, 29, 30, 31, 32] but on the contrary many studies linked the presence of GI symptoms in COVID-19 patients with decreased disease severity. [15, 16, 19, 33, 34, 35, 36]

Early management of diarrhea and other GI symptoms in a similar fashion to GI infections (ie, use of Quinolones or Cephalosporins) may prove to be beneficial, and is to be considered in subsequent studies.

Knowing studies recognized in this mini-review documents in-patient cases and there are numerous undocumented out-patient cases.

CONCLUSION.

Since the beginning of COVID-19 pandemic gastrointestinal symptoms were recognized with variable frequency depending on the type of study.

Some cases were found to have GI manifestations without pulmonary disease.

Thus awareness of this route of infection is important for early and adequate management and to decrease infection spreading.

Most reports showed GI manifestations have no significant association with worse outcomes but are associated with longer hospitalization period.

Further studies will help determine the impact of GI manifestations on disease course.

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Author	Date of acc/pub	Region of study	Type of study	N*	Mean age	n (GI)**	GI manifestations	Severe disease		Death	
								GI group	Non-GI group	GI group	Non-GI group
Huang C et al[37]	24.Jan.2020 Pub	China	Retrospective Cohort	41	49	1	Diarrhea 1	0	1	N/A	N/A
Zhang JJ et al[38]	19.Feb.2020 Acc	China	Case series	140	57	55	Diarrhea 18 Nausea 24 Vomiting 7 Abdominal pain 8 Anorexia 17	24	33	N/A	N/A
Young BE et al[33]	27.Feb.2020 Acc	Singapore	Descriptive Case series	18	47	N/A	Diarrhea 3	0	2	0	0
Guan W et al[39]	28.Feb.2020 Pub	China	Multicenter Cross-sectional	1099	47	97	Diarrhea 42 Nausea/vomiting 55	22	151	N/A	N/A
Zhou F et al[40]	9.Mar.2020 Pub	China	Retrospective multicenter cohort	191	56	16	Diarrhea 11 Nausea/vomiting 10	N/A	N/A	5	49
Zhou Z et al[41]	12.Mar.2020 Acc	China	Retrospective Cross-sectional	254	50.6	66	Diarrhea 46 Nausea 21 Vomiting 15 Abdominal pain 3	2 (ARDS)	3 (ARDS)	4	12
Jin X et al[26]	17.Mar.2020 Acc	China	Retrospective Case series	651	46.4 ± 14.19	74	N/A	0	0	0	0

Author	Date of acc/pub	Region of study	Type of study	N*	Mean age	n (GI)**	GI manifestations	Severe disease		Death	
								GI group	Non-GI group	GI group	Non-GI group
Pan L et al [15]	18.Mar.2020 Acc	China	Cross-sectional Multicenter	204	52.91	103	Diarrhea 35 Vomiting 4 Abdominal pain 2 Anorexia 81	6	10	19	17
Lin L et al[12]	24.Mar.2020 Acc	China	Case series	137	57	11	Diarrhea 11	14	6	0	0
Han C et al[13]	31.Mar.2020 Acc	China	Retrospective Cohort	206	62.5 ± 32.5	117	Diarrhea 67 Vomiting 24 Abdominal pain 9 Poor appetite 70 Low appetite 32	N/A	N/A	N/A	N/A
Nobel YR et al[19]	8.Apr.2020 Acc	USA	Retrospective Case control	278	≥ 18- >70	97	Diarrhea 56 Nausea/vomiting 63	14 (ICU)	30 (ICU)	0	9
Wan Y et al[27]	15.Apr.2020 Pub	China	Retrospective Case series	230	47.5	49	Diarrhea 49	26 (severe) 15 (ICU)	35 (severe) 20 (ICU)	4	2
Goyal P et al [42]	17.Apr.2020 Pub	USA	Retrospective Case series	393	62.2	N/A	Diarrhea 93 Nausea/vomiting 75	27/93 22/75	N/A	N/A	N/A
Redd WD et al [2]	20.Apr.2020 Acc	USA	Multicenter Cohort	318	63.4	195	Diarrhea 107 Nausea 84 Vomiting 49	20	15	16	16

Author	Date of acc/pub	Region of study	Type of study	N*	Mean age	n (GI)**	GI manifestations	Severe disease		Death	
								GI group	Non-GI group	GI group	Non-GI group
							Abdominal pain 46 Loss of appetite 110				
Klopfenstien T Et al [34]	27.Apr.2020 Pub	France	Retrospective Case series	114	56 ± 18	N/A	Diarrhea 55 Nausea 52 Vomiting 9 Abdominal pain 19	4	8	N/A	N/A
Zachariah et al [43]	13.May.2020 Acc	USA	Retrospective Case series	50	≤ 21	7	Diarrhea 2 Vomiting 3 Abdominal pain 5	4	5	N/A	N/A
Cao et al [35]	27.May.2020 Acc	China	Retrospective Cohort	157	49.3	63	Diarrhea 25 Nausea 21 Anorexia 47	8	33	N/A	N/A
Ai JW et al [28]	28.May.2020 Acc	China	Retrospective Case series	142	54.1	7	Diarrhea 6 Nausea 4 Vomiting 2 Upper abdominal Discomfort 6 Anorexia 7	3	N/A	1	N/A
Zheng T et al [14]	4.Jun.2020 Acc	China	Retrospective Cohort	1320	50	192	Diarrhea 107 Nausea/vomiting	30	114	N/A	N/A

Author	Date of acc/pub	Region of study	Type of study	N*	Mean age	n (GI)**	GI manifestations	Severe disease		Death	
								GI group	Non-GI group	GI group	Non-GI group
							57 Abdominal pain 11 Anorexia 62				
Ramachandran P Et al [36]	5.Jun.2020 Acc	USA	Retrospective Case-control	150	57 cases 63 controls	31	Diarrhea 15 Nausea/vomiting 6	9 (ICU)	32 (ICU)	13	45
Yang TY et al [7]	1.Jul.2020 Acc	China	Retrospective Single-center Case series	50	GI group 44.56 Non-GI group 42.47	23	N/A	0	0	0	0
Sulaiman T et al [16]	29.Aug.2020 Acc	Iraq	Retrospective Descriptive	140	45 ± 17	78	Diarrhea 41 Vomiting 32 Abdominal pain 42 Anorexia 40	GI only 1 GI+RESP 26	N/A	GI symptoms Only 0 GI + RESP symptoms 6	6
Menon T et al [24]	12.Feb.2021	USA	Meta-analysis	6022	49.5	N/A	N/A	385	1523	702	1334
Abro B et al [25]	17.Jun.2021 Pub	Pakistan	Retrospective Cohort	395	55.4 ± 13.7	95	Anorexia 75 Nausea 59 Vomiting 40 Diarrhea 70	17	67	11	77

N/A: not applicable, acc: acceptance date, pub: publication date, *: N: total number of patients, **: n(GI): number of patients having GI symptoms.