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COVID-19

Diarrhea Is Associated with Increased Severity of Disease in COVID-19: Systemic Review and Metaanalysis

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Abstract

COVID-19 has become a pandemic since its emergence in Wuhan, China. The disease process was initially defined by presence of respiratory symptoms; however, it is now well studied and shown in evidence that this is a multisystem process. Involvement of gastrointestinal (GI) system has been identified, and GI symptoms can be the only presenting symptoms in some patients. Hence, it is important to identify and understand the GI symptoms associated with COVID-19 for appropriate care of patient. We conducted a systematic review and metaanalysis to identify the GI symptoms of COVID-19 and identify association of diarrhea with severity of COVID-19. We performed extensive search of Medline and Embase from December 2019 to May 2020 to identify articles reporting GI symptoms in COVID-19 patients. The primary outcome was prevalence of GI symptoms in COVID-19 patients, and secondary outcome was the association of diarrhea with disease severity. A total of 38 studies with 8407 patients were included. Of the total patients, 15.47% patients had at least one GI symptom. The pooled prevalence of nausea/vomiting was 7.53% and diarrhea was 11.52%. On metaanalysis, patients with diarrhea as one of the presenting symptoms were more likely to have severe disease (OR 1.63, 95% CI: 1.11–3.38, $p = 0.01$). Our systematic review and metaanalysis demonstrated that GI symptoms are common in COVID-19. Presence of diarrhea as a presenting symptom is associated with increased disease severity and likely worse prognosis. Early recognition of patients is needed for prompt management of this at-risk population.

Keywords COVID-19 · GI · Nausea · Vomiting · Diarrhea · Metaanalysis

Introduction

Beginning of the year 2020 was marked by a major public health outbreak due to COVID-19 caused by a novel corona virus (SARS-CoV-2), initially reported in Wuhan, China [1, 2]. The severity of illness in COVID-19 usually guides management strategies and has prognostic implications [3]. Severe illness is characterized by severe interstitial pneumonia, acute respiratory distress syndrome (ARDS), and ultimately multiorgan failure, which results in considerable mortality [4, 5]. Patients with severe illness are more likely to need prolonged hospitalization, mechanical ventilation, and intensive care unit (ICU) stay [6]. The overall mortality rate is estimated to be about 1–4% in hospitalized patients, while studies have reported mortality rates up to 32% in patients with severe disease [7, 8].

Gastrointestinal (GI) symptoms are being increasingly reported as common symptoms in COVID-19 patients [9–12]. Gastrointestinal manifestations include loss of appetite, nausea, vomiting, diarrhea, abdominal pain, and deranged liver function tests [13, 14]. In addition to droplet transmission, fecal viral shedding and subsequent fecal-oral transmission have been identified as another potential route of transmission of the virus [15–17]. Understanding the pattern of GI manifestation in COVID-19 patients may have significant implication in early diagnosis, triaging, and management of patients. Some of the earlier reviews looking at the association of GI symptoms in COVID-19 have been limited to studies in China

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only, with only a few exploring global cases [17]. A trend towards increased disease severity in patients with GI symptoms has been shown in studies [11, 12]. Therefore, we conducted this systematic review to include studies reported in both China and outside China (USA, Germany, Mexico, Japan, the Netherlands, and Singapore) to provide a more comprehensive and generalizable understanding of the GI manifestations, and its association with severity in COVID-19 patients.

Methods

Data Sources and Searches

Two authors (SG and SS) independently searched Medical Literature Analysis and Retrieval System Online (MEDLINE) and EMBASE database from December 2019 to May 2020 using search terms as follows: "COVID-19" OR "SARS-CoV-2" OR "coronavirus 2019" OR "2019-nCoV" AND "Clinical features" OR "clinical manifestations" OR "nausea" OR "loss of appetite" OR "nausea" OR "vomiting" OR "abdominal pain" OR "diarrhea". Duplicate articles/ abstracts were manually removed by the investigators and through Mendeley 1.19.4 (Amsterdam, Netherlands). We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for this systematic review.

Study Selection

Our initial search yielded 380 articles and after careful screening, 38 articles were included for the purpose of study. COVID-19 infection was confirmed by RT-PCR method in all studies. Single case reports and case series were excluded in this study. Additional records which were not in English language were excluded. The study selection process is illustrated in Supplementary File 1.

Quality Assessment and Data Extraction

Independent data extraction was carried out by 2 authors (SG and SS) using Microsoft Excel spreadsheets incorporating sample size, mean/ median age, and GI manifestations (nausea, vomiting, loss of appetite, abdominal pain, diarrhea and deranged liver function). Severe COVID-19 infection was defined as: new onset hypoxia or respiratory rate > 30 breaths/ min or PaO2/FiO2 < 250 or requiring ICU admission for mechanical ventilation and/or vasopressor support or death, and the data was collected from the reporting in the study. Data collected was appraised by RB and AP, and incongruities were resolved by mutual consensus.

Outcome Measures

The primary outcome of our study was to assess the proportion of GI manifestations in COVID-19 patients in various geographic locations in the world, and to obtain pooled analysis of the same. Secondary outcome was to estimate the association of GI symptoms, especially diarrhea with severe and nonsevere COVID-19 patients.

Statistical Analysis

Comprehensive Meta-Analysis software (CMA version 2, Englewood, NJ) was used to calculate pooled prevalence and odds ratio (OR) with 95% confidence interval (CI). We estimated odds ratio (OR) between GI symptom and severity of COVID-19 disease with corresponding 95%CI and quantifying magnitude of the relationship were pooled using a random-effects model. I^2 was used to evaluate heterogeneity between studies, and I^2 value to > 75% was considered as a significant for the presence of heterogeneity. Funnel plot was used to evaluate publication bias. A 2-tailed p value of < 0.05 was considered statistically significant for all outcomes between the groups.

Results

We included 38 observational studies with 8407 confirmed cases of COVID-19 patients with detailed outlining of various GI manifestations (nausea, vomiting, loss of appetite, diarrhea, abdominal pain, deranged liver enzymes). Of these 38 studies, 9 studies reported data on manifestation of the above GI symptoms, especially diarrhea as one of the presenting symptoms in patients with severe or nonsevere COVID-19.

Of the total 38 studies, 37 studies reported data on gender of the patients. Distribution of available data based on country, gender, and mean or median age were obtained, as shown in Table 1.

Pooled data was obtained from studies with at least one GI symptom, which showed prevalence of any GI symptom to be 15.47% (95% CI 11.76–20.09, I^2 = 96.00), as shown in Table 2. Similarly, pooled prevalence of nausea/vomiting, which was reported by 26 studies was 7.53% (95% CI 5.27–10.65, I^2 = 95.03). Diarrhea was reported by 37 studies with pooled prevalence of 11.52% (95% CI 8.97–14.68, I^2 = 93.07). Several studies reported data on deranged liver enzymes as shown in Table 2.

Association between GI symptoms and severity of COVID-19: Nine out of the total 38 studies reported data on diarrhea based on severity of COVID-19, including 2192 patients. There were 1751 patients in nonsevere disease group and 441 patients in severe group as shown in Table 3. Patient with severe disease had higher odds of diarrhea as one of the presenting symptoms (OR 1.63, 95% CI 1.11–2.38, p = 0.01) (Fig. 1 and Fig. 2).

Table 1 Demographic features of studies

Study name	Type of study	Sample size	Country	Age (Mean/ Median)	Male	Female
Guan W [6]	Multicenter	1099	China	47 (median)	640	459
Young B [18]	Multicenter	18	Singapore	47 (median)	9	9
Pan L [9]	Multicenter	204	China	52.9 (mean)	107	97
Han C [19]	Single center	206	China	62.5 (mean)	91	115
Zhang JJ [20]	Single center	140	China	57 (median)	71	69
Jin X [21]	Multicenter	651	China	46.14 (mean)	331	320
Nobel Y [22]	Single center	278	USA	N/A	145	133
Zhou Z [23]	Single center	254	China	50 (Median)	115	139
Cheung K [15]	Multicenter	59	Hong Kong	58.5 (Median)	27	32
Luo S [24]	Single center	1141	China	53.8 (mean)	*N/A*	*N/A*
Wang D [25]	Single Center	138	China	56 (median)	75	63
Huang C [26]	Single Center	41	China	49 (median)	30	11
Wang Z [27]	Single Center	69	China	42 (median)	32	37
Chen N [28]	Single Center	99	China	55.5 (mean)	67	32
Wu J [29]	Multicenter	80	China	46.1 (mean)	39	41
Shi H [30]	Multicenter	81	China	49.5 (mean)	42	39
Yang X [31]	Single Center	52	China	59.7 (mean)	35	17
Mo P [32]	Single Center	155	China	54 (median)	86	69
Zhou F [33]	Multicenter	191	China	56 (median)	119	72
Chang D [34]	Multicenter	13	China	34(median)	10	3
Liu K [35]	Multicenter	137	China	57 (median)	61	76
Cai Q [36]	Single Center	298	China	47(median)	149	149
Fan Z [37]	Single Center	148	China	50.5(median)	73	75
Xu X-W [38]	Multicenter	62	China	41(median)	35	27
Zhang B [39]	Single Center	82	China	72.5(median)	54	28
Huang Y [40]	Single Center	36	China	69.22 (mean)	25	11
Wei X [41]	Single Center	20	China	N/A	13	7
Song F [42]	Single Center	51	China	49 (median)	25	26
Xiao F [43]	Single Center	73	China	N/A	41	32
Cholankeril G [44]	Single Center	116	USA	50 (median)	62	54
Tabata S [45]	Cruise Ship	104	Japan	68 (median)	54	50
Kluytmans M [46]	Multicenter	86	Netherlands	49 (median)	15	71
Hajifathalian K [47]	Multicenter	1059	USA	61 (Median)	611	448
Gritti G [48]	Single center	21	Italy	64 (Median)	18	3
Goyal [49]	Multicenter	393	USA	62 (median)	238	155
Siso [50]	Multicenter	322	Spain	56.7 (Mean)	161	161
Remes-Troche [51]	Single Center	112	Mexico	43.7 (Mean)	81	31
Redd W [52]	Multicenter	318	USA	63.4 (Mean)	174	144
		Total = 8407				

Discussion

Our study included studies from December 2019 to May 2020 to analyze the GI symptoms and their significance in COVID-19 patients. This study which includes 8407 patients is a comprehensive analysis of GI symptoms (nausea/vomiting, loss of appetite, abdominal pain, and diarrhea) in patients of COVID-19 infection. As shown in Table 2, pooled prevalence of diarrhea as one of the presenting symptoms was 11.52%. Prevalence of diarrhea reported by multiple studies included in our study ranged from 1.25 to 61.32%.

Table 2 Prevalence of GI symptoms in multiple studies

Study name	Sample size	GI symptom N (%)		Loss of appetite	Nausea/ Vomiting	Abdominal pain	Diarrhea	Deranged LFT
Guan W	1099	55	5.00%	N/A	55	N/A	42	168
Young B	18	3	16.67%	N/A	N/A	N/A	3	N/A
Pan L	204	103	50.49%	81	4	2	35	N/A
Han C	206	117	56.80%	102	24	9	67	N/A
Zhang JJ	140	55	39.29%	17	31	8	18	N/A
Jin X	651	74	11.37%	N/A	21	N/A	53	N/A
Nobel Y	278	97	34.89%	N/A	63	N/A	56	N/A
Zhou Z	254	66	25.98%	N/A	36	3	46	N/A
Cheung K	59	15	25.42%	N/A	1	7	13	N/A
Luo S	1141	183	16.04%	N/A	134	45	68	N/A
Wang D	138	55	39.86%	55	14	3	14	N/A
Huang C	38	1	2.63%	N/A	N/A	N/A	1	15
Wang Z	69	10	14.49%	7	3	N/A	10	42
Chen N	99	2	2.02%	N/A	1	N/A	2	43
Wu J	80	3	3.75%	N/A	1	N/A	1	6
Shi H	81	4	4.94%	1	4	N/A	3	43
Yang X	52	2	3.85%	N/A	2	N/A	N/A	N/A
Mo	155	7	4.52%	26	3	3	7	N/A
Zhou F	191	9	4.71%	N/A	7	N/A	9	59
Chang D	13	1	7.69%	N/A	N/A	N/A	1	N/A
Liu K	137	11	8.03%	N/A	N/A	N/A	11	N/A
Cai Q	298	9	3.02%	N/A	N/A	N/A	9	44
Fan Z	148	6	4.05%	N/A	3	N/A	6	75
Xu X-W	62	3	4.84%	N/A	N/A	N/A	3	10
Zhang B	82	10	12.20%	N/A	2	N/A	10	64
Huang Y	36	3	8.33%	N/A	N/A	N/A	3	N/A
Wei X	20	3	15.00%	N/A	2	N/A	3	N/A
Song F	51	9	17.65%	9	3	N/A	5	N/A
Xiao F	73	26	35.62%	N/A	N/A	N/A	26	N/A
Cholankeril G	116	37	31.90%	22	12	10	12	26
Tabata S	104	10	9.62%	N/A	N/A	N/A	10	9
Kluytmans M	86	16	18.60%	16	N/A	5	16	N/A
Hajifathalian K	1059	259	24.46%	240	259	72	234	N/A
Gritti G	21	5	23.81%	2	N/A	N/A	5	N/A
Goyal	393	93	23.66%	N/A	75	N/A	93	173
Siso	322	74	22.98%	N/A	N/A	N/A	74	N/A
Remes-Troche	112	23	20.54%	N/A	8	11	20	20
Redd W	318	195	61.32%	110	133	46	107	N/A

Pooled data

GI symptom: 15.47% (95% CI 11.76–20.09, I2 = 96.00)

Nausea/ vomiting: 7.53% (95% CI 5.27–10.65, I2 = 95.03)

Diarrhea: 11.52% (95% CI 8.97–14.68, I2 = 93.07)

There have been varying GI manifestations of previous corona virus outbreaks. Leung et al. [53] in 2003 published data on severe acute respiratory syndrome (SARS) patients with gastrointestinal symptoms and found that 20.3% of patients had diarrhea on presentation and up to 38.4% had diarrhea during the course of illness. A study in 2015 had shown about 30% of patients with Middle East respiratory syndrome (MERS) had diarrhea [54].

Table 3 Prevalence of diarrhea in severe and non-severe cases

	Non severe		Severe	
	Diarrhea	Total cases	Diarrhea	Total cases
Guan W	32	926	10	173
Young B	3	12	0	6
Zhang JJ	9	82	9	57
Nobel Y	42	207	11	44
Wang D	8	102	6	36
Huang C	0	13	1	25
Wang Z	8	55	2	14
Cai Q	5	240	4	58
Tabata S	7	114	3	28
N=	114	1751	46	441

(OR 1.63, 95% CI 1.11–2.38, p = 0.01)

A retrospective multicenter study from China by Guan et al. [6] comprising of more than 1000 patients showed diarrhea to be present in 3.8% of patients. Similarly, retrospective study by Luo et al. [24] showed all GI symptoms and diarrhea at 16% and 5.9% respectively. Cheung et al. [15] from Hong Kong have reported GI symptoms in 25% of patients with COVID-19. Data presented by Nobel et al. [22] from NY, USA, reported GI symptoms and diarrhea in 34.8% and 20% of patients respectively. Cholankeril et al. [44] have reported GI symptoms and diarrhea in COVID-19 patients in CA, USA, at 31.9% and 12% respectively. There appears to be regional variation in COVID-19 GI symptomatology throughout the world. A large-scale study of 16,749 patients of COVID-19 who were hospitalized in the United Kingdom (UK) reported GI symptoms in 29% of patients on admission and 4% of patients presented with GI symptoms only on admission [55].

Our metaanalysis shows that severe COVID-19 infection was significantly more in patients who had diarrhea (OR: 1.6) (Table 3 and Fig. 1). All studies included in our metaanalysis had higher prevalence of diarrhea in severe cases, except study by Young et al. [18] in Singapore. Metaanalysis on GI manifestations of COVID-19 infection done by Cheung et al. [15] has shown pooled prevalence of GI symptoms to be 15.3% similar to 15.47% in our study. They also showed stool viral RNA detected in 48.1% COVID-19 patients, and 70% samples were positive even after respiratory samples were negative [15].

SARS-COV-2 entry into human cell is facilitated by interaction between spike protein attached to viral envelope and angiotensin-converting enzyme (ACE)-2 in the human cell. This is about 10–20 times stronger than SARS-COV present in 2003. [56] ACE2 receptor is expressed in type II pneumocytes in lungs, upper esophagus and in the enterocytes in ileum and colon. When the virus attaches to enterocytes, this likely alters intestinal permeability, resulting in malabsorption and diarrhea [13].

Xiao et al. [43] examined stool samples of 73 hospitalized patients with SARS-CoV-2 and found viral RNA positive in 53.4% of patients, and this lasted up to 12 days after onset of

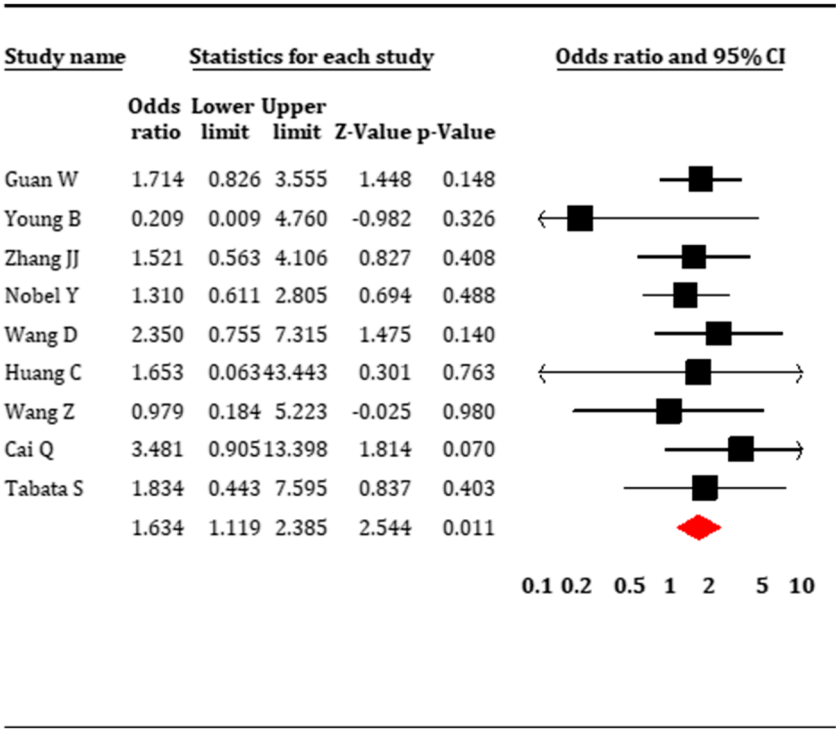

Fig. 1 Forest plot of studies with odds ratio

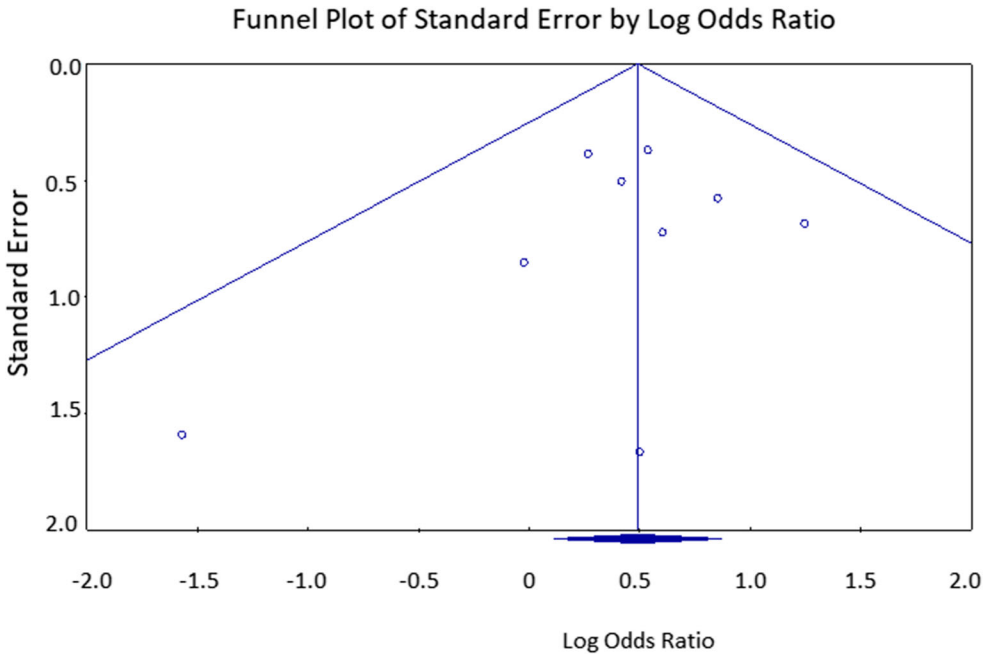

Fig. 2 Funnel plot depicting publication bias

disease. In these patients, they also demonstrated that 23% had positive stool sample despite having negative respiratory samples, which points towards prolonged viral shedding in GI tract. This raises concern for fecal-oral transmission of the virus [43]. MERS-CoV, during 2015 was detected in stools up to 24 days after diagnosis, and affected up to 15% of patients [57]. Another study demonstrated that even asymptomatic patients may be shedding infectious virus and at risk for disease transmission [58]. For discontinuation of transmission based precautions, the Center for Disease Control (CDC) currently recommends at least 2 simultaneous specimens collected from the respiratory tract ≥ 24 h apart after resolution of fever and improvement in respiratory symptoms [59]. Findings by Xiao et al. [43] suggest that feco-oral transmission might happen even after nasopharyngeal viral shedding is cleared. They also found that ACE2 receptor in the GI tract was present in cilia of glandular epithelial cells, which is the site of attachment for the virus [43]. In another study, Xiao et al. [60] examined the fecal specimen from COVID-19 patients and were able to isolate infectious virus in the feces, raising the possibility of fecal-oral transmission. The results in our study could indirectly point to the fact that patients who have diarrhea likely harbor increased viral load, which can potentially lead to an increased systemic response to the virus and associated respiratory complications from it. Our study has significance in COVID-19 patients who need endoscopic procedures. Despite respiratory specimens being negative, isolation precautions may need to be continued until fecal specimens are negative. Outpatient nonemergent GI procedures need to be performed with precautions in COVID-19 patients who have recovered from the disease. Feco-oral contamination needs to be avoided with significant level of precaution. No specific guidelines on this have been provided by American College of Gastroenterology so far [61]. Besides diarrhea, Guan et al. [6] have reported that prevalence of nausea, vomiting, and deranged liver profile was more in patients with severe disease. Similar finding for nausea/vomiting was reported by Wang et al. [25] as well.

Several investigational treatments for COVID-19 including remdesivir, hydroxychloroquine, interleukin-6 (IL-6) inhibitors, convalescent plasma and immune globulins, and lopinavir/ritonavir are currently being studied in clinical trials (CORIMUNO-TOCI, NCT04302766, NCT04347681, NCT04340544, NCT04307693). [62] With a goal of resolution of respiratory compromise, effect of these potential therapies on GI manifestation of COVID-19, including fecal viral clearance is necessary to reduce the risk of potential feco-oral transmission.

There are several limitations of this study. All the included studies were retrospective studies. GI symptoms may be underreported in studies, which unintentionally can result in lower pooled prevalence of gastrointestinal symptoms.

There was also significant heterogeneity in the prevalence of GI symptoms. There are numerous strengths of our study as well. Till date, most of the studies, including research articles on recommendations from professional societies in gastroenterology, are driven by data available from mainland China [10]. To our knowledge, our study is the most inclusive of all the studies, summating studies reported from all over the world. This decreases the geographic bias of the paper and improves external validity. It allows for meticulous estimation of the burden of gastrointestinal impact of COVID-19. Our

subgroup analysis highlights the importance of careful consideration of a patient's gastrointestinal signs and symptoms, which can get undermined while focusing solely on respiratory system involvement.

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Authors' Contributions SG, RB, and SS wrote manuscript. AP and RC performed statistics. HK and ML reviewed articles and edited manuscript. MG edited manuscript.

Data Availability Yes

Compliance with Ethical Standards

Conflict of Interest None.

A statement specifying whether or not the authors have a conflict of interest should be included. Further details on Disclosure of Potential Conflicts of Interest can be found below.

Ethics Approval (Include Appropriate Approvals or Waivers) Waived.

Consent to Participate (Include Appropriate Statements) Not applicable.

Consent for Publication (Include Appropriate Statements) Not applicable.

Code Availability (Software Application or Custom Code) Yes.

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