Gastrointestinal Manifestations and Risk Factors in Older Adult COVID-19 Patients Treated at a Secondary Care Unit

Aims: To establish the association of gastrointestinal symptoms and possible factors with COVID-19 in older adults.
Study design: An observational, cross-sectional, descriptive, retrospective study was designed using secondary sources, with a quantitative approach and non-probability convenience sampling.
Place and Duration of Study: The study included a population of 312 records of individuals aged 18 and over with COVID-19. The population was divided into two groups: one consisting of individuals aged 18 to 59 and the other of individuals aged 60 and over.
Methodology: Possible factors and gastrointestinal manifestations associated with COVID-19 in older adults were analysed using univariate and multivariate logistic regression models.
Results: In older adults, the main gastrointestinal manifestation was diarrhea (OR=2.086, 95% CI 1.007-4.322, p=0.048). The risk of COVID-19 increased in older adults with type 2 diabetes (OR=2.053, 95% CI 1.149-3.671, p=0.015), hypertension (OR=2.34, 95% CI 1.191-4.596, p=0.014), and respiratory diseases (OR=8.049, 95% CI 1.913-33.868, p=0.004).
Conclusion: In older adults, diarrhea is a symptom associated with COVID-19, and the primary risk factors were diabetes, hypertension, and respiratory diseases.

Keywords: [COVID-19, SARS-CoV-2, comorbidities, gastrointestinal manifestations]

1. INTRODUCTION.

COVID-19, is a pro-inflammatory disease that causes an acute and highly infectious respiratory syndrome, and primarily manifests with respiratory symptoms, although gastrointestinal symptoms have also been reported in virtually all populations worldwide, including Mexico.[1-4]Given its significance, vulnerability, and magnitude as a transmissible disease, it rapidly became a global public health issue that rapidly overwhelmed the capacity of healthcare systems.[2] To date, a wide variety of clinical presentations have been observed, ranging from the total absence of symptoms, mild flu-like symptoms, gastrointestinal symptoms, to severe respiratory illnesses with dyspnoea, pneumonia, and potentially fatal multi-organ failure.[2]Moreover, the exact incidence of gastrointestinal symptoms is a subject of debate, as it varies according to the population studied and the presentation of the disease.Young et al., reported that, in the first diagnosed cases of COVID-19 in Singapore, the SARS-COV-2 virus was detected in 50% of fecal samples and in 8% of blood samples, but not in urine.[5]Similarly, in Chile, diarrhea and abdominal pain were observed in 7.3% and 3.7% of affected patients, respectively.[6]Various studies conducted worldwide have reported diverse gastrointestinal symptoms in patients with confirmed SARS-COV-2 infection, including diarrhea, nausea, vomiting, and abdominal pain.[7-18]The prevalence of gastrointestinal symptoms varies among populations, and it has been suggested that they are similar in the adult, pediatric, and pregnant populations.[19-20] Additionally, the detection of SARS-COV-2 in fecal samples from infected patients during and after symptom resolution has been reported.[21]Diarrhea has been reported as the primary sign associated with SARS-COV-2 infection in older

adults.2Consequently, research indicates that further studies are needed to fully understand the implications of digestive symptoms in COVID-19 and their impact on the clinical progression of patients, particularly in elderly individuals. It has also been reported that older adults are at higher risk of death or severe disease.

2. MATERIAL AND METHODS.

2.1 Study Design, Population, and Variables.

An observational, cross-sectional, descriptive, retrospective study was designed, using secondary data with a quantitative approach. A non-probabilistic convenience sampling method was used. The unit of research was the medical records of patients hospitalized for COVID-19 from the Emergency Service at the General Hospital of Zone number 76, from the Mexican Institute of Social Security (IMSS). This medical unit was notable for being one of the second-level care hospitals converted into COVID-19 hospitals. The records included were those of patients who tested positive for SARS-CoV-2 via PCR and rapid tests and were diagnosed with COVID-19 based on their clinical-epidemiological characteristics. All information was collected on a specific Triage form by the attending physicians. The data were then compiled into a database, which included sociodemographic and clinical characteristics.

The sociodemographic information included age and gender. Clinical characteristics encompassed pre-existing comorbidities, signs, and symptoms. Comorbidities were defined as dichotomous variables (presence or absence) and included diabetes, hypertension, cardiovascular disease, obesity, overweight, chronic kidney disease, lung diseases, cancer, and others. Additionally, the number of comorbidities was recorded. The signs and symptoms included as dichotomous variables were: ageusia, hyporexia, anorexia, vomiting, diarrhea, and nausea.

2.2 Statistical Analysis.

Categorical variables are presented as absolute and relative frequencies (with their corresponding 95% confidence intervals (CI 95%)) and were compared using the chi-square test. All CI 95% were obtained using a 1000-sample bootstrap.

Numerical variables were compared using the non-parametric Mann-Whitney U test. To determine the potential factors and gastrointestinal manifestations associated with COVID-19 in older adults, the variables were analyzed as dichotomous variables.Univariate and multivariate logistic regression models were employed to estimate associations. A p-value of ≤ 0.05 was considered statistically significant for two-tailed tests.

2.3 Ethical Considerations.

This study was conducted in accordance with good clinical practices as defined by Mexican legislation and the Declaration of Helsinki for research involving human subjects. The designed database utilized an assigned folio number to maintain patient confidentiality. The principles of the 1989 United Nations General Assembly were followed: the principle of lawfulness and loyalty (data were obtained legally), the principle of accuracy (data relevance was verified), the principle of purpose (the database was specific and legitimate before creation), the principle of non-discrimination, and the principle of security. The study was approved by the Local Health Research Committee number 1401, at the Regional General Hospital 196 “Fidel Velázquez Sánchez,” with registration number R-2021-1401-062.

3. RESULTS AND DISCUSSION.

3.1 Results.

3.1.1 Clinical Characteristics of the Study Population

The study included a population of 312 records of individuals aged 18 and over who had COVID-19. The population was divided into two groups: one consisting of adults aged 18 to 59 and the other of older adults (OA) aged 60 and above. The OA group was predominantly female. The main comorbidities identified were hypertension, type 2 diabetes, and respiratory diseases. The primary gastrointestinal manifestations observed were diarrhea and nausea, with less frequent symptoms being ageusia, hyporexia, and vomiting (Table 1).

Table 1. Sociodemographic and clinical characteristics of study population.

Variables	Total population N= 312 n, % (CI 95%)	Adults n= 248 n, % (CI 95%)	OA n= 64 n, % (CI 95%)
Female*	152, 48.7 (42.9-54.5)	112, 45.2 (39.1-51.6)	40, 62.5 (50-75)
Male	160, 51.3 (45.5-57.1)	136, 54.8 (48.4-60.9)	24, 37.5 (25-50)
Overweight	1, 0.3 (0-1)	1, 0.4 (0-1.2)	
Obesity	19, 6.1 (3.5-9)	18, 7.3 (4-10.5)	1, 1.6 (0-6.3)
Diabetes*	84, 26.9 (21.8-32)	59, 23.8 (19-29.4)	25, 39.1 (26.6-51.6)
Hypertension**	96, 30.8 (25.6-36.2)	64, 25.8 (20.6-31.5)	32, 50 (37.5-60.9)
Heart disease	3, 1 (0-2.2)	2, 0.8 (0-2)	1, 1.6 (0-4.7)
Pneumopathies**	10, 3.2 (1.3-5.1)	3, 1.2 (0-2.8)	7, 10.9 (4.7-20.3)
Cancer	7, 2.2 (0.6-4.2)	6, 2.4 (0.8-4.4)	1, 1.6 (0-4.7)
CRF	19, 6.1 (3.5-9)	16, 6.5 (3.6-9.7)	3, 4.7 (0-10.9)
Rheumatoid arthritis	3, 1 (0-2.2)	2, 0.8 (0-2)	1, 1.6 (0-4.7)
Pregnancy	2, 0.6 (0-1.6)	2, 0.8 (0-2)	
Parkinson	1, 0.3 (0-1.3)		1, 1.6 (0-4.7)
ES, PH, hypothyroidism	1, 0.3 (0-1)		1, 1.6 (0-4.7)

AS	1, 0.3 (0-1)	1, 0.4 (0-1.2)	
Chronic gastritis	1, 0.3 (0-1)	1, 0.4 (0-1.2)	
CH	1, 0.3 (0-1)	1, 0.4 (0-1.2)	
hypothyroidism	8, 2.6 (1-4.5)	7, 2.8 (1.2-4.8)	1, 1.6 (0-4.7)
PVI	1, 0.3 (0-1.3)	1, 0.4 (0-1.2)	
Cerebral palsy	1, 0.3 (0-1)	1, 0.4 (0-1.2)	
HIV	2, 0.6 (0-1.6)	2, 0.8 (0-2)	
HPV	1, 0.3 (0-1)	1, 0.4 (0-1.2)	
MG in Triage	68, 21.8 (17.6-27.2)	48, 19.4 (14.5-24.2)	20, 31.3 (20.3-43.8)
Ageusia	12, 3.8 (1.9-6.4)	8, 3.2 (1.2-5.6)	4, 6.3 (1.6-12.5)
Hyporexia	10, 3.2 (1.3-5.1)	7, 2.8 (0.8-4.8)	3, 4.7 (0-10.9)
Anorexy	1, 0.3 (0-1)	1, 0.4 (0-1.2)	
threw up	12, 3.8 (1.9-6.1)	10, 4 (2-6.5)	2, 3.1 (0-7.8)
diarrhea	40, 12.8 (9-17)	27, 10.9 (7.3-14.9)	13, 20.3 (10.9-31.3)
Nausea	16, 5.1 (2.6-7.7)	11, 4.4 (2-7.3)	5, 7.8 (1.6-14.1)

Confidence intervals calculated using 1,000 bootstrap samples. CRF = chronic renal failure. SS= systemic scleroderma, PH= pulmonary hypertension. AS = ankylosing spondylitis. CH= congenital hydrocephalus. PVI = peripheral venous insufficiency. HIV = human immunodeficiency virus. HPV = human papillomavirus. MG= gastrointestinal manifestations on the Triage sheet. OA= older adults. * Probability value <0.05. ** Probability value <0.01. The probability value was calculated using Yates' corrected chi-square test and Fisher's exact test as appropriate.

Notably, in the OA group, no patients were observed to have overweight, ankylosing spondylitis, chronic gastritis, pulmonary hypertension, peripheral venous insufficiency, cerebral palsy, HIV infection, or human papillomavirus infection.

3.1.2 Comorbidities and clinical manifestations associated with COVID-19 in Older Adults aged 60 and over.

The univariate model showed a higher risk of COVID-19 in individuals with a history of type 2 diabetes, hypertension, and respiratory diseases. Similarly, in the multivariate model, the risk increased in OA with type 2 diabetes and respiratory diseases (Table 2).

Table 2. Comorbidities associated to COVID-19 in Older Adults aged 60 and over.

Variables	Crude OR (CI 95%)	*P value*[a]	Ajusted OR (CI 95%)	*P value*[b]
Female	Reference	1	Reference	1
Male	0.494 (0.281-0.869)	0.014	0.564 (0.306-1.038)	0.066
Obesity	0.203 (0.027-1.549)	0.124	0.237 (0.03-1.863)	0.171
Diabetes	2.053 (1.149-3.671)	0.015	1.284 (0.647-2.549)	0.475
Hypertension	2.875 (1.631-5.066)	0.0003	2.34 (1.191-4.596)	0.014
Heart disease	1.952 (0.174-21.876)	0.587	2.573 (0.206-32.14)	0.463
Pneumopathies	10.029 (2.516-39.98)	0.001	8.049 (1.913-33.868)	0.004
Cancer	0.64 (0.076-5.415)	0.682	0.462 (0.051-4.18)	0.492
CRF	0.713 (0.201-2.527)	0.6	0.435 (0.11-1.719)	0.235

OR= odds ratio. b. p value calculated for the variables introduced in the multivariate model: sex, obesity, diabetes, hypertension, heart disease, pneumopathies, cancer, and CRD = chronic renal failure.

Table 3 reports that the only clinical manifestation associated with COVID-19 in OA was diarrhea.

Table 3. Clinical manifestations associated to COVID-19 in Older Adults aged 60 and over.

Variables	Crude OR (CI 95%)	P value[a]	Adjusted OR (CI 95%)	P valure[b]
Ageusia	2.000 (0.583-6.864)	0.271	2.348 (0.661-8.347)	0.187
Hyporexia	1.693 (0.425-6.74)	0.455	1.062 (0.243-4.634)	0.936
Threw up	0.768 (0.164-3.594)	0.737	0.316 (0.050-2.016)	0.223
Diarrhea	2.086 (1.007-4.322)	0.048	2.102 (0.986-4.483)	0.055
Nausea	1.826 (0.611-5.457)	0.281	2.680 (0.690-10.406)	0.154

OR= odds ratio. b p value calculated for the variables introduced in the multivariate model: ageusia, hyporexia, threw up, diarrhea, and nausea.

3.2 Discussion.

3.2.1 COVID-19 and Its Multifactorial, Pro-inflammatory Nature

COVID-19 is a multifactorial, pro-inflammatory disease affecting all age groups, regardless of their social determinants of health, with different predictors depending on the population

and age group studied.[2] The average age of the total population in this study was higher than the average ages reported by other authors (42 to 43 years).[2,22-24] Among older adults, the most prevalent age group was those in their sixties (67.2%, 95% CI 54.7-78.1), followed by those in their seventies (29.7%, 95% CI 18.8-40.6). There were only 2 patients in their eighties.

In the Mexican adult population aged 20 to 59, rhinorrhea and chest pain have been reported as predictors of SARS-CoV-2 infection.[2] However, diarrhea was an independent predictor only in older adults,[2] similar to the findings of the present study. The prevalence of diarrhea in our study was similar to that reported by other authors in Mexico (a non-significant increase of 3.7 percentage points).[2] Nonetheless, many patients present a wide variety of gastrointestinal symptoms, including nausea, vomiting, abdominal pain, diarrhea, and anorexia.[25] Additionally, reports indicate that the prevalence of gastrointestinal symptoms in adult patients with confirmed COVID-19 varies from 3-79%.[7,25-28] According to Tian et al., anorexia was the most commonly reported gastrointestinal symptom in adults (ranging from 39.9-50% of confirmed cases), followed by diarrhea (reported in 2-49.5% of patients), which differs from our results.[12,25-26,28-31] The prevalence of nausea and vomiting ranged from 1% to 29.4%, similar to what we observed in our study (2.3%; 95% CI 0.6-4.2).[25-26] On the other hand, abdominal pain has been less frequently reported in the literature, with a prevalence ranging from 2.2-6% of patients with confirmed COVID-19.[12,25-26,28] However, we did not observe reports of this symptom, although several studies support the varying clinical manifestations among COVID-19 patients and their different proportions across populations.[2,23,32-33] Olfactory dysfunction and anorexia are the most frequently reported complaints, followed by nausea, vomiting, diarrhea, and abdominal pain,[34] but we did not observe reports of anosmia, olfactory dysfunction, or anorexia. Ageusia was observed in less than 10% of the older adults. In our study, the three most frequent gastrointestinal manifestations were diarrhea, nausea, and ageusia, which differs from reports in Mexico by López-Hernández, who reported odynophagia (32.6%), diarrhea (16.6%), and abdominal pain (10.1%).[2] Other authors in different settings reported fever (temperature ≥ 38°C), cough and/or difficulty breathing, accompanied by tachypnea,[2,23,35] or fever with non-specific symptoms such as cough and sore throat, or the presence of anosmia and ageusia.[2,23,36]

3.2.2 Comorbidities and Their Association with COVID-19

In our study population, type 2 diabetes, hypertension, and respiratory diseases were associated with an increased risk of developing COVID-19. Similarly, studies in Mexico have reported that diabetes and pneumonia increase the risk of COVID-19 in both adult and older populations.[2,37] They also report that obesity and smoking increase the risk of COVID-19.[2,37] However, our study shows that hypertension increases the risk of COVID-19, unlike other studies conducted on the Mexican population.[2] Our data, combined with literature reports, show that the factors increasing the risk of COVID-19 are pro-inflammatory clinical conditions that favour an immunocompromised state in older adults. Moreover, several reports suggest the involvement of the angiotensin-converting enzyme II (ACE2) receptor as a mediator of SARS-CoV-2 infection, expressed in type 2 alveolar (AT2) cells, as well as in the oesophagus, ileum, and colon (stratified and absorptive epithelial cells).[38-42] There are also reports showing the presence of SARS-CoV-2 viral ribonucleic acid (RNA) in faecal samples from rectal and anal swabs of COVID-19 patients.[38-42] These findings have been associated with the gastrointestinal manifestations of COVID-19. The role of the immune system in the gastrointestinal tract differs from systemic immunity; it constitutes a protective barrier against the constant presence of invasive and harmless antigens from food. This system continuously processes food antigens and the normal flora of the intestinal lumen without inducing disease, a process known as physiological inflammation, partly mediated by the mechanism of oral tolerance to antigens. [38-42] Consequently, the

physiological response is the absence of an immune response. There is evidence that the SARS-CoV-2 virus, like other coronaviruses, enters lung cells by binding to the angiotensin-converting enzyme II (ACE2), part of the renin-angiotensin system.[38-42] Therefore, it is logical to think that the binding of the virus to the receptor plays a crucial role as an entry route[38-42] to infect cells of the oesophagus, ileum, and colon in a similar manner, disrupting the intestinal barrier mechanisms and generating an immune response associated with the gastrointestinal and systemic manifestations in patients. This mechanism appears to more reliably explain the occurrence of respiratory and gastrointestinal symptoms in COVID-19 patients.[38-42] The gastrointestinal clinical manifestations of SARS-CoV-2 are heterogeneous, with highly variable incidence and prevalence across different populations and age groups worldwide.[2,38-42]

4. CONCLUSION

In our study, the main gastrointestinal manifestations in older adult patients with COVID-19 are diarrhea, nausea, and ageusia. Diarrhea is a symptom significantly associated with COVID-19 in this population group. The primary risk factors in this group are diabetes, hypertension, and respiratory diseases. It is crucial to recognise the symptoms most compatible with COVID-19 to ensure timely and accurate diagnosis, thereby preventing patients with gastrointestinal symptoms from being undiagnosed with the disease.

CONSENT (WHEREEVER APPLICABLE)

No applicate

ETHICAL APPROVAL (WHEREEVER APPLICABLE)

The study was approved by the Local Health Research Committee number 1401, at the Regional General Hospital 196 “Fidel Velázquez Sánchez,” with registration number R-2021-1401-062.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.

2. López-Hernández, D. Clinical Presentation and Factors Associated to COVID-19 Disease in Mexican Patients. Current Journal of Applied Science and Technology. 2022;41(1):40–58.

3. Pappa S, Ntella V, Giannakas T, Giannakoulis VG, Papoutsi E, Katsaounou P. Prevalence of depression, anxiety, and insomnia among healthcare workers during the COVID-19 pandemic: A systematic review and meta-analysis. Brain Behav Immun. 2020;88:901-907. doi: 10.1016/j.bbi.2020.05.026. Epub 2020 May 8. Erratum in: Brain Behav Immun. 2021 Feb;92:247. PMID: 32437915; PMCID: PMC7206431.

4. Zaka A, Shamloo SE, Fiorente P, Tafuri A. COVID-19 pandemic as a watershed moment: A call for systematic psychological health care for frontline medical staff. J Health Psychol. 2020 Jun;25(7):883-887.

5. Young B, Ong X, Kalimuddin S. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA. 2020;323(15):1488–1494.

6. Diaz P, Espino A. Manifestaciones gastrointestinales de pacientes infectados con el nuevo Coronavirus SARS-CoV-2. Gastroenterol. latinoam. 2020;31(1):35-38.

7. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513.

8. Chen Q, Quan B, Li X. A report of clinical diagnosis and treatment of nine case of coronavirus disease 2019. J Med Virol. 2020; 395: 507–513.

9. Guan W, Zheng N, Yu H, Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382:1708-1720.

10. Huang C, Wang Y, Li X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet.

11. Lin L, Jiang X, Zhang Z. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut.

12. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol. 2020;115(5):766-773.

13. Zhang J, Dong X, Cao Y. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(7):1730-1741.

14. Parasa S, Desai M, Thoguluva Chandrasekar V, Patel HK, Kennedy KF, Roesch T, et al. Prevalence of Gastrointestinal Symptoms and Fecal Viral Shedding in Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3(6):e2011335. doi: 10.1001/jamanetworkopen.2020.11335.

15. Singh G, Priya H, Mishra D, Kumar H, Monga N, Kumari K. Oral manifestations and dental practice recommendations during COVID-19 pandemic. J Family Med Prim Care. 2021;10(1):102-109. doi: 10.4103/jfmpc.jfmpc_1605_20.

16. Ministerio de Salud de Chile. SITUACIÓN EPIDEMIOLÓGICA COVID-19. CHILE. https://www.minsal.cl/nuevocoronavirus-2019-ncov/informeepidemiologico-covid- 19/.

17. Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, et al. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. Gastroenterology. 2020 Jul;159(1):81-95. doi: 10.1053/j.gastro.2020.03.065.

18. Spiteri G, Fielding J, Diercke M, Campese C, Enouf V, Gaymard A, et al. First cases of coronavirus disease 2019 (COVID-19) in the WHO European Region, 24 january to 21 february 2020. Euro Surveill. 2020 Mar;25(9):2000178. doi: 10.2807/1560-7917.ES.2020.25.9.2000178.

19. Ludvigsson J. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatrica.

20. Khan M, Khan N, Mustagir G, Rana J, Haque R, Rahman M, et al. COVID-19 infection during pregnancy: a systematic review to summarize possible symptoms, treatments, and pregnancy outcomes. medRxiv.

21. Sanz Segura P, Arguedas Lázaro Y, Mostacero Tapia S, Cabrera Chaves T, Sebastián Domingo JJ. Involvement of the digestive system in covid-19. A review. Gastroenterol Hepatol. 2020 Oct;43(8):464-471.

22. CDC COVID-19 Response Team. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 - United States, February 12-March 28, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(13):382-386.

23. Lan FY, Filler R, Mathew S, Buley J, Iliaki E, Bruno-Murtha LA, et al. COVID-19 symptoms predictive of healthcare workers' SARS-CoV-2 PCR results. PLoS One. 2020;15(6):e0235460.

24. INEGI. Characteristics of deaths registered in Mexico during 2020, preliminary. Press Release no. 402/21, July 29.2021;1-5. [Manuscript in Spanish]

25. Groff A, Kavanaugh M, Ramgobin D, McClafferty B, Aggarwal CS, Golamari R, Jain R. Gastrointestinal Manifestations of COVID-19: A Review of What We Know. Ochsner J. 2021 Summer;21(2):177-180.

26. Tian Y, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. Aliment Pharmacol Ther. 2020;51(9):843-851.

27. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(7):1730-1741.

28. Fang D, Ma J, Guan J, Wang M, Song Y, Tian D, et al. Manifestations of digestive system in hospitalized patients with novel coronavirus pneumonia in Wuhan, China: a single-center, descriptive study [in Chinese]. Chin J Dig. 2020;E005.

29. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-1720.

30. Liang W, Feng Z, Rao S, Xiao C, Xue X, Lin Z, et al. Diarrhoea may be underestimated: a missing link in 2019 novel coronavirus. Gut. 2020;69(6):1141-1143.

31. Cholankeril G, Podboy A, Aivaliotis VI, Tarlow B, Pham EA, Spencer SP, et al. High prevalence of concurrent gastrointestinal manifestations in patients with severe acute respiratory syndrome coronavirus 2: early experience from California. Gastroenterology. 2020;159(2):775-777.

32. Pazgan-Simon M, Rorat M, Buczyńska I, Zińczuk A, Simon K. Gastrointestinal symptoms as the first, atypical indication of severe acute respiratory syndrome coronavirus 2 infection. Pol Arch Intern Med. 2020;130(4):338-339.

33. Wong SH, Lui RN, Sung JJ. Covid-19 and the digestive system. J Gastroenterol Hepatol. 2020;35(5):744-748.

34. Alukal, J.J., Thuluvath, P.J. (2021). Gastrointestinal Manifestations of COVID-19. In: Pitchumoni, C.S., Dharmarajan, T. (eds) Geriatric Gastroenterology. Springer, Cham.

35. Alberta Health Services. COVID-19 Scientific Advisory Group. COVID-19 Symptoms: Symptoms Predictive of a Positive COVID-19 Test, Duration of Symptoms, and Duration of RT-PCR and Viral Culture Positivity.COVID-19 Scientific Advisory Group Rapid Evidence Report;March 31, 2021.

36. Song JY, Yun JG, Noh JY, Cheong HJ, Kim WJ. Covid-19 in South Korea - Challenges of Subclinical Manifestations. N Engl J Med. 2020;382(19):1858-1859. doi: 10.1056/NEJMc2001801.

37. Venancio-Guzmán S, Aguirre-Salado AI, Soubervielle-Montalvo C, Jiménez-Hernández JDC. Assessing the Nationwide COVID-19 Risk in Mexico through the Lens of Comorbidity by an XGBoost-Based Logistic Regression Model. Int J Environ Res Public Health. 2022;19(19):11992.

38. Borruel N. Interacciones bacterianas con el sistema inmunológico intestinal: inmunomodulación. Gastroenterol Hepatol. 2003;26(Supl 1):13-22.

39. Lamas-Barreiro JM, Alonso-Suárez M, Fernández-Martín JJ, Saavedra-Alonso JA. Angiotensin II suppression in SARS-CoV-2 infection: a therapeutic approach. Nefrologia (Engl Ed). 2020 May-Jun;40(3):213-216.

40. Wan Y, Shang J, Graham R, Baric R.S, Li F. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS coronavirus. J Virol. 2020;94:e00127-20.

41. Yan R, Zhang Y, Li Y, Xia L, Gui Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 2020;367:1444–1448.

42. Higuera-de la Tijera F, Servín-Caamaño S, Pérez-Hernández JL. Gastrointestinal symptoms and disorders related to COVID-19. Revista Médica del Hospital General de México. 2022;85(4):169-178.

DEFINITIONS, ACRONYMS, ABBREVIATIONS

Here is the Definitions section. This is an optional section.

Term: Definition for the term

APPENDIX