

# Independent Predictors and Causes of Thirty-Day Gastrointestinal Readmissions Following COVID-19-Related Hospitalizations: Analysis of the National Readmission Database

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## Abstract

**Background:** The coronavirus disease 2019 (COVID-19) pandemic led to significant mortality and morbidity in the United States. The burden of COVID-19 was not limited to the respiratory tract alone but had significant extrapulmonary manifestations. We decided to examine the causes, predictors, and outcomes of gastrointestinal (GI)-related causes of 30-day readmission following index COVID-19 hospitalization.

**Methods:** We used the National Readmission Database (NRD) from 2020 to identify hospitalizations among adults with principal diagnosis of COVID-19. We identified GI-related hospitalizations within 30 days of index admission after excluding elective and traumatic admissions. We identified the top causes of GI-related readmission, and the outcomes of these hospitalizations. We used a multivariate Cox regression analysis to identify the independent predictors of readmission.

**Results:** Among 1,024,492 index hospitalizations with a primary diagnosis of COVID-19 in the 2020 NRD database, 644,903 were

included in the 30-day readmission study. Of these 3,276 (0.5%) were readmitted in 30 days due to primary GI causes. The top five causes of readmissions we identified in this study were GI bleeding, intestinal obstruction, acute diverticulitis, acute pancreatitis, and acute cholecystitis. Multivariate Cox regression analysis done adjusting for confounders showed that renal failure, alcohol abuse, and peptic ulcer disease were associated with increased odds of 30-day readmission from GI-related causes.

**Conclusions:** GI manifestations of COVID-19 are not uncommon and remain an important cause of readmission. Targeted interventions addressing the modifiable predictors of readmission identified will be beneficial in reducing the burden on already limited healthcare resources.

**Keywords:** COVID-19; 30-day readmission; GI bleeding; Intestinal obstruction; Acute pancreatitis

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) and led to a global pandemic of significant proportions. The clinical course ranges from asymptomatic to life-threatening acute respiratory syndrome with multi-organ involvement [1, 2]. Similar to other coronaviruses, SARS-CoV-2 infects the gastrointestinal (GI) tract [3]. In addition to common GI symptoms such as diarrhea and vomiting, several case reports have described the occurrence of GI bleeding and other inflammatory processes involving the GI tract [4-7]. The recovery course ranges from 2 - 6 weeks based on the severity of the disease; however, little is known about readmissions following COVID-19 hospitalizations particularly GI-related readmissions. The probability of 30-day readmission is a complex interplay of comorbidities, disease severity, and outpatient management. Understanding the causes and independent predictors of 30-day readmission in patients admitted with COVID-19 would allow the healthcare system to focus already limited resources on the modifiable factors

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to improve patient outcomes. This study aimed to investigate the causes, outcomes, and independent predictors of GI-related 30-day readmission following index COVID-19 hospitalization.

## Materials and Methods

This was an observational retrospective study involving COVID-19-related adult hospitalizations, derived from the Nationwide Readmissions Database (NRD) for 2020. The NRD provides data for readmission analysis at the national level and is one of the largest readmission databases in the United States [8]. It contains clinical and non-clinical data about patients' index hospitalization and subsequent readmissions. The NRD contains three main tables which provide information on the disease, patient, and hospital [9]. It includes demographics, admission diagnosis, and discharge information.

The study involved hospitalizations with COVID-19 infection as the principal diagnosis using the International Classification of Diseases, 10th Revision (ICD-10) diagnostic codes (U.071, U.00, U.49, U.50, U.85, J.1282, and B.342). This was deemed as the index hospitalization. We excluded elective hospitalizations as well as hospitalizations with patients less than 18 years. Hospitalizations in December were excluded during the 30-day readmission analysis. We identified one subsequent admission with 30 days and tagged this as readmission. We excluded elective and traumatic admissions during the readmission analysis.

We assessed patient demographics as well as hospital-specific variables from the variables included in the NRD. We also assessed the comorbidity index using the Elixhauser Comorbidity Index (ECI) which has been used in prior Healthcare Cost and Utilization Project (HCUP) database research [10].

Rate and reasons for GI causes of readmission classified as "gastrointestinal diseases" by ICD codes were the primary outcomes of the study. We then assessed independent predictors of readmissions, readmission mortality, total hospital charges (THC) and mean length of stay (LOS).

We analyzed the data using Stata<sup>®</sup> Version 17 software. We group age into three categories: 18 - 44 years for young adults, 45 - 64 years for middle-aged adults, and 65 years above for the elderly. We compared readmission mortality, THC, and LOS using univariable regression analysis. In order to identify variables associated with readmission to obtain GI predictors of 30-day all-cause readmission, we used a univariable pre-screening model. We screened age categories, sex, hospital location, hospital bed size, mean household income, and the 31 ECI comorbidities. Variables with P value less than 0.1 were included in the final multivariable regression analysis. We set a P value of < 0.05 as the threshold for statistical significance to identify the independent predictors of readmission during the multivariable Cox regression analysis. This has been adopted in prior HCUP database research [11, 12].

## Ethical compliance

In keeping with other HCUP database research we did not re-

quire the Institutional Review Board approval for this study. This was a national database study that had no patient identifiers, and we had no direct contact with human/animal subjects.

## Results

Among 1,024,492 index hospitalizations with a primary diagnosis of COVID-19 in the 2020 NRD database, 644,903 (62.9%) were included in the 30-day readmission study. Of these, 3,276 (0.5%) were readmitted in 30 days due to primary GI causes. Amongst hospitalizations within 30 days, 56% were male and 44% were female. The mean age of male hospitalizations ( $66.4 \pm 15.1$ ) was significantly lower compared to that of female ( $69.1 \pm 16.1$ ) hospitalizations ( $P < 0.001$ ). Most of the readmitted cohort were elderly and had more than three comorbidities. Table 1 provides the demographic and clinical characteristics of hospitalizations assessed for 30-day readmission stratified by biological sex.

The top five causes of readmissions we identified in this study were GI bleeding, intestinal obstruction, acute diverticulitis, acute pancreatitis, and acute cholecystitis (Table 2). Mortality was higher in the index admission (11.6 %) compared to the 30-day readmission (5.1%). LOS and THC were also higher during index admission compared to 30-day readmission for GI-related hospitalizations (Table 3). There was no difference in outcomes (mortality, LOS and THC) between the male and female sex in the 30-day readmission study (Table 4).

Cox regression analysis adjusting for confounders revealed that private insurance (adjusted hazard ratio (aHR): 0.59; 95% confidence interval (CI): 0.49 - 0.72;  $P < 0.001$ ) and obesity (aHR: 0.86; 95% CI: 0.76 - 0.98;  $P < 0.025$ ) were associated with lower odds of 30-day readmission. Congestive heart failure (aHR: 1.39;  $P < 0.001$ ), renal failure (aHR 3.06;  $P < 0.001$ ), alcohol abuse (aHR: 2.67;  $P < 0.001$ ), coagulopathy (aHR: 1.47;  $P < 0.001$ ), and peptic ulcer disease (aHR: 1.92;  $P = 0.021$ ), were associated with increased odds of 30-day readmission from GI-related causes shown in the Forrest plot (Fig. 1). Table 5 shows the aHR, CI, and P values of the independent predictors associated with 30-day GI-related readmission following index COVID-19 admission.

## Discussion

This analysis, to the best of our knowledge, is the first observational report from a national representative database on GI-related causes and predictors of readmissions following COVID-19 hospitalizations. The pathophysiology of GI-related injury in COVID-19 is not clearly understood but it is thought to include a combination of direct virus-mediated tissue damage, intestinal edema, diffuse endothelial and submucosal vascular inflammation, and virally mediated alterations to the intestinal microbiome [13-15]. Given the above, there are potentially several plausible processes by which COVID-19 may result in GI sequelae of infection. GI bleeding was the most common cause of 30-day readmission in our study, followed by intestinal obstruction, acute diverticulitis, acute pancreati-

**Table 1.** Baseline Characteristics of Patients Evaluated for Gastrointestinal Etiologies of 30-Day Readmissions Following Index COVID-19 Admission Stratified by Biological Sex

Characteristic	Males	Females	P value
N = 3,276	54%	46%	
Mean age $\pm$ SD (years)	66.4 $\pm$ 15.1	69.1 $\pm$ 16.1	< 0.001
Age category			0.005
18 - 44	9.2	8.8	
45 - 64	33.6	26.2	
$\geq$ 65	57.2	65.0	
Insurance type (%)			0.005
Medicaid	63.5	71.0	
Medicare	16.5	11.0	
Private	17.4	15.1	
Uninsured	2.6	2.9	
Elixhauser Comorbidity Index score (%)			0.066
0	2.8	2.4	
1	6.2	3.7	
2	11.6	9.5	
3	15.9	15.6	
4	63.5	68.8	
Median household income (%)			0.311
< \$49,999	34.8	37.7	
$\geq$ \$50,000 to < \$64,999	31.4	27.7	
$\geq$ \$65,000 to < \$85,999	19.1	20.7	
$\geq$ 86,000	14.7	13.9	
Location/teaching status of the hospital (%)			0.791
Rural	17.4	18.8	
Urban non-teaching	72.4	71.0	
Urban teaching	10.2	10.2	
Hospital bed size (%)			0.403
Small	17.3	19.4	
Medium	24.3	25.6	
Large	58.4	55.0	

COVID-19: coronavirus disease 2019; SD: standard deviation.

**Table 2.** The Five Most Common Gastrointestinal Etiologies of 30-Day Readmissions Following Index COVID-19 Admission.

N= 3,276	Proportion (%)
Gastrointestinal hemorrhage	29.7
Intestinal obstruction	5.5
Diverticulitis	4.3
Acute pancreatitis	3.8
Acute cholecystitis	3.1

COVID-19: coronavirus disease 2019.

**Table 3.** Mortality, Length of Stay, and Total Hospitalization Charges on Index Admission Compared With 30-Day Readmission.

Outcomes	Index admission	30-day readmission
Mortality (%)	11.6	5.1
Length of stay (days $\pm$ SD)	8.1 $\pm$ 0.1	6.4 $\pm$ 0.2
Total hospitalization charges (\$)	20,135	16,738

SD: standard deviation.

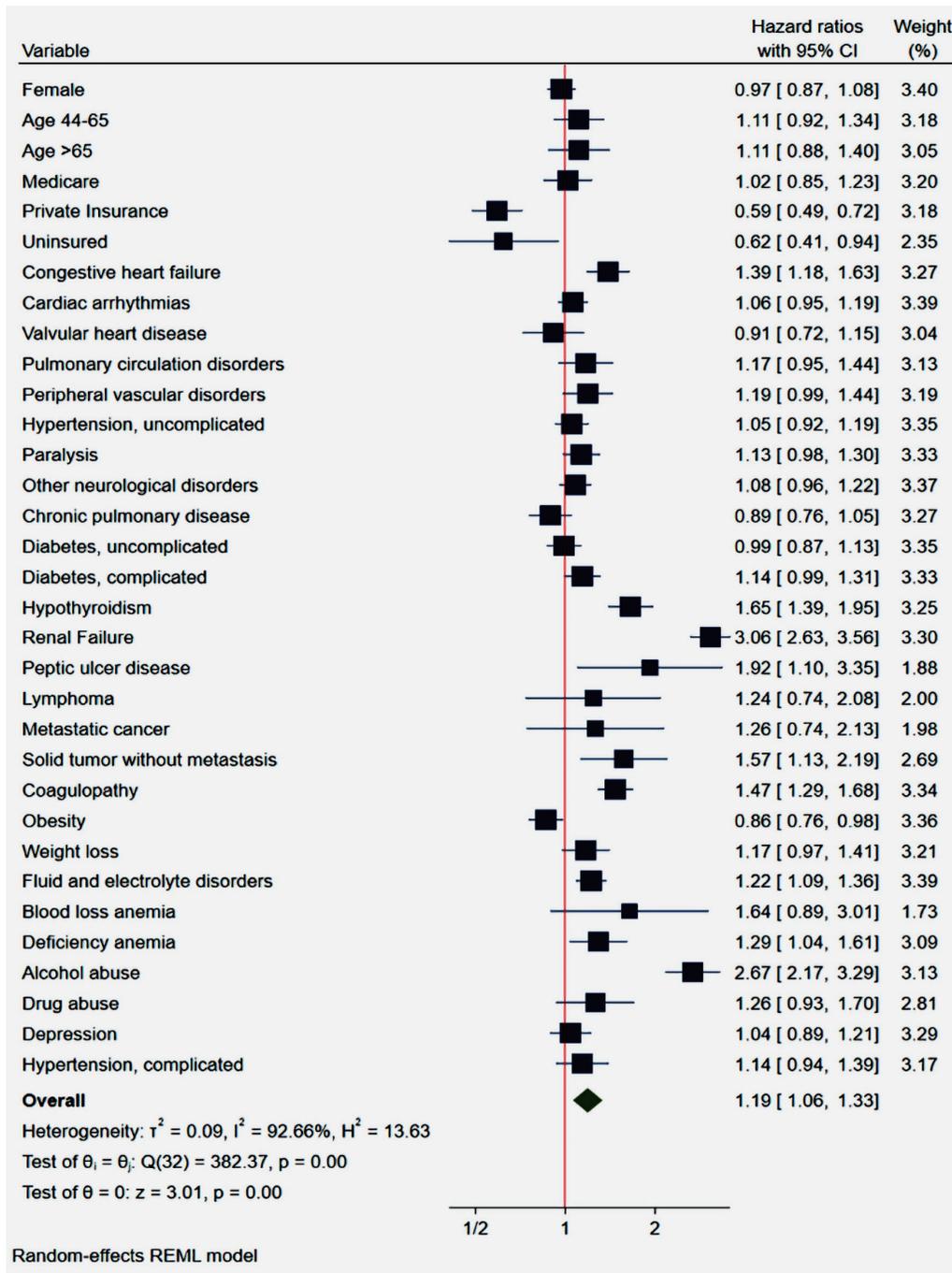
**Table 4.** Mortality, Length of Stay, and Total Hospitalization Charges on 30-Day Readmission Stratified by Biological Sex

Outcomes	Male	Female	P value
Mortality (%)	4.94	5.35	0.700
Length of stay (days ± SD)	6.4 ± 0.3	6.5 ± 0.1	0.952
Total hospitalization charges (\$)	16,770	16,700	0.962

SD: standard deviation.

tis, and acute cholecystitis.

The rate of GI bleeding in patients with COVID-19 was pegged at 2% in a meta-analysis by Marasco et al. Not many studies exist comparing rates of GI bleeding in non-COVID-19 and COVID-19 patients making accurate comparisons difficult. Nonetheless, pooled data on GI bleeding rates in COVID-19 suggest an increased risk when compared to the general population [16]. The mechanisms thought to cause GI bleeding in COVID-19 include a combination of use of sys-



**Figure 1.** Forrest plot of multivariate analysis of independent predictors associated with 30-day readmissions. CI: confidence interval.

**Table 5.** Independent Predictors of 30-Day GI-Related Readmission Following Index COVID-19 Hospitalization

Variable	Hazard ratio (adjusted)	P value	Confidence interval
Female	0.96	0.521	0.87 - 1.07
Age 44 - 65	1.11	0.281	0.92 - 1.35
Age > 65	1.11	0.381	0.88 - 1.40
Medicare	1.02	0.816	0.85 - 1.23
Private insurance	0.59	0.000	0.49 - 0.72
Uninsured	0.62	0.027	0.41 - 0.95
Congestive heart failure	1.39	0.000	1.18 - 1.63
Cardiac arrhythmias	1.06	0.311	0.95 - 1.19
Valvular heart disease	0.91	0.415	0.72 - 1.15
Pulmonary circulation disorders	1.17	0.116	0.96 - 1.45
Peripheral vascular disorders	1.19	0.069	0.99 - 1.44
Hypertension, uncomplicated	1.05	0.432	0.93 - 1.20
Paralysis	1.13	0.082	0.98 - 1.29
Other neurological disorders	1.08	0.216	0.96 - 1.22
Chronic pulmonary disease	0.89	0.181	0.76 - 1.05
Diabetes, uncomplicated	0.99	0.879	0.87 - 1.13
Diabetes, complicated	1.14	0.061	0.99 - 1.30
Hypothyroidism	1.65	0.000	1.39 - 1.95
Renal failure	3.06	0.000	2.63 - 3.56
Peptic ulcer disease	1.92	0.021	1.10 - 3.35
Lymphoma	1.24	0.415	0.74 - 2.09
Metastatic cancer	1.26	0.393	0.74 - 2.12
Solid tumor without metastasis	1.57	0.008	1.13 - 2.19
Coagulopathy	1.47	0.000	1.29 - 1.68
Obesity	0.86	0.025	0.76 - 0.98
Weight loss	1.17	0.096	0.97 - 1.40
Fluid and electrolyte disorders	1.22	0.000	1.09 - 1.36
Blood loss anemia	1.64	0.109	0.89 - 3.00
Deficiency anemia	1.29	0.021	1.04 - 1.61
Alcohol abuse	2.67	0.000	2.17 - 3.29
Drug abuse	1.26	0.119	0.94 - 1.71
Depression	1.04	0.626	0.89 - 1.21
Hypertension, complicated	1.14	0.170	0.94 - 1.39

COVID-19: coronavirus disease 2019; SD: standard deviation; GI: gastrointestinal.

temic corticosteroids, use of antiplatelets and anticoagulants given evidence of thrombotic risks in COVID-19 patients, inflammation induced coagulopathy, and direct mucosal damage from SARS-CoV-2 as it can infect enteric cells via angiotensin-converting enzyme 2 (ACE), a viral binding site abundantly expressed in the enterocytes [15, 17].

Intestinal obstruction following COVID-19 has been reported in a few case reports [18-20]. One was of a patient who presented with large bowel obstruction due to colonic strictures, subsequent colectomy showed chronic active inflamma-

tion on histology [18]. Bowel ischemia and COVID-19 colitis have been reported in other case reports which can be potential causes of bowel obstruction [21-23]. The exact mechanism of the intestinal obstruction following COVID-19 is unclear; it may, however, be related to post-inflammatory changes from the direct viral invasion of enterocytes or electrolyte derangement with subsequent adynamic ileus from COVID-19-induced diarrhea and vomiting.

Karime et al studied 81 patients with first-time acute diverticulitis following COVID-19 at a large academic center

[5]. This and a few other case reports have suggested an association between diverticulitis and COVID-19 [24, 25]. The pathophysiology of acute diverticulitis remains unclear, but some studies have reported an association between alteration of the intestinal microbiome and chronic inflammation as part of the processes involved in the development of acute diverticulitis [26, 27]. Given the generalized inflammatory state noted in COVID-19 and the direct viral invasion of enterocytes, it is possible to speculate that COVID-19 can lead to acute diverticulitis in susceptible individuals via inflammation-mediated tissue damage [5].

Viruses including varicella-zoster, human immunodeficiency virus (HIV), mumps, and cytomegaloviruses have been implicated as causes of acute pancreatitis. SARS-CoV-2 has been isolated from pancreatic specimens during autopsies of infected patients [28]. It is entirely plausible that other causes (alcohol, gallstones) might have been implicated here, but the association between COVID-19 and acute pancreatitis is difficult to ignore as many case reports have suggested an association between COVID-19 and acute pancreatitis [6, 29, 30].

Acalculous cholecystitis usually results from stasis, gallbladder ischemia, and endothelial injury. It has been described in association with COVID-19 in some case reports [7, 31, 32]. SARS-CoV-2 has been identified in gallbladder and bile specimens following cholecystectomy in patients with COVID-19 [31, 33]. This gives credence to the theory that direct viral invasion of the gallbladder wall may lead to acute acalculous cholecystitis via virus-mediated tissue damage and diffuse endothelial and submucosal vascular inflammation [13, 15].

Several comorbidities are associated with a higher risk of GI-related readmission after recent COVID-19 hospitalization as shown in Figure 1. The strongest predictor of GI-related 30-day readmission following index COVID admission is renal failure (hazard ratio (HR): 3.06; 95% CI: 2.63 - 3.56). Renal failure has a well-established association with GI hemorrhage [34], which is the most common GI etiology of readmission after COVID-19 hospitalization in our analysis (Table 2). Several mechanisms have been postulated in literature for the increased rates of GI bleeding in the renal failure cohort. Uremic toxins lead to direct platelet dysfunction leading to an increased risk of bleeding despite normal levels of platelets [35]. Similarly, uremia has been associated with dysfunctional von Willebrand factor which raises the risk of bleeding as well [36]. Renal failure has also been established as an independent risk factor for cardiovascular disease [37], and frequent use of antiplatelet agents and anticoagulants for cardiovascular disease may increase the bleeding risk in such population. Lastly, vascular malformation (angiodyplasia) frequently seen in renal failure patients increases the risk of GI bleeding four to six times as compared to healthy adults [38]. In summary, the virus-mediated damage to the intestinal mucosa in addition to renal failure-associated dysfunction can explain the higher risk of GI hemorrhage in short-term follow-up after COVID-19.

Alcohol use is the second strongest predictor with a greater than two-fold increase in the likelihood of GI-related 30-day readmission (HR: 2.67; 95% CI: 2.17 - 3.29) after recent COVID-19 infection. The most common mechanisms reported are alcohol-induced gastritis, acute pancreatitis, chronic liver

disease complicated by esophageal varices, and hemostatic disease associated with dysfunction of coagulation cascades [39]. Peptic ulcer disease regardless of etiology was also associated with an increased risk of readmission (HR: 1.92; 95% CI: 1.10 - 3.35).

Other significant but weak predictors of increased 30-day readmissions included congestive heart failure (HR: 1.39; 95% CI: 1.18 - 1.63), hypothyroidism (HR: 1.65; 95% CI: 1.39 - 1.95), solid tumor without metastasis (HR: 1.57; 95% CI: 1.13 - 2.19), coagulopathy (HR: 1.47; 95% CI: 1.29 - 1.68) and fluid and electrolyte disorders (HR: 1.22; 95% CI: 1.09 - 1.36).

Obesity has been shown to be associated with increased severity and higher mortality among COVID-19 patients [40]. This may be due to the over-expression of ACE receptors associated with obesity [41]. Interestingly however, we found obesity to be associated with lower odds of 30-day readmission in our study. There is currently no data that support reduced odds of 30-day readmission for GI-related conditions amongst patients with obesity except a weak association with lower odds of 30-day readmission amongst obese patients admitted with portal venous thrombosis [11]. The reason for this observation is unclear to us.

Private insurance has been shown to be associated with reduced odds of 30-day readmissions for some prevalent cardiopulmonary conditions and GI bleeding [42, 43]. Hospitalizations with private insurance were associated with reduced odds of 30-day readmission in our study. This is likely due to restrictions in care and unequal access to newer technologies based on insurance coverage.

There were some limitations in our study despite this being a comprehensive study of a nationally representative sample. This was an observational study using the NRD database and thus our findings cannot establish causation. Also, the database limits the ability to capture patient-level data regarding the underlying etiology of the various causes of readmissions identified as some may not necessarily be related to COVID-19. Despite the limitations, the data were from a large national database and allowed us to provide insights into our primary and secondary outcomes to statistically significant levels.

Extra-pulmonary manifestations of COVID-19 are not uncommon and remain an important cause of readmission. We have with this analysis shown the most common causes of GI-related readmissions and thrown more light on the proposed pathophysiological mechanisms underlying COVID-19 and GI tract pathology. Targeted interventions addressing the independent predictors of readmissions identified here may help reduce overall healthcare costs.

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## Financial Disclosure

None to declare.

## Conflict of Interest

None to declare.

## Informed Consent

This was a National Readmission Database study hence informed consent is not applicable to this study.

## Author Contributions

Robert Kwei-Nsoro participated in the writing and review of this manuscript. Bashar Attar, Pius Ojemolon, Abdul Tawab Shaka, Naveen Baskaran, Philip Kanemo, and Mohankumar Doraiswamy participated in the review of this manuscript. Ha-feez Shaka and Muhammad Sana participated in the writing this manuscript.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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