High Prevalence of Gastrointestinal Manifestations of COVID-19 Infection in Hospitalized Patients with Cancer

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Abstract

BACKGROUND AND AIM: Gastrointestinal (GI) symptoms have been reported with SARS-CoV-2 infection, but data on the prevalence and severity of GI symptoms in patients with cancer are limited. We sought to characterize the GI manifestations of COVID-19 in oncology patients.

METHODS: We performed a multicenter cohort study of adult patients hospitalized with COVID-19 in 9 Massachusetts medical centers and identified those with an active malignancy. We evaluated the prevalence and severity of GI symptoms among hospitalized COVID-19 patients with cancer.

RESULTS: Of 395 hospitalized patients with COVID-19, 36 (9%) had an active malignancy. Of the 36 cancer patients, 23 (63%) reported 1 new GI symptom. The most prevalent symptoms were anorexia (12, 52%), diarrhea (9, 39%), and vomiting (8; 35%). GI symptoms were the initial symptom in 4/36 (11%) patients, were the predominant symptom in 5/36 (14%) patients, and were severe in 4/23 (17%) patients. Four of 5 patients with GI symptoms at presentation reported concurrent fever; notably 1 patient had no fever or respiratory symptoms. Twelve (33%) patients

had elevations in liver transaminases at presentation; patients with elevated transaminases were more likely to have associated GI symptoms (83 vs 54%, p=0.04).

CONCLUSIONS: Acute GI symptoms associated with COVID-19 are highly prevalent in hospitalized cancer patients and can occur as a presenting symptom without respiratory symptoms. Symptoms are severe in a small subset of patients.

Keywords

Cancer; COVID-19; SARS-CoV-2; gastrointestinal symptoms; diarrhea; elevated liver tests; transaminase elevations

Introduction

Coronavirus disease-19 (COVID-19) caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has rapidly emerged as a global pandemic. Patients with COVID-19 most commonly present with fever, dry cough, myalgia, or fatigue; however, the disease may progress rapidly to cause acute respiratory distress syndrome (ARDS) and death. Gastrointestinal (GI) symptoms have also been reported in a minority of patients with COVID-19 [1,2]. Among COVID-19 patients with cancer the prevalence and course of GI symptoms is unclear [3,4,5]. Furthermore, the impact of antineoplastic therapy, which is associated with a range of GI toxicities, on COVID-19 manifestations is also unknown. Therefore, we performed a multicenter cohort study to evaluate the prevalence, severity, and spectrum of GI symptoms among hospitalized COVID-19 patients with cancer.

Materials and Methods

Study design

Our observational cohort consisted of adult (age 18 years) patients with active malignancy with a confirmed diagnosis of SARS-CoV2 infection. We identified all consecutive adults (age 18 years) hospitalized between January 1, 2020 and April 19, 2020, at 9 hospitals (2 tertiary care and 7 community hospitals) in Massachusetts. Only patients with laboratory-confirmed SARS-CoV-2 on polymerase chain reaction nasopharyngeal swab testing were included. Patients with an active malignancy were identified using oncology notes. The type of preexisting cancer, stage and cancer treatment was made based on documentation of this in the medical records prior to their hospitalization with COVID-19. Positive SARS-CoV-2 infection was defined by detection of SARS-CoV-2 on polymerase-chain reaction (PCR) testing via either a nasopharyngeal swab or tracheal aspirate. Patients with initial negative or indeterminate testing were included only if subsequent testing (via PCR detection) was positive during the index hospitalization. All patients with an initial negative SARS-CoV-2 PCR routinely underwent a second test during the study period. Patient demographics, cancer history, presenting systemic, respiratory, and GI symptoms, comorbid conditions, laboratory data, and clinically-relevant hospitalization outcomes (intensive care unit [ICU] admission, need for mechanical ventilation, and in-hospital mortality) were obtained through medical record review. A subset of the patients (n=19) have been recently reported in publications by our group but subgroup analyses were not performed and their cancer-

related characteristics were not evaluated [9]. This study was approved by the Partners Healthcare Institutional Review Board (2020P0000983).

Statistical Analyses

The primary outcome was prevalence of any GI symptoms at initial presentation in patients with an active malignancy and COVID-19. Categorical and continuous variables were summarized descriptively using percentages and means, respectively. Bivariable analyses were used to assess the association between GI symptoms and covariates of interest. Covariates of interest among patients with cancer included patient characteristics, specific antineoplastic therapy, biochemical and laboratory data, and clinically-relevant hospitalization outcomes (including ICU admission, need for mechanical ventilation, and in-hospital mortality). Fisher's exact tests were performed for categorical variables and Wilcoxon rank-sum tests for continuous data. P values are two-sided and a nominal (unadjusted) value 0.05 was considered statistically significant. All statistical analyses were performed using Statistical Analysis Software 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Of the 395 patients with confirmed COVID-19 hospitalized across nine medical centers during the study period, 36 had an active malignancy (Table 1). Of these, 23 (64%) were on antineoplastic therapy for cancer. The mean time from last cancer treatment and date of hospitalization for COVID-19 was 21 days (range 0–97 days).

Clinical presentation

Gastrointestinal symptoms—Of the 36 individuals with cancer hospitalized with COVID-19, a total of 23 (63%) patients reported at least one GI symptom on presentation. The most prevalent GI symptoms were diarrhea (n=9/23, 39%), nausea (n=3/13, 23%), vomiting (n=8/23, 35%), anorexia (n=12/23, 52%) and abdominal pain (n=6/23, 26%) (Table 1). GI symptoms were the initial symptoms in 5 (14%) patients and the predominant symptom in 4 (11%). Four of five patients with GI symptoms at initial presentation reported concurrent fever. GI symptoms occurred in the absence of associated fever or respiratory symptoms in one patient. GI symptoms were severe in a subset of patients (n=4; 17%) but resolved with supportive care during their hospitalization.

Respiratory and systemic symptoms—Fever was the most frequent clinical symptom (n=29; 81%) at presentation but was not a universal finding. Other common presenting symptoms included cough (n=16; 70), dyspnea (n=10; 44%), and fatigue (n=13; 57%). Anosmia and ageusia were reported in 4 (17%) patients and 1 (4%) patient, respectively (Table 2).

Hepatic manifestations—Twelve patients (33%) had elevations in liver transaminases at initial presentation. Of these, 6 patients (50%) had new elevations and no preexisting liver disease; 3 patients had new elevations in the setting of preexisting liver disease (1 each with hepatitis B cirrhosis, hepatitis C cirrhosis, and metastatic disease to the liver and concurrent

immunotherapy with nivolumab), and in 3 patients elevations in transaminases represented an increase from baseline.

Of the 6 patients with new elevations in liver transaminases and no preexisting liver disease, 2 patients had mild elevations (2–5 times the upper limit of normal [ULN]) in both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and 4 patients had borderline isolated elevations in AST or ALT (<2 times the ULN). Patients with elevations in liver tests at presentation were more likely to have associated GI symptoms (83% vs 54%, p 0.04). Patients with GI symptoms had higher mean AST and ALT levels as compared with patients without new GI symptoms (Table 2).

Outcomes

Fifteen (42%) required care in an intensive care unit (ICU), 6 (17%) needed mechanical ventilation, and 8 (22%) deaths occurred in this hospitalized cohort of cancer patients with COVID-19. There were no differences in the need for ICU stay, mechanical ventilation, or overall mortality between cancer patients with and without GI symptoms and those with and without elevations in liver tests at presentation (Table 3).

Risk Factors for Gastrointestinal Symptoms

There were no differences in the clinical characteristics between cancer patients with GI symptoms of COVID-19 and those without (Table 1). COVID-related GI symptoms were seen in 70% of patients on active treatment as compared with 53% of patients who were not on active treatment. However, these results were not statistically significant. There were no differences in the incidence of GI symptoms on COVID-19 based the specific treatment modality. (Table 3)

Discussion

In this multicenter cohort study of patients with an active malignancy at the time of hospitalization with SARS-CoV-2 infection, we found that more than half had at least one GI symptom on presentation and that GI symptoms can occur in the absence of respiratory symptoms. Elevations in liver transaminase levels at presentation were noted in nearly one third of patients. To our knowledge, this study represents the first U.S. cohort to analyze the prevalence and clinical impact of GI symptoms in hospitalized cancer patients with COVID-19.

There are limited data on the prevalence of GI symptoms in patients with COVID-19 and cancer, and data on the severity and course of these symptoms are lacking. In a retrospective study of 28 cancer patients in China, diarrhea was noted in 3 (11%) patients [5]. While our study was performed early in the course of the COVID-19 pandemic in Massachusetts, our results suggest a high prevalence of GI symptoms in hospitalized patients with cancer. The prevalence of GI symptoms in our cohort of cancer patients appears to be comparable to those noted in a prior publication by our group (that largely included patients without cancer), with the exception of a higher prevalence of elevated liver enzymes in COVID-19 patients with cancer [9]. Liver transaminase elevations in COVID-19 patients with cancer were comparable with prior studies from China that included patients without cancer [6,7,8].

There are several limitations to our study. We relied on retrospective review of medical records of patients at nine different institutions who were hospitalized for COVID-19. Baseline symptom characteristics and severity were not elicited using standardized and validated study instruments and there may have been differences in symptom determination between institutions. This study was also performed early in the COVID-19 pandemic at a time when there was limited awareness of its GI symptoms. It is possible that milder GI symptoms may not have been elicited or documented in patients with fever or respiratory symptoms or that there was increased awareness over time. GI symptoms are a frequent side effect of antineoplastic therapy in patients with cancer and are not specific to COVID-19. In addition, cancer patents particularly those on active treatment, may have been more likely to treat these symptoms with previously prescribed medication. GI symptoms such as anorexia while frequent in patients with COVID-19 and in patients with cancer are not specific to COVID-19. However, symptoms of anorexia and diarrhea combined with loss of smell, taste, and fever have a high specificity for COVID-19 infection [10].

While we did not find any differences in the prevalence of GI symptoms by cancer/treatment characteristics (primary cancer, stage, specific antineoplastic therapy, and the time since last treatment), our study was limited by sample size. To our knowledge, this is one of the first U.S. studies to-date to systematically evaluate GI manifestations of COVID-19 specifically in hospitalized cancer patients. We also included patients hospitalized in both tertiary care and community settings making our results more generalizable.

In conclusion, in our cohort of hospitalized, COVID-19-positive cancer patients, acute GI symptoms associated with COVID-19 were highly prevalent and occurred as a presenting symptom without respiratory symptoms. Fever was not a universal symptom in our cohort of cancer patients and GI symptoms were severe only in a small subset of patients. Further studies are needed to validate our findings.

Acknowledgments

REFERENCES

1. Chen N, Zhou M, Dong X, 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. [PubMed: 32007143]

2. Cheung KS, Hung IF, Chan PP, et al. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples from the Hong Kong Cohort and Systematic Review and Meta-analysis. Gastroenterology. 2020 4 3 pii: S0016-5085(20)30448-0 DOI: 10.1053/j.gastro.2020.03.065.

3. Liang W, et al., Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China.Lancet Oncol, 2020 21(3): p. 335–337. [PubMed: 32066541]

4. Yu J, et al., SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. JAMA Oncol, 2020 3 25 DOI: 10.1001/jamaoncol.2020.0980.

5. Zhang L, et al., Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. Ann Oncol, 2020 3 26 pii: S0923-7534(20)36383-3 DOI: 10.1016/j.annonc.2020.03.296

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6. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of 2019 novel coronavirus infection in China. N Engl J Med 2020; published online 2 28 DOI:10.1056/NEJMoa2002032

7. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–506. [PubMed: 31986264]

8. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020; published online 2 24 DOI:10.1016/S1473-3099(20)30086-4.

9. Redd WD, Zhou JC, Hathorne KE, et al. Prevalence and Characteristics of Gastrointestinal Symptoms in Patients With SARS-CoV-2 Infection in the United States: A Multicenter Cohort Study Gastroenterology 2020 4 22;S0016–5085(20)30564–3. doi: 10.1053/j.gastro.2020.04.045.

10. Chen A, Agrawal A, Ravindran N, et al. Gastroenterology 2020 5 16;S0016-5085(20)30664-8. doi: 10.1053/j.gastro.2020.05.036.

Table 1:

Baseline clinical characteristics of hospitalized COVID-19 patient cohort

	Cancer Patients (N=36)		
	All Cancer N=36	Any GI symptoms N=23	No GI symptoms N=13
Age (years, ± SD)	64.1±14.6	61.1±15.5	69.3±11.7
Female, n (%)	18 (50.0)	13 (56.5)	5 (38.5)
Body mass index (kg/m^2, ± SD)	28.8±5.0	28.9±4.6	28.7±6.0
Medical History, n (%)			
Coronary artery disease	3 (8.3)	2 (8.7)	1 (7.7)
Congestive heart failure	3 (8.3)	3 (13.0)	0 (0)
Cardiac arrhythmia	4 (17.4)	2 (8.7)	4 (30.8)
Hypertension	20 (55.6)	11 (47.8)	9 (69.2)
Hyperlipidemia	10 (27.8)	8 (34.8)	2 (15.4)
Diabetes	8 (22.2)	3 (13.0)	5 (38.5)
Cerebrovascular accident	2 (5.6)	2 (8.7)	0 (0)
Pulmonary disorders	11 (30.6)	6 (26.1)	5 (38.5)
Chronic renal insufficiency	3 (8.6)	2 (9.1)	1 (7.7)
Thyroid disorder	3 (8.3)	2 (8.7)	1 (7.7)
Gastroesophageal reflux disease	14 (38.9)	9 (39.2)	5 (38.5)
Irritable bowel syndrome	0 (0)	0 (0)	0 (0)
Inflammatory bowel disease	0 (0)	0 (0)	0 (0)
Peptic ulcer disease	0 (0)	0 (0)	0 (0)
Cancer site			
Lung cancer	7 (19.4)	5 (21.7)	2 (15.4)
Leukemia	5 (13.9)	1 (4.3)	4 (30.8)
Lymphoma	4 (11.1)	3 (13.0)	1 (7.7)
Breast	4 (11.1)	3 (13.0)	1 (7.7)
Melanoma	3 (8.3)	1 (4.3)	2 (15.4)
Colorectal cancer	2 (5.6)	1 (4.3)	1 (7.7)
Hepatocellular carcinoma	2 (5.6)	2 (8.7)	0 (0)
Other	9 (25.0)	5 (21.7)	4 (30.8)
Glioblastoma multiforme	1 (2.8)	1 (4.3)	0 (0)
Esophageal adenocarcinoma	1 (2.8)	1 (4.3)	0 (0)
Cholangiocarcinoma	1 (2.8)	1 (4.3)	0 (0)
Sarcoma	1 (2.8)	1 (4.3)	0 (0)
Gastric gastrointestinal stromal tumor (GIST)	1 (2.8)	1 (4.3)	0 (0)
Gastric neuroendocrine tumor	1 (2.8)	0 (0)	1 (7.7)
Prostate	1 (2.8)	0 (0)	1 (7.7)
Multiple myeloma	1 (2.8)	0 (0)	1 (7.7)
Vaginal squamous cell			

	Cancer Patients (N=36)		
	All Cancer N=36	Any GI symptoms N=23	No GI symptoms N=13
Social History, n (%)	4 (11.4)	3 (13.6)	1 (7.7)
Alcohol use	6 (16.7)	5 (21.7)	1 (7.7)
Tobacco use			

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Table 2:

Clinical manifestations and laboratory findings at presentation of hospitalized COVID-19 patient cohort

	Cancer Patients			
	All Cancer N=36	**Any GI symptoms N=23**	**No GI symptoms N=13**	**_p_-value**
Any GI symptoms, n (%)				
Anorexia	12 (33.3)	12 (52.2)	0 (0)	-
Diarrhea	9 (25.0)	9 (39.1)	0 (0)	-
Nausea	7 (19.4)	7 (30.4)	0 (0)	-
Vomiting	8 (22.2)	8 (34.8)	0 (0)	-
Abdominal pain	6 (16.7)	6 (26.1)	0 (0)	-
Weight loss	11 (30.6)	7 (30.4)	4 (30.8)	-
Constipation	1 (2.8)	1 (4.4)	0 (0)	-
Dysphagia	1 (2.8)	1 (4.4)	0 (0)	-
Melena	0 (0)	0 (0)	0 (0)	-
Reflux	0 (0)	0 (0)	0 (0)	-
Odynophagia	0 (0)	0 (0)	0 (0)	-
Hematochezia	0 (0)	0 (0)	0 (0)	-
General symptoms, n (%)				
Fever	29 (80.6)	19 (82.6)	10 (76.9)	0.6789
Fatigue	20 (55.6)	13 (56.5)	7 (53.9)	0.8767
Myalgia	10 (27.8)	7 (30.4)	3 (23.1)	0.6359
Chills	9 (25.0)	5 (21.7)	4 (30.8)	0.5478
Diaphoresis	1 (2.8)	1 (4.4)	0 (0)	0.4458
Arthralgia	2 (5.6)	2 (8.7)	0 (0)	0.2739
Airway symptoms				
Cough	26 (72.2)	16 (69.6)	10 (76.9)	0.6359
Dyspnea	19 (52.8)	10 (43.5)	9 (69.2)	0.1371
Sore throat	3 (8.3)	1 (4.4)	2 (15.4)	0.2498
Sputum production	4 (11.1)	3 (13.0)	1 (7.7)	0.6236
Rhinorrhea	4 (11.1)	4 (17.4)	0 (0)	0.1108
Loss of smell or taste				
Anosmia	4 (11.1)	4 (17.4)	0 (0)	0.1108
Ageusia	1 (2.8)	1 (4.4)	0 (0)	0.4458
Laboratory results				
White blood cell count (×10^9/L)	14.4±28.2	11.7±23.3	19.2±35.9	0.5068
Hemoglobin (g/L)	14.2±9.0	14.2±7.9	14.3±11.1	0.9631
Platelets (×10^9/L)	210.4±109.6	220.2±122.1	193.2±84.9	0.4848
INR	1.20±0.25	1.16±0.23	1.26±0.28	0.3432
PTT	37.3±12.4	34.8±14.8	40.5±8.4	0.3810
AST	38.3±28.7	**44.2±34.0** [*]	**27.9±9.67**	**0.0406**

	Cancer Patients			
	All Cancer N=36	**Any GI symptoms N=23**	**No GI symptoms N=13**	***p*-value**
ALT	32.3±32.5	**39.6±38.4** *	**19.5±9.8**	**0.0247**
Alkaline phosphatase	105.7±69.3	111.8±79.0	94.9±48.6	0.4901
Total bilirubin	0.58±0.40	0.55±0.41	0.62±0.39	0.6166
CRP	88.8±82.2	89.9±82.5	135.9±95.6	0.1560
D-Dimer (nmol)	1691±2007	1782±2384	1517±1034	0.6640
Ferritin	638.7±440.3	623.9±334.5	664.3±599.8	0.8402
Lactate	1.81±1.00	1.71±0.91	2.00±1.19	0.4969

CRP: C-reactive protein; GI: gastrointestinal; INR: International normalized ratio; PTT: Partial thromboplastin time

*
p-values are two-sided and a nominal (unadjusted) value 0.05 was considered statistically significant.

Table 3:

Cancer characteristics and COVID-19 related outcomes

	Total N=36	Cancer patients with COVID-19 and Any GI symptoms N=23	Cancer Patients with COVID-19 and No GI symptoms N=13	*p*-value[*]
Primary Type				
GIcancer	8 (22.2)	6 (75.0)	2 (25.0)	0.46
Non-GIcancer	28 (77.8)	17 (60.7)	11 (39.3)	
Active treatment for cancer	23 (64)	16 (69.5)	7 (53)	0.28
Molecular targeted therapy	7 (19.4)	4 (17.4)	3 (23.1)	1.00
Immunotherapy	9 (25.0)	5 (21.7)	4 (30.8)	1.00
Chemotherapy	14 (38.9)	10 (43.5)	4 (30.8)	0.44
Radiation therapy	6 (16.7)	4 (17.4)	2 (15.4)	1.00
Hormonal therapy	3 (8.3)	2 (8.7)	1 (7.7)	1.00
Time since last treatment	20.9±29.9	19.1±26.2	25.1±39.1	0.66
Hospitalization outcomes				
ICU stay	15 (41.6)	8 (34.8)	7 (58.3)	0.28
Mechanical ventilation	6 (16.7)	2 (8.7)	4 (30.8)	0.09
Death	8 (22.2)	5 (21.7)	3 (23.1)	1.00

GI: gastrointestinal; ICU: intensive care unit

[*] *p*-values are two-sided and a nominal (unadjusted) value   0.05 was considered statistically significant.