ORIGINAL ARTICLE

Gastrointestinal Manifestation and In-hospital Mortality among End-Stage Renal Disease Patients with COVID-19: A Single-center Retrospective Cohort Study

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ABSTRACT

Background and Objective. Gastrointestinal (GI) manifestations among COVID-19 patients are common; however, their relation with patient outcomes remains unclear. The study, therefore, aims to determine the association of GI manifestation with in-hospital mortality among end-stage renal disease patients (ESRD).

Methods. This is a retrospective cohort design. All 501 ESRD patients with COVID-19 and admitted to the National Kidney and Transplant Institute from June 2020 to 2021 were included. GI manifestation was defined as the presence of any of the following signs and symptoms on admission: dysgeusia, anorexia, abdominal pain, nausea, vomiting, diarrhea, and jaundice. The outcome of interest was in-hospital mortality, defined as death due to any cause during hospital stay. Stata17 was used for data analysis.

Results. The overall prevalence of GI manifestation was 58.08% (95% CI: 53.63-62.45). The most common symptoms were abdominal pain (27.15%), loss of appetite (24.35%), and nausea (19.76%). Patients with GI manifestation had a higher proportion of stroke, lower median systolic blood pressure, and a lower proportion of abnormal oxygen saturation and diastolic blood pressure than those without GI manifestation. Across all clinical outcomes, only hospital stay significantly differ between those with and without GI manifestation. In-hospital mortality was 31.14% (95% CI: 27.10-35.39%) and showed no significant association with GI manifestation (OR= 0.94, p=0.749).

Conclusions. GI manifestation was common among ESRD patients with moderate-to-severe COVID-19. The in-hospital mortality rate is also high; however, GI manifestation was not associated with this outcome. Meanwhile, GI manifestation leads to longer hospital stay.

Keywords: digestive symptoms, kidney disease, SARS-CoV-2

INTRODUCTION

Coronavirus disease (COVID-19) is a viral respiratory illness that rapidly spread worldwide, eventually leading to a pandemic. World Health Organization estimates show that over 700 million cases and 7 million deaths were recorded globally as of July 2023.[1] But since the availability of the COVID-19 vaccine, the incidence of COVID-19 declined continuously.[1] However, the end of the disease transmission remains uncertain, and some individuals remain vulnerable to infection and its negative health consequences.

As a respiratory illness, most COVID-19 cases present with symptoms like cough and shortness of breath. However, it has been observed by several studies that gastrointestinal

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(GI) symptoms are also common such as diarrhea, nausea and/or vomiting, anorexia, and abdominal pain.[2–10] In two large meta-analyses, the overall prevalence of GI manifestation was 20%.[3,9]

The influence of GI manifestation on patient prognosis remains unclear due to the conflicting findings of previous studies. Some studies concluded that GI manifestation of COVID-19 increases the probability of mortality, while some failed to find a significant association.[5,6,11–14] Moreover, a meta-analysis even concluded that GI manifestation is a protective factor against mortality among COVID-19 patients.[9]

The previous studies, however, mainly included individuals from the general population diagnosed with COVID-19. In certain vulnerable groups, the factors influencing prognosis may differ. End-stage renal disease (ESRD) patients are considered vulnerable to more severe COVID-19 infection and poorer outcomes since most belong to the older age groups besides having multiple comorbidities. In addition, due to their poorer immune status, ESRD patients on renal replacement therapy (RRT) are more prone to complications and death.[4,15–18] Previous studies reported that in-hospital mortality among ESRD patients with COVID-19 reached 38%.[7,11,17-27]

Published studies among COVID-19-infected ESRD patients have remained limited for over three years since the COVID-19 pandemic started, especially in the local setting. Given the high burden of kidney disease in the Philippines, a better understanding of the factors influencing the outcomes of these patients when infected with COVID-19 is warranted. Therefore, the present study aims to determine the association between gastrointestinal manifestation and in-hospital mortality among ESRD patients with COVID-19 admitted to the National Kidney and Transplant Institute (NKTI), the country's specialty center for treating renal disease, dialysis, and organ transplantation.

METHODS

The researcher utilized a retrospective cohort design wherein all eligible ESRD patients on RRT diagnosed with COVID-19 and admitted at NKTI from June 1, 2020 to June 30, 2021 were included in the study. Included were adults aged 18 years, clinically diagnosed with ESRD, currently undergoing RRT, and confirmed to have moderate-to-severe COVID-19 thru Reverse transcription polymerase chain reaction (RT-PCR) or COVID GeneXpert. Excluded were patients who did not have RT-PCR/COVID GeneXpert results and those with pre-existing GI disease.

Ethics approval was obtained from the NKTI Research Ethics Committee (Protocol No. 2020-87). Data gathering was performed from July 15 to August 15, 2021. A study flow diagram is presented in Appendix A. Medical charts were reviewed, and the following variables on admission were collected: age, sex, comorbidities, vital signs [heart rate (HR), respiratory rate (RR), oxygen saturation, systolic blood pressure (SBP), diastolic blood pressure (DBP), highest temperature], hepatic manifestation (i.e., abnormality on any of the following laboratory parameters: ALT, AST, ALP, GGT, bilirubin, albumin and LDH, and COVID-19 management performed. GI manifestation, the exposure of interest, is defined as the presence of any of the following signs and symptoms on admission: dysgeusia, anorexia, abdominal pain, nausea, vomiting, diarrhea, and jaundice. The primary outcome of interest was in-hospital mortality, defined as death due to any cause during the patient's hospital stay. Secondary outcomes included length of hospitalization, intubation, and intensive care unit (ICU) admission. Operational definition of variables was presented in Appendix B.

Stata MP version 17 software was used for data processing and analysis. Continuous variables were presented as median (interquartile range/IQR) due to the non-normal data distribution, and categorical variables were expressed as frequencies and percentages. Mann-Whitney U test was used to compare continuous variables, while Chi Square and Fisher's Exact tests were used for categorical variables. In order to determine the association between GI manifestation and in-hospital mortality, logistic regression analysis was performed. Potential confounders were screened using simple logistic regression based on $p<0.20$ criteria.[28] Multiple logistic regression analysis was performed, and model building was done based on the change-in-estimate criterion of 10%. Median imputation was done to replace the missing data for vital signs. P values ≤0.05 were considered statistically significant.

RESULTS

A total of 501 moderate-to-severe COVID-19 ESRD patients were included in the study. The majority of the patients were on hemodialysis (78%), while the rest were on peritoneal dialysis (13%) or both (8%). GI manifestation on admission was observed in 291 patients, having a prevalence of 58.08% (95% CI: 53.63-62.45). As seen in Figure 1, the most common GI symptoms were abdominal pain (27.15%), loss of appetite (24.35%), and nausea (19.76%).

Table 1 presents the characteristics of the patients. The median age was 53 and ranged from 19 to 92 years old. Most patients were males. The most common comorbidities included hypertension, diabetes mellitus, and coronary artery disease. The majority of the patients had normal HR, respiratory rate, oxygen saturation, DBP (60%), and temperature on admission. Meanwhile, half of the patients had high SBP on admission. Patients were mostly managed using azithromycin (62%) and dexamethasone (62%).

Stroke and vital signs significantly differ between patients with and without GI manifestation. A significantly higher proportion of patients with GI manifestation had a history of stroke than those without. Meanwhile, abnormal oxygen saturation and median SBP were significantly lower among

those with GI manifestations than those without. Compared to those without GI manifestation, the proportion with high DBP was significantly lower among patients with GI manifestation.

The overall incidence of in-hospital mortality was 31.14% (95% CI: 27.10-35.39%), and there was no significant difference between patients with and without GI manifestation. The median length of hospitalization was 17 days (range: 1 to 137 days), which was significantly longer among patients with GI manifestation compared to those without (Table 2). There was no significant difference in intubation and ICU admission rates by GI manifestation.

Univariable analysis was performed to identify significant confounders (Appendix C). No significant association between GI manifestation and in-hospital mortality was observed, even after controlling for significant confounders, as seen in Table 3.

DISCUSSION

COVID-19 was initially identified as a respiratory disease, but recent studies have concluded that the virus also affects other body systems, including the GI tract. The present study's overall prevalence of GI manifestation is 58.08%. A study done in China among maintenance hemodialysis (MHD) patients with COVID-19 revealed that 57% had anorexia, although the overall prevalence of GI manifestation was not reported.[4] In contrast, two large meta-analyses reported an overall prevalence of GI manifestation among COVID-19 patients, generally equal to 20%.[3,9] The higher incidence among dialysis patients could have been explained by the fact that chronic kidney disease (CKD) patients, the target population of the present study, have two times higher odds of GI manifestation.[3] Furthermore, the meta-analyses by Elshazli et al. also found a significant association between GI manifestation and hypertension (OR=2.12) and diabetes (OR=2.06),[3] wherein most of the patients in the present study currently have. Nevertheless, the large variation in prevalence estimates may also be attributed to the differences in each study's definition of GI manifestation.

In the present study, abdominal pain (27.15%) was the most common GI symptom reported by patients on admission. In contrast, this symptom is rare based on previous meta-analyses (3-4%).[9,29] It has been suggested by Hayashi et al. that abdominal pain was more likely to be observed among patients with severe COVID-19.[29] Including only hospitalized moderate-to-severe cases in the present study could explain the high incidence of this symptom. Nevertheless, the mechanism involved in how COVID-19 leads to abdominal pain is not yet well understood. Chen et al. believe that the infection causes visceral pain that involves the peritoneum, thus, leading to this symptom occurrence.[30]

Loss of appetite, a surrogate marker for anorexia, affected 24.35% of patients in the present study. Most studies reported the loss of appetite/anorexia as the most common GI symptom, including some meta-analyses (19-57%).[3–6] Meanwhile, several studies that only included MHD patients reported a lower prevalence of this symptom (5-7%).[7,23] Similar to abdominal pain, the mechanism of how COVID-19 leads to anorexia is not yet clear. Gustatory dysfunction has been hypothesized to be associated with anorexia;[31] however, only 3% reported a loss of taste in this study. Another possible reason for this high incidence is that altered taste and anorexia are quite common among CKD patients.[32,33]

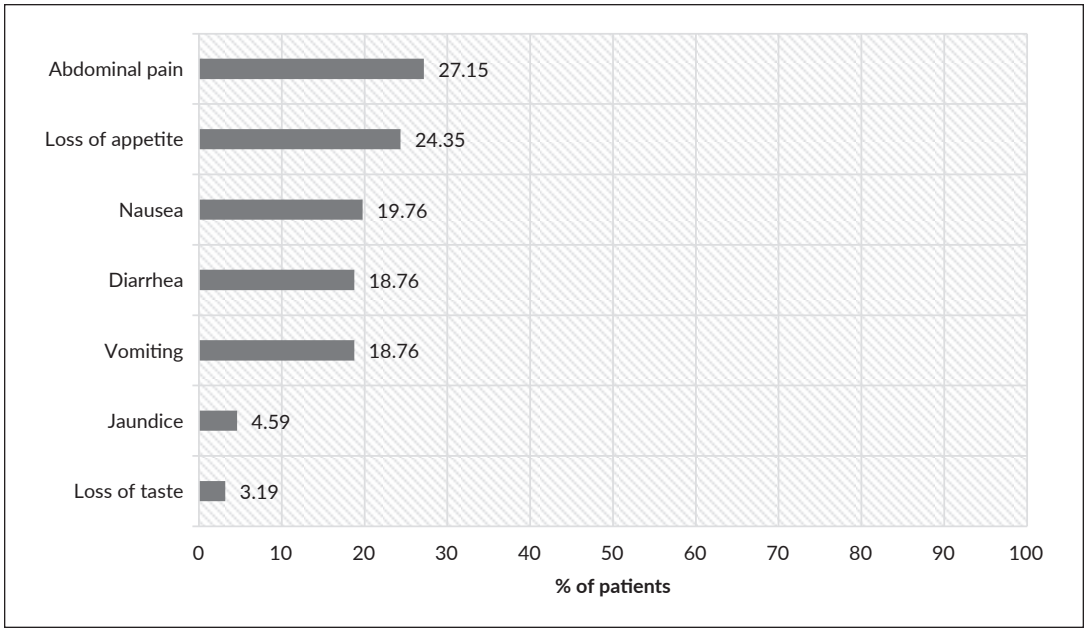

Figure 1. Specific GI manifestations of COVID-19 ESRD patients on RRT (n=501).

Table 1. Characteristics and Management of COVID-19 ESRD Patients on RRT (n=501)

Characteristics	All patients	GI manifestation		P value
		With	Without	
Age (in years), median	53 [IQR: 40-62]	53 [IQR: 40-62]	53 [IQR: 41-63]	0.9534
Sex				
Male	284 (57)	162 (56)	122 (58)	0.589
Female	217 (43)	129 (44)	88 (42)	
Comorbidities, % yes				
Hypertension	371 (74)	210 (72)	161 (77)	0.257
Diabetes mellitus	202 (40)	122 (42)	80 (38)	0.389
Coronary artery disease	196 (39)	116 (40)	80 (38)	0.720
Heart failure	86 (17)	44 (15)	42 (20)	0.153
Other cardiac disease	38 (8)	18 (6)	20 (10)	0.164
Asthma	12 (2)	9 (3)	3 (1)	0.229
Chronic obstructive pulmonary disease	15 (3)	7 (2)	8 (4)	0.363
OSA	4 (1)	1 (1)	3 (1)	0.314
PTB	54 (11)	28 (10)	26 (12)	0.326
Stroke	57 (11)	40 (14)	17 (8)	0.049*
Seizure	23 (5)	15 (5)	8 (4)	0.478
Encephalopathy	32 (6)	21 (7)	11 (5)	0.372
Other neurologic disease	4 (1)	2 (1)	2 (1)	1.000
Other disease	4 (1)	1 (1)	3 (1)	0.314
Vital signs on admission				
Heart rate (in bpm), median	88 [IQR: 80-100]	88 [IQR: 80-100]	89 [IQR: 82-99]	0.8069
Normal	385 (77)	221 (76)	164 (78)	0.823
Low	6 (1)	4 (1)	2 (1)	
High	110 (22)	66 (27)	44 (21)	
Respiratory rate (in cpm), median	20 [IQR: 20-22]			0.1409
Normal	323 (65)	196 (67)	131 (62)	0.249
High	174 (35)	95 (33)	79 (38)	
Oxygen saturation (in %), median	98 [IQR: 95-98]	98 [IQR: 96-98]	98 [IQR: 94-98]	0.1359
Normal	383 (76)	234 (80)	149 (71)	0.014*
Abnormal	118 (24)	57 (20)	61 (29)	
Systolic blood pressure (in mmHg), median	130 [IQR: 120-155]	130 [IQR: 120-150]	140 [IQR: 120-160]	0.0450*
Normal	201 (40)	122 (42)	79 (38)	0.198
Low	50 (10)	33 (11)	17 (8)	
High	250 (50)	136 (47)	114 (54)	
Diastolic blood pressure (in mmHg), median	80 [IQR: 70-90]	80 [IQR: 70-90]	90 [IQR: 70-100]	0.0052*
Normal	302 (60)	181 (62)	121 (58)	0.035*
Low	34 (7)	25 (9)	9 (4)	
High	165 (33)	85 (29)	80 (38)	
Highest temperature (in °C), median	37.1 [IQR: 36.9-37.9]	37.1 [IQR: 36.9-37.9]	37.1 [IQR: 36.8-37.9]	0.3745
Normal	362 (72)	214 (74)	148 (70)	0.480
Fever	139 (28)	77 (26)	62 (30)	
Management (Treatment received), %yes				
Azithromycin	310 (62)	179 (62)	131 (62)	0.843
Tocilizumab	21 (4)	15 (5)	6 (3)	0.205
Remdesivir	7 (1)	5 (2)	2 (1)	0.705
Dexamethasone	308 (62)	189 (65)	119 (57)	0.069
Hemoperfusion	52 (10)	35 (12)	17 (8)	0.154

bpm – beats per minute, cpm – cycles per minute, ESRD – end-stage renal disease, GI – gastrointestinal, OSA – obstructive sleep apnea, PTB – pulmonary tuberculosis, RRT – renal replacement therapy, °C – degree Celsius, mmHg – millimeter mercury, IQR – Interquartile range

Table 2. Outcomes of COVID-19 ESRD Patients on RRT: with and without GI manifestation (n=501)

Outcomes	GI manifestation		*P* value
	With (n=291), n (%)	Without (n=210), n (%)	
In-hospital mortality			
Yes	91 (31)	65 (31)	1.000
No	200 (69)	145 (69)	
Length of hospitalization (in days), median	18 [IQR: 11-29]	14 [IQR: 9-24]	0.0029*
Intubation			
Yes	54 (19)	41 (20)	0.799
No	236 (81)	169 (80)	
ICU admission			
Yes	16 (6)	9 (4)	0.533
No	274 (94)	201 (96)	

ESRD – end-stage renal disease, GI – gastrointestinal, ICU – intensive care unit, RRT - renal replacement therapy, IQR – Interquartile range

Table 3. Association between GI Manifestation and In-hospital Mortality among COVID-19 ESRD Patients on RRT (n=501)

	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI) [a]	*P* value
GI manifestation				
Without	Ref	Ref	Ref	Ref
With	1.02 (0.69-1.49)	0.939	0.94 (0.63-1.39)	0.749

Ref – Reference category,

[a]Adjusted for the confounding effects of encephalopathy and stroke

ESRD – end-stage renal disease, GI – gastrointestinal, RRT – renal replacement therapy

Nausea and vomiting were typical symptoms of COVID-19, possibly caused by the effect of the virus on the digestive and central nervous symptoms.[30] Nausea was present in 2-12%,[4–10] while vomiting ranged from 2-11%[4–6,8-10]. Meanwhile, the estimates were higher in the present study, wherein 20% had nausea and 19% experienced vomiting.

Diarrhea occurred in 19% of patients included in the present study and was close to the estimates of previous publications (11-18%).[3–6,9,10,34] Two studies, including a local study among dialysis patients, reported that diarrhea was rare (3-4%) among COVID-19 patients.[8,23] Chen et al. suggested that the virus causes a disturbance in the gut microbiota that causes diarrhea occurrence.[30,35]

A higher proportion of patients with GI manifestation had a history of stroke, but this was not observed in other studies.[13] In a large meta-analysis, hypertension, diabetes, and malignancy were also positively associated with GI manifestation,[3] which were not observed in this study. Several studies also reported other clinical and laboratory parameters that differ between patients with and without GI manifestation, but findings were inconsistent.[5,6,13] Unfortunately, most of these laboratory parameters were not measured in the current study; thus, the researchers could not support nor contradict these previous findings.

The median length of hospitalization was significantly longer among patients with GI manifestations than those without. A US study also showed that diarrhea, nausea, and vomiting were associated with prolonged hospital stay.[10] In a recent meta-analysis, the authors concluded that patients with GI manifestations were more likely to develop complications like acute respiratory distress syndrome and acute cardiac injury, prolonging the length of stay.[3] It is possible that patients in the study also developed complications; however, this retrospective review did not assess the reason for the longer length of hospitalization.

Intubation and ICU admission were not significantly different by the presence of GI manifestation, similar to previous studies.[5,6,36] In contrast, one meta-analysis showed that patients with GI manifestation had three times the risk of ICU admission.[9] Furthermore, the same meta-analysis reported a higher mortality rate among patients with GI symptoms, although this was not observed in the present study.[9] Previous studies showed contrasting findings about the influence of GI manifestation on mortality.[5,6,11–14] One recent meta-analysis even concluded that GI manifestation is a protective factor against mortality among COVID-19 patients.[9]

The study has several limitations. First, the study included hospitalized moderate-to-severe ESRD patients admitted at NKTI. As these patients require hospitalization and given their current health status, a poorer prognosis is expected, as evidenced by the high mortality rate. The characteristics of patients admitted to NKTI may also differ from those hospitalized in other institutions (i.e., private hospitals). Thus, the generalizability of the results of this study is limited. Second, it has been known that the predominant COVID-19 variant had changed over time, and the differences in the COVID-19 variant could have influenced the presenting signs and symptoms and patient outcomes in the study. However, the researcher could not control for its potential confounding effect due to the lack of data regarding the COVID-19 variant from medical charts. Third, COVID-19 vaccination may improve patient outcomes; however, this cannot be controlled in this study since all patients were still unvaccinated at the time of data collection. Last, due to the retrospective nature of data collection, information bias may have occurred. The researcher only assumes that all data in medical charts are accurate.

The main strength of this study is the large sample size of ESRD patients with COVID-19, that provided reliable estimates of the clinical outcomes. However, post-hoc power analyses revealed low statistical power (3%) obtained for the association between GI manifestation with in-hospital mortality that could explain the non-significant findings even after controlling for the effects of confounders. Future studies with larger sample sizes are warranted. Long-term

studies are also needed to determine the effects of GI manifestations even after patient recovery.

CONCLUSION

GI manifestation was common among ESRD patients with moderate-to-severe COVID-19. The in-hospital mortality rate is also high; however, GI manifestation was not associated with this outcome. Meanwhile, GI manifestation leads to longer hospital stay. ESRD patients already face various complications, and the additional burden of GI manifestations should be addressed. Future prospective studies should determine if these manifestations eventually subside after recovery or continue progressing, leading to poorer patient prognosis

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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