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***Observational Study***

**Gastrointestinal manifestations of long-term effects after COVID-19 infection in patients with dialysis or kidney transplantation: an observational cohort study**

Chancharoenthan W *et al.* GI symptoms of Long-COVID in dialysis or KT

Wiwat Chancharoenthana, Supitcha Kamolratanakul, Asada Leelahavanichkul, Wassawon Ariyanon, Sutatip Chinpraditsuk, Rattanaorn Saelim, Somratai Vadcharavivad, Weerapong Phumratanaprapin, Polrat Wilairatana

**Abstract**

**BACKGROUND**

Prolonged symptoms after corona virus disease 2019 (Long-COVID) in dialysis-dependent patients and kidney transplant (KT) recipients are important as a possible risk factor for organ dysfunctions, especially gastrointestinal (GI) problems, during immunosuppressive therapy.

**AIM**

To identify the characteristics of GI manifestations of Long-COVID in patients with dialysis-dependent or KT status.

**METHODS**

This observational, prospective study included patients with COVID-19 infection, confirmed by reverse transcription polymerase chain reaction, with the onset of

symptoms between 1 January 2022 and 31 July 2022 which was explored at 3 mo after the onset, either through the out-patient follow-up or by telephone interviews.

## RESULTS

The 645 eligible participants consisted of 588 cases with hemodialysis (HD), 38 patients with peritoneal dialysis (PD), and 19 KT recipients who were hospitalized with COVID-19 infection during the observation. Of these, 577 (89.5%) cases agreed to the interviews, while 64 (10.9%) patients with HD and 4 (10.5%) cases of PD were excluded. The mean age was  $52 \pm 11$  years with 52% women. The median dialysis duration was  $7 \pm 3$  and  $5 \pm 1$  years for HD and PD groups, respectively, and the median time post-transplantation was  $6 \pm 2$  years. Long-COVID was identified in 293/524 (56%) and 21/34 (62%) in HD and PD, respectively, and 7/19 (37%) KT recipients. Fatigue was the most prevalent (96%) of the non-GI tract symptoms, whereas anorexia (90.9%), loss of taste (64.4%), and abdominal pain (62.5%) were the first three common GI manifestations of Long-COVID. Notably, there were 6 cases of mesenteric panniculitis from 19 patients with GI symptoms in the KT group.

## CONCLUSION

Different from patients with non-chronic kidney disease, there was a high prevalence of GI manifestations of Long-COVID in dialysis-dependent patients and KT recipients. An appropriate long-term follow-up in these vulnerable populations after COVID-19 infection is possibly necessary.

**Key Words:** Corona virus disease 2019; Kidney transplant; Post-acute corona virus disease 2019 syndrome; Long-corona virus disease 2019; Gastrointestinal

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**Core Tip:** Prolonged symptoms after corona virus disease 2019 (COVID-19) or prolonged symptoms after COVID-19 (Long-COVID) in dialysis-dependent patients and kidney transplant (KT) recipients are important as a possible risk factor for organ dysfunctions, especially gastrointestinal (GI) problems. In this study, we observed that a GI manifestation of Long-COVID is a frequent condition in patients with dialysis-dependence and kidney-transplant recipients. Long-COVID was significantly more prevalent in peritoneal dialysis patients than in hemodialysis patient or KT cases. We also found that patients who experienced either abdominal pain or diarrhea had a longer duration of other GI manifestations of Long-COVID, suggesting a need for closer observation of these patients during COVID-19 infection.

## INTRODUCTION

The coronavirus disease (COVID-19) pandemic has a significant impact on the management of dialysis-dependent patients and kidney transplant (KT) recipients, while the chronic kidney disease (CKD) condition in these patients is also affecting the clinical manifestation of COVID-19 infection. The persistence of post-COVID-19 syndrome for weeks to months after the infection is a growing public health concern worldwide<sup>[1]</sup>. Currently, the definition of post-acute COVID-19 syndrome (PACS), also known as the post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (PASC) or prolonged symptoms after COVID-19 (Long-COVID) syndrome, depends on the population being studied, the post-infection timing, and the assessment tools<sup>[2,3]</sup>. Moreover, the overlap in its pathophysiology between overwhelming pro-inflammatory immune responses and direct viral cytopathic effects remains inconclusive<sup>[4]</sup>. In general, PACS mainly includes fatigue, pain, headache, neurological and cognitive impairments, cardio-pulmonary symptoms, and anosmia-dysgeusia<sup>[5]</sup>. The British National Institute for Health and Care Excellence (NICE) defines Long-COVID as any signs and

symptoms that develop during or after an infection consistent with COVID-19, continue for over 12 wk, and cannot be explained by an alternative diagnosis<sup>[6]</sup>. A clinical case definition of Long-COVID by a Delphi consensus has crystallized the case definition of Long-COVID as clinical symptoms that occur in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 mo from the onset of COVID-19 with symptoms, that last for at least 2 mo without an alternative explainable condition<sup>[7]</sup>.

Both dialysis-dependent patients and KT recipients are classified as vulnerable populations due to their immunosuppressive status derived from their CKD condition and the high number of comorbidities<sup>[8]</sup>. Thus, a more frequent prevalence of long-term after-effects of COVID-19 infection than in the general population is possible. Accordingly, aggressive approaches, along with prompt management of acute illness, should be used in these populations, making the subject of Long-COVID even more challenging. Recent reports have revealed an incidence of post-COVID-19 syndrome in dialysis patients and KT recipients of approximately 40%-70% of those who experience a COVID-19 infection<sup>[9-13]</sup>. The Long-COVID symptoms include respiratory-related symptoms, fatigue, peripheral neuropathy, venous thromboembolism, memory impairment, and *de novo* diabetes mellitus<sup>[9-11]</sup>. Notably, 60% of dialysis patients *vs* 10% of KT recipients had residual symptoms at 6 mo post-COVID-19 infection<sup>[11,14]</sup>.

Even without the gastrointestinal (GI) symptoms, the severity of COVID-19 is associated with the GI tract as the translocation of pathogen molecules from the gut into the blood circulation (leaky gut) is reported<sup>[15]</sup>, possibly from a quiescent the SARS-CoV-2 infection in the intestine<sup>[16]</sup>. Indeed, the cell entry of SARS-CoV-2 virus through angiotensin-converting enzyme 2 (ACE2) receptors on the squamous and columnar epithelial cells, including enterocytes, is well-known<sup>[17]</sup>. One large study of hospitalized COVID-19 revealed that 30% of the patients reported GI symptoms, such as abdominal pain, nausea and vomiting, and diarrhea, in addition to their respiratory tract symptoms<sup>[18]</sup>. Nevertheless, the impacts of COVID-19 infection, and particularly Long-COVID-19, in the GI spectrum is not fully understood in either dialysis patients or KT patients, and data on this topic remain scarce. Of note, data from the most recent report

on post-acute SARS-CoV-2 infection sub-phenotype by Zhang *et al*<sup>[19]</sup> found that GI tract-related symptoms are one of the four most common characteristics in post-acute viral symptoms.

Hence, the aim of the present study was to determine the prevalence and characteristics of Long-COVID in a cohort of these patients. We hypothesize that Long-COVID, especially in the GI symptoms, may be underestimated in these populations and may need more clarification, particularly in the post-pandemic period.

## **MATERIALS AND METHODS**

### ***Study populations***

The study is a cohort longitudinal study performed in dialysis-dependent patients and KT recipients with COVID-19 infection under the care of three renal referral tertiary care centers. Eligible participants were those with a diagnosis of COVID-19 confirmed by an RT-PCR test from oro-nasopharyngeal swabs from January 2022 to 31 July 2022. The KT recipients with the following conditions were excluded: (1) those who died before the follow-up interview, (2) those we were unable to contact, and (3) those without or unable to provide informed consent. The remaining dialysis-dependent patients and KT recipients who had experienced a post-COVID-19 infection for at least 3 mo were included in the study. Purposive sampling was used in order to ensure the representation of a range of characteristics and experiences of analytic relevance. Informed consent for participation in interviews was obtained either written or verbally over the phone from all participants in the study and the study was approved by the Research Ethics Commission of the Faculty of Tropical Medicine, Mahidol University, Thailand (MUTM 2022-081-01) along with adhered to STROBE guideline.

### ***Interview conduct and data collection***

An interview consisting of a set of open-ended questions regarding symptoms during COVID-19 and post-COVID-19 infection periods. Then, interviews were designed to explore the specific persistent or emerging symptoms potentially due to GI tract-

associated Long COVID-19 syndrome, as previously described<sup>[20]</sup>. Participants were interviewed either in person or by telephone by trained research nurses. Participants were considered to have GI tract-associated symptoms of Long COVID-19 if they showed one of the following signs: loss of appetite, nausea, weight loss, abdominal pain, heartburn, dysphagia, diarrhea, constipation, altered bowel motility, or irritable bowel syndrome <sup>[20]</sup>. In addition, the participant's electronic medical records were used to obtain clinical data, including baseline demographics and transplant-related immunological risk, comorbidity, and data about COVID-19 admission. Although abnormal laboratory tests, such as elevated alanine aminotransferase, can present as GI tract-associated Long COVID-19 syndrome <sup>[21]</sup>, only clinical signs and symptoms were explored in the present study.

### ***Statistical analysis***

Descriptive characteristics were presented as means and standard deviation (means  $\pm$  SD) unless otherwise noted. The Kolmogorov-Smirnov and Levene's tests were performed to establish data distribution and homogeneity, respectively. Chi-square tests were performed to compare categorical variables, whereas Tukey-Kramer multiple comparisons were used for continuous variables. Independent risk factors were assessed by applying a backward elimination stepwise binary regression and removing the least significant variables at each step. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated.  $P < 0.05$  was considered statistically significant. Data analysis was performed using the PASW 18.0.0 statistical software package (SPSS Inc., Chicago, IL, United States) and GraphPad Prism 9.3.1 software (GraphPad Software, Inc., La Jolla, CA, United States).

## **RESULTS**

### ***Comparison baseline characteristics among participants of hemodialysis, peritoneal dialysis, and kidney transplantation***

This study enrolled 645 eligible participants with COVID-19 infection, including 588 cases with hemodialysis (HD), 38 patients with peritoneal dialysis (PD), and 19 KT recipients. Of these, 577 (89.5%) participants agreed to interviews (Figure 1). All eligible KT recipients were enrolled in the study, and none of the transplant recipients in the KT cohort died or returned to dialysis.

The mean patient age was  $52 \pm 11$  years, 300 (52%) were women, and the median dialysis duration was  $7 \pm 3$  and  $5 \pm 1$  years in the HD and PD groups, respectively. Hypertension (92%) and type 2 diabetes mellitus (77%) were the two most common comorbidities among the three groups of participants. The mean post-transplantation time was  $6 \pm 2$  years (Table 1). Most of the HD patients had three dialysis sessions per week while continuous ambulatory PD (CAPD) was the most treatment modality used in PD patients. The three most common initial symptoms detected in both the dialysis and KT cohorts were fever (98%), coryza (96%), and cough (94%). Of note, the PD patients had a significant predominance of all symptoms compared to the HD and KT groups ( $P < 0.0001$ ); this could be because the highest comorbidities and uttermost severity of COVID-19 were observed in the PD group. For this reason, the combination therapy of Remdesivir (88.2%) and tocilizumab (63.1%) was prescribed significantly more frequently in this group with also correspondent the highest mean levels of both high-sensitivity C-reactive protein and D-dimer compared with HD and KT groups ( $P < 0.0001$ ) (Table 1).

#### *Different prevalence of GI manifestations of Long-COVID among the dialysis-dependent and KT populations*

The Thai national guidelines for COVID-19 management in high-risk patients (during this study period) stipulate that all patients with CKD or CKD-equivalent disorders must be hospitalized for intensive care and monitoring during acute COVID-19 infection. As such, all participants in the study were hospitalized. During the early post-COVID-19 infection period, Long-COVID was identified in 293/524 (56%) of the HD, 21/34 (62%) of the PD, and 7/19 (37%) of the KT groups. Fatigue was the most



prevalent symptom (96%) of the non-GI tract symptoms and was accompanied by loss of appetite or anorexia (81%), loss of taste (63%), hoarse voice (28%), unusual muscle pains (23%), hair loss (22%), a persistent cough (22%), headache (11%), and impaired cognitive and memory function (9%). Among the GI manifestations of Long-COVID, anorexia was the most prevalent symptom (525 cases, 90.9% from all groups), followed by loss of taste (372 cases, 64% from all groups), and abdominal pain (367 cases, 62.5% from all groups) (Figure 2A). Although anorexia and loss of taste were common in all three groups, they were more predominant in dialysis patients, but most cases showed much improvement by two months after the onset of COVID-19 infection. Abdominal pain and diarrhea were the symptoms that persisted for over 3 mo (Figure 2B).

Notably, our investigation of the causes of abdominal pain, which was reported by 87% of the patients, revealed that non-specific abdominal pain or probably acute gastritis was the main etiology in dialysis-dependent patients, whereas mesenteric panniculitis was the main etiology of abdominal pain (6 from 19 cases) in the KT group with a good response to oral corticosteroids (20 mg prednisolone), which were slowly tapered off in 8 wk. All six cases of mesenteric panniculitis had complete resolution, as indicated by the follow-up abdominal computer tomography.

Figure 2C shows the factors associated with the GI manifestation of Long-COVID. We found that COVID-19 patients who were older than 65 years (ORs 2.00, 95%CI 1.2-2.8), who had chronic lung disease (ORs 2.10, 95%CI 1.1-4.2), who were on PD (ORs 1.80, 95%CI 1.4-2.5), or who had high levels of both C-reactive protein (CRP) and D-dimer at the onset (ORs 4.40, 95%CI 1.4-8.8) were significantly likely to have GI manifestations of Long-COVID.

## **DISCUSSION**

In this study, we observed that a GI manifestation of Long-COVID is a frequent condition in patients with dialysis dependence and KT recipients. Long-COVID was significantly more prevalent in PD patients than in HD or KT cases. Notably, patients who experienced either abdominal pain or diarrhea had a longer duration of other GI

manifestations of Long-COVID, suggesting a need for closer observation of these patients during COVID-19 infection.

COVID-19 has brought forth a multitude of challenges to healthcare systems across the globe. Apart from the significant morbidity and mortality associated with COVID-19 during its initial phase, recognition and concern are growing regarding the long-term consequences of COVID-19<sup>[2,3,22]</sup>. Dialysis-dependent patients and KT recipients are clearly high-risk groups associated with higher numbers of comorbidities and immunosuppressive issues and require more aggressive courses of COVID-19 treatment in terms of acute and chronic complications<sup>[8,23,24]</sup>. Although the most visible manifestation of Long-COVID in the general population is asthenia, or brain fog<sup>[22,25]</sup>, we found that anorexia was the most common GI manifestation of Long-COVID in both dialysis-dependent patients and KT recipients, followed by abdominal pain and loss of taste (Figure 2A).

The prevalence and characteristics of Long-COVID in the present cohort seem to differ from its manifestations in other populations, in which diarrhea was the most persistently encountered GI symptom<sup>[26-31]</sup>. This difference could be explained by the combination of pre-existing uremic toxins in dialysis-dependent patients, as well as a delayed clearance of inflammatory cytokines<sup>[32]</sup> and enhanced oxidative stress associated with end-stage renal disease (ESRD)<sup>[33]</sup>. As such, restoration of renal function in KT recipients resulted in a decrease in the incidence of GI manifestations of Long-COVID compared with ESRD patients (Figure 2A). However, kidney transplantation does not entirely reverse T cell functions<sup>[34]</sup>, and the underlying mechanisms of epigenetic changes induced by any combination of inflammation and oxidative stress associated with uremia are not easily reversible<sup>[35]</sup>. For these reasons, KT recipients with COVID-19 infection still have a persistently increased risk for Long-COVID.

As shown in Figure 2B, most of the participants experienced much improvement in the manifestations of Long-COVID after 4 wk and nearly complete resolution by three months. However, the differential diagnosis between the functional limitation during the COVID rehabilitation phase *vs* the Long-COVID syndrome may be difficult.

Accordingly, the need for a robust clarification of the sequelae after COVID-19 infection is another concern in the post-pandemic era. The British NICE suggests that the term PASC must refer to any clinical <sup>4</sup> signs and symptoms that develop during or after an infection consistent with COVID-19, that continue for more than 12 wk, and that cannot be explained by any other conditions<sup>[6]</sup>. Similarly, the World Health Organization (WHO) defines the PASC syndrome as any symptoms without an alternative diagnosis from three months onwards and that last for at least 2 mo<sup>[7]</sup>. Based on our findings, we found a significant difference in the clinical spectrum between patients with a symptom duration longer than 3 mo *vs* less than 3 mo post-COVID-19 infection (Figure 2B), in agreement with the COVID Symptom Study<sup>[36]</sup>. One explanation for the persistence of clinical signs and symptoms following COVID-19 infection may involve the underlying biological factors, such as an aberrant immune response<sup>[37]</sup>, diverse functional autoantibodies<sup>[38]</sup>, or gut dysbiosis<sup>[39]</sup>, that drive other virus-initiated chronic syndromes.

We support using the 12-week cut-off duration as recommended by NICE and WHO for the diagnosis of PASC, and we propose an additional revision of the specific nomenclature for early and late Long-COVID syndrome. We propose using the term “post-acute COVID-19 syndrome (PACS)” for the clinical syndrome that develops three months from post-COVID-19 infection and using “chronic COVID-19 syndrome” thereafter (Figure 3). We further recommend reserving the term “Long-COVID syndrome” for the clinical syndrome that develops beyond three months post-COVID-19 infection and lasts for at least six months, because Long-COVID syndrome may be another post-viral illness spectrum, like myalgic encephalomyelitis/chronic fatigue syndrome<sup>[40]</sup>.

The mechanisms underlying the GI manifestations of Long-COVID are not completely understood. One plausible explanation might be that an impairment of gut homeostasis is explained by disruption of gut-lung communication<sup>[41]</sup>. <sup>1</sup> The manifestations during acute COVID-19 are believed to be related to an increased expression of ACE2 on the small bowel mucosa<sup>[17]</sup>, endotoxemia<sup>[16,42]</sup>, leaky gut<sup>[16]</sup>, and

alterations in hepatic blood flow due to sinusoidal thrombi<sup>[43]</sup>, all triggered by an increased proinflammatory state and intestinal dysbiosis. Undoubtedly, the greater severity of COVID-19 infection in the elderly (high C-reactive protein > 5 mg/L, high D-dimer > 500 ng/mL with > 65 years old), as shown in Figure 2C), also leads to a greater risk of GI manifestations of Long-COVID<sup>[44]</sup>. Although COVID-19 outcomes are comparable between PD and HD patients<sup>[45]</sup>, the findings of the present study demonstrated that PD patients have a greater risk of developing GI manifestations of Long-COVID. Being elderly and having more symptoms (Table 1) may constitute key risk factors for developing Long-COVID in PD patients<sup>[46]</sup>.

Irritable bowel syndrome, a condition with diverse symptoms, including diarrhea, constipation, and mixed bowel habits according to the Rome criteria<sup>[47]</sup>, has been recently proposed as a possible consequence of COVID-19 infection due to disruption of the diversity and stability of the gut microbiota<sup>[48]</sup>. For this reason, evaluation of whether diarrhea and indigestion manifestations of Long-COVID alter the gut microbiome would be worth investigating<sup>[49]</sup>. This possibility also suggests that the use of specific probiotics and prebiotics in COVID-19 clinical treatment may help KT recipients with COVID-19 infections to rebalance their gut and lung microbial ecology, thereby boosting their immune responses against the virus in response to a new metabolic milieu<sup>[50]</sup>.

Moreover, little is known about the pathophysiology of the abdominal pain manifestation of Long-COVID-19. Prolonged shedding of SARS-CoV-2 from the GI tract has been observed and could be responsible for some of the GI manifestations of Long-COVID<sup>[51]</sup>. Interestingly, we found that over one-third of our KT recipients had been diagnosed with mesenteric panniculitis-related Long-COVID. Although this is a rare condition, concern is growing regarding the conditional pain associated with COVID-19<sup>[52,53]</sup>. Notably, all of our recipients with mesenteric panniculitis fully recovered after corticosteroid administration, suggesting that systemic inflammation is the process involved here<sup>[54]</sup>. Although renal allograft dysfunction and graft loss following COVID-19 infection are possibly resulted from direct toxicity of SARS-CoV-2, cytokine storm-

induced tubular injury, reduced immunosuppressive drugs during infection and decreased renal allograft blood flow from multiple organ failure<sup>[55-57]</sup>, there was no reported case of acute kidney injury in the cohort.

<sup>1</sup> The strengths of the present study are that we compiled the data available on the prevalence, symptomatology, and specific treatment of the particular GI manifestations of Long-COVID symptoms; this will help to guide clinicians in dealing with the pandemic. The identification of GI manifestations of Long-COVID in KT recipients could also help to define the contours of this new SARS-CoV-2 virus. Some limitations of the present study should also be acknowledged. This was a renal referral center study with a limited diversity of patient characteristics. No non-COVID-19 patients were included in the study, and the small number of participants made the study underpowered for investigating the risk factors associated with GI symptoms. Thus, the results need confirmation with larger cohorts that can apply the structural equation modeling for analysis, which has greater statistical power in terms of the probability of rejecting of a false null hypothesis than multiple regression analysis does<sup>[58]</sup>. In addition, the influence of different SARS-CoV-2 variants on GI manifestations of Long-COVID in dialysis-dependent and KT patients was not clarified, nor was the vaccination status against different variants addressed in our cohorts. However, based on the timing of the pandemic, the main strain circulating at the time of our study was the Delta (B.1.617) strain, accompanied by an early wave of the Omicron (B.1.1.529) variants<sup>[59,60]</sup>. Accordingly, an in-depth analysis of confounders should also be performed in larger, multinational cohorts. It is also challenging to find unrecovered pathophysiology of the long-term GI effects of COVID-19. Future research should not overlook other organ interactions to GI manifestations of Long-COVID, for instance, <sup>5</sup> mental health symptoms (e.g., depression and anxiety symptoms) nor additional post-infectious symptoms that were not assessed in the present study (e.g., cardiovascular disease), as depression<sup>[61-63]</sup>, gut-brain axis<sup>[64]</sup> or cardiovascular diseases<sup>[65]</sup> are the main etiology of long-term comorbidity of COVID-19<sup>[5]</sup>, especially in HD patients<sup>[66]</sup>. In addition to lack of appetite, ESRD is recognized as a high risk of pre-existing



undernutrition (malnutrition), including micronutrient deficiencies from malnutrition-inflammation-cachexia complex<sup>[67]</sup>, which has been linked to increased mortality in patients with COVID-19<sup>[68]</sup>. Thus, nutrition support could be another critical intervention during COVID-19 infection in ESRD that robust research is needed for clarification as, vice versa, reduced long-term GI sequelae is probably part of the overall benefit from nutritional support.

## **CONCLUSION**

In conclusion, at 3 mo after infection with SARS-CoV-2, renal replacement therapy patients and KT recipients with COVID-19 show high rates of GI manifestations of Long-COVID after discharge following their initial episode. These data point to optimized management as a potential line of research for decreasing Long-COVID syndrome in these populations.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

The characteristics of persistent COVID-19 symptoms or Long-COVID in dialysis-dependent patients and kidney transplant (KT) is remain underestimate and urgent needs for investigation to prevent long-term complication in these vulnerable population.

### ***Research motivation***

End stage renal disease is a well-known condition for high mortality risk following COVID-19 infection. Thus, it is essential to explore the Long-COVID in these population as an early preventive strategy for preventing further morbidity and mortality.

### ***Research objectives***

To identify the characteristics of gastrointestinal (GI) manifestations of Long-COVID in patients with dialysis-dependent or KT status.

### ***Research methods***

A prospective, observational study was conducted during January 2022 to July 2022 in patients with COVID-19 infection to explore the Long-COVID symptoms in 3-months after the onset by interviewing.

### ***Research results***

As of 577 cases agreed to the interviews, the mean age was 52±11 years with 52% women. Long-COVID was identified in 56%, 62% and 37% in hemodialysis, peritoneal dialysis, and KT respectively. While fatigue was the most prevalent (96%) of the non-GI tract symptoms, anorexia (90.9%), <sup>1</sup>loss of taste (64.4%), and abdominal pain (62.5%) were the first three common GI manifestations of Long-COVID. Of note, there were 6 cases of mesenteric panniculitis from 19 patients with GI symptoms in the KT group.

### ***Research conclusions***

Renal replacement therapy patients and KT recipients with COVID-19 show high rates of GI manifestations of Long-COVID after discharge following their initial episode.

### ***Research perspectives***

Further study should aim to explore the pathophysiology of the long-term GI effects of COVID-19 in renal replacement therapy and KT patients, which may have different immune response to Long-COVID symptoms compared to those with immunocompetent.

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