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Hyperlipidemia, COVID-19 and acute pancreatitis: A tale of three entities



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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the ongoing pandemic of coronavirus disease 2019 (COVID-19), which presented as not only respiratory symptoms, but various digestive manifestations including pancreatic injury and acute pancreatitis (AP). The underlying mechanism is still unclear. Hypertriglyceridemia has become one of the leading causes of AP in recent years and hyperlipidemia is highly reported in COVID-19 cases. The current narrative review aimed to explore the associations between AP, COVID-19 and hyperlipidemia. Substantial cases of COVID-19 patients complicated with AP were reported, while the incidence of AP in the COVID-19 population was relatively low. Hyperlipidemia was common in COVID-19 patients with a pooled incidence of 32.98%. Hyperlipidemia could be a mediating factor in the pathogenesis of AP in COVID-19 patients. Further studies are warranted to clarify the relationship among AP, lipid metabolism disorders and COVID-19.

Key Indexing Terms: COVID-19; SARS-CoV-2; Hyperlipidemia; Acute pancreatitis; Pancreatic injury. [*Am J Med Sci* 2022;364(3):257–263.]

INTRODUCTION

The ongoing pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-induced coronavirus disease 2019 (COVID-19) has led to over 164 million infected cases and 3 million deaths worldwide by May 20, 2021. Although most of the infected adults have self-limited disease courses, about 5% of infections may progress to critical illness, featured as severe acute respiratory distress syndrome (ARDS), thrombosis complications, myocardial dysfunction, acute kidney injury, gastrointestinal symptoms, hyperlipidemia, and even multiple organ dysfunction syndrome (MODS).^{1,2} Amongst, the gastrointestinal symptoms mainly include anorexia, nausea, vomiting, diarrhea, and abdominal pain, which have been observed at disease onset or prior to respiratory symptoms in patients diagnosed with COVID-19.

Acute pancreatitis (AP) is the inflammatory disease of the exocrine pancreas characterized by severe abdominal pain and elevated pancreatic enzymes (amylase and lipase), the incidence of which is increasing rapidly in recent years.³ In published literature, numerous cases of COVID-19 complicated with AP have been reported (Table 1).^{4–46} However, no robust causative relationship has been established between them.

Given the considerable presence of hyperlipidemia in COVID-19 cases, we postulated that hyperlipidemia might play a potential role between COVID-19 and AP. Hence, this narrative review aimed to accumulate evidence on the incidence of hyperlipidemia and AP in the COVID-19 population, and demonstrate whether

hyperlipidemia acted as a mediating factor in COVID-19 patients combined with AP.

THE CORRELATION BETWEEN AP AND COVID-19

We used “COVID-19” and “acute pancreatitis” as search terms to retrieve related articles in PubMed database. The results of different studies were controversial. An epidemiological study from Spain including 63,822 COVID-19 patients showed that the incidence of AP in COVID-19 patients was 0.71% compared with 1.59% in the non-COVID-19 population (OR 0.44, 95% CI 0.33–0.60).⁴⁷ In another study which included 74,814 COVID-19 patients, 54 patients were complicated with AP (0.72%) and the incidence rate was lower than that in the non-COVID-19 population (1.61%).⁴⁸ However, a case-control study that included 112 COVID-19 children and 8047 non-COVID-19 children came to the opposite conclusion, the incidences of AP in two groups were 1.8% and 0.14%, respectively.⁴⁹ In addition, another study reported that 1.25% of 398 pediatric COVID-19 patients were complicated with AP.⁵⁰ It seems that AP was more prevalent in pediatric COVID-19 patients than in adult patients. It was shown in one study that almost no AP occurred in COVID-19 patients with mild disease courses, while most of AP cases were present in critically ill COVID-19 patients.⁵¹

For AP patients, the coexistence of COVID-19 could lead to a worse prognosis of AP. A prospective multicenter cohort study compared the outcomes of AP patients with or without COVID-19, with the results showing that

TABLE 1. Reported cases of COVID-19 patients with acute pancreatitis.

Author	Age	Gender	TG	BMI	Outcome
Wafi, M. N.	72	F	81 mg/dL	33.14	Discharged
Tollard, C.	32	F	Normal	40.4	Died
Sandhu, H.	25	F			Discharged
Samies, N. L.	15	M		34.4	Discharged
Samies, N. L.	11	M	251 mg/dL	29.5	Discharged
Samies, N. L.	16	F	Normal	18.7	Discharged
Narang, K.	20	F	Normal	36.1	Discharged
Mohammadi Arbati, M.	28	M	122 mg/dL		Discharged
Maalouf, R. G.	62	M	Normal		Discharged
Bouali, M.	60	F		24	Died
Bineshfar, N.	14	M			Discharged
Ali, E.	53	M	1.4 mmol/L		Died
AlHarmi, R. A. R.	52	F	3.4 mmol/L		Discharged
Abraham, G.	61	F			Discharged
Abbas, M.	14	M	5.5 mmol/L	21.6	Discharged
Zielecki, P.	38	M			Discharged
Wang, K.	42	M	3.2 mmol/L		Died
Wang, K.	35	M	3.97 mmol/L		Discharged
Szatmary, P.	29	M	2.7 mmol/L	32.9	Discharged
Szatmary, P.	41	M	2.7 mmol/L	35.8	Discharged
Szatmary, P.	42	M	2.7 mmol/L	29.7	Discharged
Szatmary, P.	47	M	2.7 mmol/L	25.7	Discharged
Szatmary, P.	53	M	2.7 mmol/L	30	Discharged
Simou, E. M.	67		2.40 mmol/L	34	Died
Shinohara, T.	58	M	Normal		Discharged
Rabice, S. R.	36	F		44	Discharged
Purayil, N.	58	M			Discharged
Pinte, L.	47	M			Discharged
Patnaik, R. N. K.	29	M	84 mg/dL		Discharged
Miao, Y.	26	F	Normal		Discharged
Meyers, M. H.	67	M	Normal		Discharged
Meireles, P. A.	36	F	TC:119 mg/dL		Discharged
Mazrouei, S. S. A.	24	M			Discharged
Lakshmanan, S.	68	M			Discharged
Kurihara, Y.	55	M	185 mg/dL		Discharged
Kumaran, N. K.	67	F		27.5	Discharged
Kataria, S.	49	F			Discharged
Karimzadeh, S.	65	F	80 mg/dL		Discharged
Kandasamy, S.	45	F			Discharged
Hassani, A. H.	78	F			Died
Hadi, A.	47	F	Normal		Discharged
Hadi, A.	68	F	Normal		Discharged
Gonzalo-Voltas, A.	76	F			Discharged
Gadiparthi, C.	40	M	4245 mg/dL	38.8	Discharged
Cheung, S.	38	M	Normal		Discharged
Brikman, S.	61	M	3.18 mmol/L		Discharged
Bokhari, S.	32	M	150 mg/dL		Discharged
Anand, E. R.	59	F			Discharged
Alwaeli, H.	30	M	133 mg/dL	21.4	Discharged
Alves, A. M.	56	F	209 mg/dL		Discharged
Alloway, B. C.	7	F			Discharged

Abbreviations: TC, total cholesterol; TG, total glycerides

AP patients infected by SARS-CoV-2 were more likely to develop local complications, persistent organ failure, have prolonged hospital stay, higher 30-day mortality,

and require ICU admission.⁵² A retrospective observational study included 189 AP cases, 32 of them were COVID-19 positive and these patients required more

mechanical ventilation and had a longer length of hospital stay (OR=5.65, 3.22, respectively).⁵³

THE CORRELATION BETWEEN HYPERLIPIDEMIA AND COVID-19

We used “COVID-19” and “hyperlipidemia” as search terms to retrieve related articles in PubMed database. Thirty-four papers were reviewed after screening, which reported the incidence of hyperlipidemia in COVID-19 patients (Table 2).^{54–88} The incidence of hyperlipidemia ranged from 0.30% to 81.82% in COVID-19 patients among different studies. Potential reasons for the variations could be: (1) Regional factors led to the difference in baseline lipids levels; (2) The definition of hyperlipidemia varied in different studies. An epidemiological study in Iran focusing on COVID-19 patients with diabetes reported that only 49 cases of hyperlipidemia presenting

in 16,391 COVID-19 patients (0.30%), however, the incidences of hyperlipidemia in COVID-19 patients from other studies were all much higher than those in the normal population. The aggregated incidence was 32.98% in pooled COVID-19 patients.

Hyperlipidemia was commonly presented in critically ill COVID-19 patients and the potential causes for it could be: hemophagocytic lymphohistiocytosis, medication and acute liver injury.⁸⁹ For instance, some studies suggested that ARDS patients with COVID-19 experienced a higher rate of propofol-associated hypertriglyceridemia than non-COVID-19 induced ARDS patients, even after adjusting for propofol administration doses.⁸¹ It was reported that the incidence of propofol-associated hypertriglyceridemia was 18%-45% in the non-COVID-19 population, but could be as high as 56.6% in COVID-19 patients.⁹⁰ Besides, there was a case report presenting 2 cases of tocilizumab-induced hypertriglyceridemia

TABLE 2. Incidence of hyperlipidemia in Covid-19 patients in different studies.

Author	Specific Population	Total	Hyperlipidemia	Rate
Wu, B.	COVID-19	9822	6309	64.23%
Wang, D.	COVID-19 patients in Fangcang hospital	349	32	9.17%
Tzur Bitan, D.	COVID-19 with schizophrenia	25539	10981	43.00%
Spoulou, V.	Newborns with COVID-19	14	6	42.86%
Qureshi, A.I.	COVID-19 with stroke	7709	2613	33.90%
Pérez-García, C.N.	COVID-19 died in hospital	324	187	57.72%
Pareek, M.	COVID-19	586	226	38.57%
Moftakhar, L.	COVID-19 with diabetes	16391	49	0.30%
Karimi, F.	COVID-19 with AIDS	252	49	19.44%
Mirzaei, H.	COVID-19	164	10	6.10%
Giannis, D.	COVID-19 with venous thrombosis	146	21	14.38%
Chetboun, M.	COVID-19	1461	423	28.95%
Aldhaeefi, M.	COVID-19	530	204	38.49%
Xu, H.	COVID-19 with pulmonary embolism	101	32	31.68%
Wong, K.	COVID-19 with pneumothorax	75	24	32.00%
Wei, Z.Y.	COVID-19 with myocardial injury	400	11	2.75%
Wang, B.	COVID-19 with multiple myeloma	58	36	62.07%
Tee, L.Y.	COVID-19 in immigrant workers	240	11	4.58%
Tan, W.Y.T.	COVID-19	717	156	21.76%
Shady, A.	COVID-19 admitted in community hospital	371	102	27.49%
Rameez, F.	COVID-19 with stroke	11	9	81.82%
Piazza, G.	COVID-19	1114	319	28.64%
Palaodimos, L.	COVID-19	200	92	46.00%
Nimkar, A.	COVID-19 with AKI	327	114	34.86%
Newton, S.	COVID-19	991	224	22.60%
Nakanishi, H.	COVID-19	60	13	21.67%
Mori, S.	COVID-19	45	8	17.78%
Kenes, M.T.	COVID-19 with propofol infusion	27	9	33.33%
He, S.	COVID-19	420	45	10.71%
Gómez Antúnez, M.	COVID-19 with COPD	10385	4071	39.20%
Fernandes, N.D.	COVID-19	37	15	40.54%
Ebert, T.J.	COVID-19	95	53	55.79%
Dashti, H.T.	COVID-19	4140	1530	36.96%
Best, J.H.	COVID-19	3471	566	16.31%
Miguel León Sanz	ARDS-COVID-19 receiving parental nutrition	87	32	36.78%

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease.

during the treatment of COVID-19, and one of them developed into AP in the later disease course.

It is unclear whether hyperlipidemia leads to deterioration of disease course and prognosis of COVID-19 patients. Previous research has showed that patients older than 50 were prone to have hyperlipidemia,⁷⁶ which led to an increased risk of hospital admission (OR=1.8)⁷⁸ and disease deterioration (OR=2.15).⁹¹ In addition, previous reviews suggested that patients with hypercholesterolemia had increased risk for COVID-19 and the related complications.^{92,93} However, one study compared between two cohorts, namely COVID-19 patients discharged alive and those that died, and multiple regression analysis showed that hyperlipidemia had a protective effect on reducing the likelihood of death (OR=0.75).⁹⁴ Another study carried out cluster analysis in a large cohort of 12,066 COVID-19 patients, and the results showed that hyperlipidemia had no significant effects on COVID-19 prognosis.⁹⁵

THE CORRELATION BETWEEN ACUTE PANCREATITIS AND HYPERLIPIDEMIA

In the general population

It is widely acknowledged that gallstones and alcohol intake are two major causes of AP followed by hypertriglyceridemia (HTG) and others. HTG has been a major cause of AP over the last decade and accounts for about 10% of total AP worldwide.^{96,97} Especially in East Asia, HTG has become the second leading cause of total AP and the incidence of HTG-AP could reach up to 15–25%.^{98–100}

HTG is one of the predominant subtypes of hyperlipidemia, and it has been reported to deteriorate disease severity, progression, and outcomes of AP. A meta-analysis of 15 studies compared 1,564 HTG-AP patients to 5,721 AP cases with other etiologies, the results showed that the occurrence of renal failure, respiratory failure, shock, and mortality was significantly higher in HTG-AP patients.¹⁰¹ A retrospective study classified AP patients into a normal triglyceride group or mild HTG (<200 mg/dL) group, a moderate HTG (200–749 mg/dL) group, and a severe HTG (>750 mg/dL) group, and demonstrated that higher serum triglyceride level was independently associated with a more severe disease course of AP.¹⁰²

Previous studies suggested that the potential mechanisms of the deteriorating effects of HTG on AP may lie in the accumulation of free fatty acid and thereafter, activation of inflammatory response in the pancreas.¹⁰³ Free fatty acid has been reported to cause the increase in the levels of inflammatory mediators, such as TNF-alpha, interleukin-6, interleukin-10, which might strengthen the systemic inflammatory response and local pancreatic injury. Moreover, *in vitro* experiments also presented that free fatty acid had direct cytotoxic effects on acinar cells and vascular endothelial cells.

In the COVID-19 population

When it comes to the causes of AP in the COVID-19 population, some studies suggested that SARS-CoV-2 could cause pancreatic injury and AP directly. Angiotensin-converting enzyme 2 (ACE2) is widely expressed in human vascular endothelium, respiratory endothelium, and other cell types, which is thought to be a primary mechanism of SARS-CoV-2 entry and infection.¹⁰⁴ An inflamed/injured endothelium promotes neutrophilia and systemic inflammatory cascades, leading to involvement of multi-organs. A review concerning the role of endothelium in COVID-19 suggested that endothelial cells were a crucial link between SARS-CoV-2 and host immune responses and thus may serve many roles in determining the disease severity and mortality in COVID-19.¹⁰⁵ Receptor proteins of SARS-CoV-2 including ACE2 were also highly expressed in the epithelial cells of gastrointestinal tract, so do the pancreatic duct epithelium, pancreatic acinar cell, and islet cell. SARS-CoV-2 could infect the gastrointestinal epithelial cells through the gastrointestinal tract and spread into the pancreas. This hypothesis was supported by a few studies, one study showed the existence of SARS-CoV-2 in gastrointestinal tract epithelium, and RNA of the virus could be detected by real-time reverse transcriptase polymerase chain reaction from feces.¹⁰⁶ Furthermore, SARS-CoV-2 was also isolated from pancreatic pseudocyst tissue.¹⁰⁷ However, this hypothesis was not validated by robust evidence and it is unable to explain the relatively low incidence of AP in COVID-19 patient in some large epidemiological researches.^{47,48}

Taking into consideration of the high incidence of hyperlipidemia in COVID-19 patients, we hypothesized that hyperlipidemia could also be a mediator in the pathogenesis of pancreatic injury and AP in COVID-19 patients besides direct virus infection. The detrimental effects of HTG mentioned above should also exist in COVID-19 patients combined with AP. To support the hypothesis, we wondered whether the incidence of AP was higher in patients with hyperlipidemia compared to patients without hyperlipidemia in the COVID-19 population. However, no well-designed study has yet to report the related data, we thereby retrospectively collected the information of all case reports of AP with COVID-19 (Table 1). From the retrospective analysis, the levels of total triglycerides and total cholesterol increased slightly in COVID-19 patients complicated with AP, which suggested that hyperlipidemia may be the reason for the occurrence of AP.

CONCLUDING REMARKS

- (1) A small portion of COVID-19 patients presented with acute pancreatitis, but the underlying mechanism was still unknown.
- (2) The occurrence of hyperlipidemia was high in the COVID-19 population.
- (3) In general population, hyperlipidemia has become one of the major causes of AP. And in the COVID-19 population, presuming the detrimental effects of hyperlipidemia

still exist, hyperlipidemia could also be a mediating factor in the pathogenesis of pancreatic injury and AP.

(4) Further studies are warranted to clarify the relationship between AP, hyperlipidemia, and COVID-19.

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DECLARATION OF COMPETING INTEREST

The authors declare that there is no conflict of interest regarding the research, authorship, and/or publication of this paper.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Qiuyi Tang: Conceptualization, Visualization, Data curation, Formal analysis, Writing – review & editing. **Lin Gao:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Zhihui Tong:** Writing – review & editing. **Weiqin Li:** Writing – review & editing.

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