Case study

Reviewer's notes: All corrections including additions and alterations are done in blue prints. Words intended to be deleted are enclosed between blue brackets (……)

Association of Gastrointestinal Symptoms and clinical outcomes in hospitalized corona disease 2019 patients

ABSTRACT

The coronavirus pandemic 2019 (COVID-19) poses a serious threat to global health. Initially, the respiratory symptoms are at the forefront and dominate the prognosis of the disease. The gastrointestinal symptoms, initially described as rare, are reported more and more frequently in the latest studies.

Our work aimed to determine the prevalence of gastrointestinal manifestations related to COVID 19 and their impact on the prognosis of the disease.

Materials and methods: Prospective analytical descriptive study collecting 93 files of patients hospitalized for a COVID-19 infection confirmed by RT-PCR over a period ranging from October 28, 2021 to April 8, 2022. Data related to patient's demographics, clinical symptoms, comorbidities , vitalsigns at presentation , admission laboratory tests , and outcomes were collected. The patients were divided into 2 groups to compare: Group I COVID 19 patients with digestive manifestations and Group II COVID 19 patients without digestive manifestations.

Digestive manifestations were defined by the presence of at least one of the following symptoms: nausea, vomiting, diarrhoea and abdominal pain.

Results: 91 patients were included in the study with a male predominance in the two groups (Group I sex ratio = 3.25 vs Group II sex ratio = 3.06). Digestive manifestations were indicative of the disease in 37.4% of cases and isolated without respiratory signs in 2.19% of cases. The main digestive symptoms were diarrhoea (25.3%), nausea (14.3%), vomiting (11%), acute abdominal pain (15.4%).

By comparing the 2 groups, we found that young subjects (less than 50 years old) presented more digestive manifestations than elderly subjects (p=0.012).

In terms of comorbidities and smoking, there was no statistically significant difference between the two groups. The mean hospitalization time was 7 days for Group I compared to 9 days for Group II (p=0.114).

A chest CT scan was performed in all patients and found a pulmonary embolism in 10 patients, 4 of whom had initially presented with acute abdominal pain of epigastralgia type with a statistically significant association found: (OR: 4.267, 95% CI (1.02-17.8), p 0.047). In terms of severity of lung involvement, there was no significant difference between the 2 groups (p=0.569).

In terms of mortality, clinical severity of the disease, use of mechanical or non-invasive ventilation and other complications, we found no statistically significant difference between the two groups.

Conclusion: The results of this study suggest that the digestive manifestations linked to COVID 19 occur mainly in young subjects and that their presence is nonspecific and not related to the severity of the disease and does not increase the mortality rate.

In the end, it is suggested to eliminate pulmonary embolism in the face of acute abdominal pain complicated by respiratory distress.

Keys words : corona disease 2019, gastrointestinal symptoms, outcome, association.

INTRODUCTION:

The pandemic caused by severe acute respiratory syndrome corona virus 2 (SARS-COV-2), initially referred to as the 2019 novel coronavirus and termed COVID 19 by the World Health Organization, (it) has been impacting the entire world since December 2019 and causing a massive crisis for global health .

The virus (is) mainly spreads through direct exposure (respiratory droplets, person to person). However, it is also assumedto transmit(ted) by contaminated object(if)s, airborne transmission and faecal-oral transmission [1]. The

COVID 19 is predominantly a respiratory disease, however gastrointestinal (GI) symptoms suchas diarrhoea, abdominal pain and (us) vomiting are increasingly being recognized as important manifestations of COVID 19. The distribution of angiotensi(o)n converting enzyme type 2 receptors in multiple organs in the body and highly in the gastrointestinal tract and the liver provides a possible explanation for the digestive symptoms [1-2] GI symptoms can coexist or even precede respiratory manifestations. Rarely COVID 19 patients can present with only GI symptoms without respiratory symptoms.

It has been of increasing interest (in) whether GI symptoms are associated with severe disease and itis still unclear if the presence of GI symptoms is associated with poor outcomes in COVID 19 or not . Therefore, In our study, we aimed to analyse if the presence of GI symptoms at the time of hospitalization is associated with the severity of disease and poor outcome when compared to those who did not have GI symptoms .

METHODS

Study design and Data source

This is a prospective cohort study conducted in a cohort of COVID19 patients who were admitted to our service, to help COVID 19 patients in the middle of the crisis of the second wave of the disease . We included consecutive patients who were admitted to the hospital with confirmed diagnosis of COVID 19 on nasopharyngeal polymerase chain reaction testing for SARS-COV-2 from 24 October 2021 to 8 January 2022.

Data related to patient's demographics, clinical symptoms, comorbidities, vitalsigns at presentation, admission laboratory tests, and outcomes were collected .

The definition of positive GI symptoms required that the patients have at least one of the following symptoms : nausea , vomiting and diarrhoea or abdominal pain. GI symptoms were recorded in admission, excluding the influence of other medical therapy and externals factors . We've also eliminated all other abdominal emergencies by carrying out a lipase assay and abdominal CT scan (which came back normal) in all our patients with acute abdominal pain.

Demographic variables such as age, sex, smoking status and BMI were obtained. Dataof multiple comorbid conditions such as the history of hypertension, diabetes, heart disease, chronic liver disease, chronic renal disease or chronic obstructive pulmonary disease, the history of cancer or any condition of immunosuppression werecollected. Clinical data included the respiratory symptoms, oxygen status and duration of symptoms.

Laboratory data such as haemoglobin level, haematocrit, WBC, absolute lymphocyte and neutrophils counts, platelet count, ferritin level, C-reactive protein, D-dimer, aspartate aminotransferase and alanine aminotransferase, creatinine and lactate dehydrogenase were noted. Finally, CT findings were noted too.

Stratification of study cohort and outcomes

In our study, the GI symptoms were defined as the presence of nausea, vomiting, diarrhoea, or abdominal pain at the time of admission. The study cohort was stratified into 2 groups based on the presence of GI symptoms: COVID 19 with symptoms (cases) and COVID-19 without GI symptoms (controls) . The primary outcome was death from any cause. Secondary outcomes were identified as total hospital length of stay (LOS) and need for mechanical ventilation during that hospitalization .

Statistical Analysis

Statistical analysis was performed using Jamovi version1.2.27. For continuous variables, mean (SD) and median (IQR) were respectively used for normality and abnormality data, followed by unpaired t-test and non-parametric test when appropriate such as the Mann-Whitney U to compare the groups. Categorical variables were expressed as numbers with percentages (%) and compared using the χ^2 test. A two-sided α of < 0.05 was considered statistically significant.

RESULTS

Baseline Demographics and clinical characteristics

A total of 93 patients were hospitalized with confirmed COVID-19 during the study period from 24 October 2021 to 08 January 2022. 2 patients were excluded because of unavailability of records.

A total of 91 patients met the inclusion criteria and formed our final study population. Of these, 34 (37.4%) patients presented with at least one GI symptoms(nausea, vomiting, abdominal pain and diarrhoea), and 57 (62.6%) had no GI symptoms (controls). (Table 1-2)

In detail, diarrhoea was the most common GI symptoms, which was reported in 14.3% of the cohort, followed by vomiting or nausea, reported in 9.8% of patients and abdominal pain was found in 6.6%.In addition, five patients (5.5%) had all the GI symptoms of diarrhoea, vomiting and abdominal pain, while only three had the symptoms of both vomiting and diarrhoea. For history of contact with patient COVID 19, in controls, we reported 24.6% of the patients compared to 17.6% in the counterparts but there was no statistic significant difference (p=0.441).

Patients were predominantly males in two groups with a mean age of 57.5 years in cases as compared to 63.1 years in controls without any significant difference , while comparing the 2 groups with age > 60 years we find out that patients without GI symptoms are much older than patients with GI symptoms with significant difference ($p<0.05$) . (Table 3)

The mean BMI and the percentage of current smokers were similar in the two groups (23.7). Comorbidities such as hypertension, diabetes, chronic liver or renal disease, heart disease, obstructive pulmonary disease and cancer were similarly distributed between the two groups without any significant difference. (Table 3)

The clinical characteristics of patients with GI symptoms are shown in Table 4. Fever, cough, fatigue and dyspnoea were the most common symptoms but there was no difference in the presence of other symptoms between the two groups. Our patients with acute abdominal pain demonstrate evidence of COVID19 incidentally through abdominal CT imaging at the lung bases. All abdominal CT imaging were normal. Furthermore, We've analysed the association between patients with abdominal pain and the risk of having pulmonary embolism and interestingly we find out that patients with abdominal pain were more likely to present pulmonary embolism (risk x 4.27) compared with those with other symptoms . (Table 5)

Laboratory Data and CT findings (Table 6)

There was no statistical difference between the two groups in values of laboratory data such as leucocytes, lymphocytes, platelets, haemoglobin and haematocrits.

Concerning infection-related markers, such as C-reactive protein, there was no significant difference between medians (83.5 mg/l in cases vs 97.5 mg/l in controls with $p = 0.853 > 0.05$) .

The median ferritin level, LDH level and Albumin level were lower in cases than in controls but did not reach statistical significance (p of the three parametric was > 0.05).

Median of D-Dimers, Aspartate aminotransferase (ASAT) and total bilirubin were higher but not statistically significant in both groups as noted in table 5 .

Finally , (Although) most radiographic presentations were similar between the 2 groups and same for the severity of the lesions ($p=0.569 > 0.05$).

Outcomes (Table5-7)

As shown in table 6, 3 (8.8%) patients in cases had a complication of ARDS and six others (17.6 %) had pulmonary embolism, this rates were higher than the corresponding groups of seven (12.2%) and four (7%) in patients without GI symptoms(, respectively).

Four (11.8 %) patients with GI symptoms needed mechanical ventilation and 12 (35.3%) were treated with non-invasive ventilation which was lower compared tocorrespoonding rates of 21.8% and 47.4% in the patients (COVID19) without GI symptoms . No significant difference were noted in meanLOS 7 days (7-10)

vs 9 days (7-14), p=0.114) and mortality (five (14.7%) vs 13(23.2%), p= 0.328). But there was a significant correlation between mortality and abdominal pain in multiple logistic regression.

Discussion

SARS-Cov-2 may cause digestive symptoms either by direct viral invasion in target cell and/or immune-mediated symptomsof tissue and end organ injury. However symptoms of COVID19 might be indirectly caused by infection-induced respiratory complications , which lead to tissue hypoxia , loss of cell integrity , cell injury and finally cell death [3]

The reports of GI symptoms increased in studies as much as the awareness increasing among health care workers about them. Our study shows that 37.4% of the patients hospitalized with COVID19 presented with at least one GI symptom. In literature, approximately 5-70% of patients COVID19 reported GI symptoms [4-5], this big variation in proportion of patient with GI symptoms among different studies might be related to geographical region and whether symptom were reported on admission or during hospitalization[4], and itis worth mentioning that different studies have adopted different criteria for what constitutes gastrointestinal symptoms . Of the gastrointestinal symptoms, diarrhoea, nausea, vomiting, anorexia, and abdominal pain are the main symptoms found in the majority of studies. We excluded anorexia from our study because it's a non-specific symptom that could be related to an overall infectious or inflammatory process.
While rarer, researchers have also found cases of acid reflux, upper gastrointestinal bleeding, haematochezia, constipation, and melena [4-5].(In our study , we??? Is there some point that the authors want to put in here but decided to abandon it? If not we should delete this sentence altogether.)
In terms of patient demographics, we found that patients with GI symptoms were younger, with less comorbidities, this is an interesting finding whichis in line with an European study [7]

There has been controversy regarding the presence of gastrointestinal symptoms and the poor outcomes of these patients. Our results were similar to many studies such as Preethi's (R.) et al. involving 150 patients [8], moreover, (in) a meta-analysis involving a total of 78 studies with 12797 patients found that mortality in patients with gastrointestinal symptoms was similar to that of the overall mortality and death in patients with COVID19 could be due to the infection itself or to underlying co-morbidities[8-9].

Contrarily, a study of Alexandra and colleagues (that) has proven, by using human intestinal biopsy tissues obtained from patients with COVID19 and uninfected control individuals for microscopic examination, that there is an absence of a pro-inflammatory response in the GI tract despite detection of SARS-COV-2[9-10]. In parallel, disease severity and mortality were examined in patients with and without GI symptoms in 2 large independent cohorts of hospitalized patients, one in the USA (n=634) and another in Europe (n=287) using multivariate logistic regression,(and) they find the same results of reduced mortality in patients with COVID19 presenting with GI symptoms . They suppose that there is a potential role of GI tract in attenuating SARS-COV-2 associated inflammation that needs to be further examined [9-11].

Furthermore, we find out that acute abdominal pain could be associated with risk of pulmonary embolism and then mortality. Three studies, including 380 patients, were analysed in a meta-analysis [11]. The results suggest that patients with severe SARS-CoV-2 infection were almost seven times more likely to have abdominal pain than their counterparts with non-severe disease. Based on these results, abdominal pain could potentially be used as an indicator of severity in patients infected with COVID-19 to aid triage. A meta-analysis of gastrointestinal manifestations of COVID19 pooled data from 17 studies concluded that patients with severe disease are more likely have abdominal pain as compared with patients with non-severe disease[12-13].

Acute abdominal pain, which is known asa regular symptom of basal pulmonary embolism,(that) could explain partially this association, so we must be aware about this eventuality and pay more attention for these patients.

Conclusion

The results of this study suggest that COVID 19-related digestive manifestations occur mainly in young subjects and that their presence is non-specific and unrelated to the severity of the disease, and does not increase the mortality rate.However, after ruling out other digestive emergencies, pulmonary embolism should be considered in the presence of acute abdominal pain complicated by respiratory distress.

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Tables

Table 1: prevalence of GI symptoms in the entire cohort

Total of GI symptoms	**N (%)**
GI symptoms	34 (37.4%)
Diarrhoea	23 (25.3%)
Vomiting	10 (11%)
Nausea	13 (14.3%)
Abdominal pain	14 (15.4%)

Table 2 : Prevalence of individual gastrointestinal (GI) symptoms in the COVID-19 cohort with GI symptoms (cases)

GI symptoms	**N (%)**
Nausea/vomiting	9 (9.8%)
Diarrhoea	13 (14.3%)

Nausea/vomiting + Diarrhoea	3 (3.3%)
vomiting + Diarrhoea + Abdominal Pain	5 (5.5%)
Diarrhoea + abdominal pain	2 (2.2%)
Nausea/vomiting + Abdominal Pain	1 (1.1%)
Acute adominal pain	6 (6.6%)

Table 3 : Demographic and epidemiological characteristics of patients with COVID-19 with and without GI symptoms

Characteristic	**COVID-19 with GI symptoms (N = 34)**	**COVID-19 without GI symptoms (N =57)**	**p value**
Age , M±SD	57.5±10.6	63.1±14.3	0.054
Age> 60 years, N (%)	11 (32.4%)	34 (59.68 %)	**0.012**
Sex (female) , N (%)	8 (23.5%)	14 (24.6%)	0.911
BMI , M±SD	23.7±4.03	23.7±4.14	0.963
Comorbidities N (%)			
Any	12 (35.3%)	14 (24.6%)	0.273
Hypertension	8 (23.5%)	14 (26.3%)	0.767
Diabetes	13 (38.2%)	22 (38.6%)	0.973
Chronic liver disease	1 (2.9%)	0 (0.0%)	0.374
Chronic renal disease	0 (0.0%)	6 (10.5%)	0.080
Heart disease	5 (14.7%)	10 (17.5%)	0.724
COPD	2 (5.9%)	7 (12.3 %)	0.475

Cancer	2 (5.9%)	4 (7%)	1.000
immunosuppression	4(11.8%)	6(10.5%)	1.000
Smoker N (%)	10 (29.4%)	13 (22.8%)	0.483
Contact with patients	6 (17.6%)	14 (24.6%)	0.441

COPD :chronic obstructive pulmonary disease

Table 4 : Clinical characteristics of patients with COVID-19 with and without GI sumptoms

Characteristic	**COVID-19 with GI symptoms (N = 34)**	**COVID-19 without GI symptoms (N = 57)**	**p value**
Period of symptoms before hospitalization (days) , M±SD	9.24±4.13	8.75±3.79	0.573
Symptoms n (%)			
Fever	24 (70.6%)	37(64.9%)	0.577
Cough	22(64.7%)	39(68.4%)	0.715
Sore throat	9(26.5%)	18(31.6%)	0.606
Nasal obstruction	10(29.4%)	12(21.1%)	0.368
Myalgia	14(41.2%)	28(49.1%)	0.462
Fatigue	32(94.1%)	48(84.2%)	0.210
Dyspnea	17(50%)	40(70.2%)	0.054
Headache	11(32.4%)	21(36.8%)	0.664
Dysgeusia	5(19.2%)	8(16.3%)	0.752
Anosmia	5(19.2%)	11(22.4%)	0.746

Table 5 : association between acute abdominal pain and risk of pulmonary embolism in binomial logistic regression

	ODDS RATIO	CI (95%)	P
PULMONARY EMBOLISM ABSENCE- PRESENCE	4.267	1.02 17.8	***0.047***

Table 6 : Laboratory tests CT findings of both cohorts at the time of admission

Characteristic	GI symptoms (N = 34)	No GI symptoms (N = 57)	p value
Laboratory tests , Median (IQR)			
C-reactive protein (mg/L , normal range <5)	83.5 (31.5-182)	97.5(24-212)	0.853
Leucocytes(x 10^3/μL normal range 4-10)	7.05 (5.30-10.37)	8.20 (6.50-10.9)	0.166
Lymphocytes(x10^3/μl normal range 1-4)	0.976 (0.768-1.504)	0.844(0.60-1.28)	0.196
Neutrophils (x10^3/μl normal range 2-7)	5.12(3.62-9.31)	6.80(5.10-9.43)	0.073
Platelets (x10^3/μl normal range 150-303)	220(151.3-196)	248 (279.3-334)	0.053
Haemoglobin (g/dL , 12-16)	13.9(13-14.9)	13.7(12.8-14.5)	0.315
Haematocrit (%, normal range 36-47%)	40.1(37.8-42.9)	39.9(38-42.9)	0.957
Prothrombin ratio (%, normal range 70-100%)	85(76-91)	73(63.9-91)	0.065
Albumin (g/L , normal range 40-55)	31.5 (27.5-36.8)	33.5(30-36)	0.637
Aspartate aminotransferase (ASAT) (U/L , normal range <35)	45(24-67)	40(27-50)	0.441
Alanine aminotransferase (ALAT) (U/L , normal range (< 40)	35(19.5-46)	39(19.6-55)	0.469
Alkaline phosphatase (U/L normal range 32-91)	70.5(56.5-103)	93.5(66.3-128)	0.107
GGT (U/L normal range <32)	47(37-72)	49.5 (30.8-97.5)	0.832
Total bilirubin (g/ml , normal range 3-12)	10 (6.75-13.3)	7 (5.75-10.3)	0.059
Lactate dehydrogenase (U/L, normal range 120 – 250)	545(318-850)	601(349-793)	0.902
D-Dimer (ng/ml normal range <500)	719(503-923)	611(320-867)	0.606

Ferritin(mg/l normal range 12 – 400)	269(170-416)	535(269-1103)	0.442
Creatinine (mg/l normal range 6-13)	9.7(8-11)	10(9-11)	0.175
CT findings, N (%)			
Distribution			
Normal	1(2.9%)	0(0.0%)	
Unilateral pneumonia	1(2.9%)	3(5.4%)	0.590
Bilateral pneumonia	33(97.1%)	53(94.6%)	
Severity			0.569
- **Critique**	4(11.7%)	7(12.5%)	
- **Severe**	11(32.4%)	25(44.6%)	
- **Moderate**	16(47.1%)	21(37.5%)	

All laboratory values are presented as medians (IQR=interquartile)

Table 7: Outcome data of both cohorts in patients with COVID-19 with and without GI symptoms

Variable	GI symptoms (N=34)	No GI symptoms (N=57)	p value
Complications n (%)			
Acute respiratory distress syndrome	3(8.8%)	7(12.2%)	0.467
Shock	1(2.9%)	0(0.0%)	0.543
Neural deterioration	0(0.0%)	3(5.26%)	0.567
Pulmonary embolism	6(17.6%)	4(7%)	0.180
Heart failure	1(2.9%)	4(7%)	0.056
Mortality n (%)	5(15%)	13(23%)	0.328
Length of stay (days) , mean ±SD	7 (7-10)	9(7-14)	0.114
Mechanical ventilation, n (%)	4(11.8%)	13(22.8%)	0.191
Non-invasive ventilation, n (%)	12(35.3%)	27(47.4%)	0.260