Propofol-Associated Hypertriglyceridemia in Coronavirus Disease 2019 Versus Noncoronavirus Disease 2019 Acute Respiratory Distress Syndrome

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Objectives: To characterize the incidence and characteristics of propofol-associated hypertriglyceridemia in coronavirus disease 2019 versus noncoronavirus disease 2019 acute respiratory distress syndrome.

Design: Single-center prospective, observational cohort study.

Setting: Medical ICU and regional infectious containment unit.

Patients: Patients with acute respiratory distress syndrome admitted from April 7, 2020, to May 15, 2020, requiring continuous propofol administration.

Interventions: None.

Measurements and Main Results: Of 50 patients enrolled, 54% had coronavirus disease 2019 acute respiratory distress syndrome. Median Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores were 35.5 (interquartile range, 30.2–41) and 8 (interquartile range, 6–9). \(\text{PaO}_2/\text{FiO}_2\) ratio was 130.5 (interquartile range, 94.5–193.8). Patients with coronavirus disease 2019-associated acute respiratory distress syndrome experienced a higher rate of hypertriglyceridemia (triglyceride \(\geq 500\) mg/dL) than noncoronavirus disease 2019-associated acute respiratory distress syndrome (9 [33.3%] vs 1 [4.3%]; \(p = 0.014\)). Those with coronavirus disease 2019, compared with those without, received more propofol prior to becoming hypertriglyceridemic (median, 5,436.0 mg [interquartile range, 3,405.5–6,845.5 mg] vs 4,229.0 mg [interquartile range, 2,083.4–4,972.1 mg]; \(p = 0.027\)). After adjustment for propofol dose with logistic regression (odds ratio, 5.97; 95% CI, 1.16–59.57; \(p = 0.031\)) and propensity score matching (odds ratio, 8.64; 95% CI, 1.27–149.12; \(p = 0.025\)), there remained a significant difference in the development of hypertriglyceridemia between coronavirus disease 2019-associated acute respiratory distress syndrome and noncoronavirus disease 2019-associated acute respiratory distress syndrome. There was no difference between groups in time to hypertriglyceridemia (\(\rho = 0.063\)). Serum lipase was not different between those who did or did not develop hypertriglyceridemia (\(\rho = 0.545\)). No patients experienced signs or symptoms of pancreatitis.

Conclusions: Patients with coronavirus disease 2019 acute respiratory distress syndrome experienced a higher rate of propofol-associated hypertriglyceridemia than noncoronavirus disease 2019 acute respiratory distress syndrome patients, even after accounting for differences in propofol administration.

Key Words: coronavirus disease 2019; hypertriglyceridemia; inflammation; propofol; sedation; sedation
at levels over 1,000 mg/dL (2, 3). In one study, 18% of patients receiving propofol developed hypertriglyceridemia and 10% of these patients developed pancreatitis (4). Mortality from acute pancreatitis in the critically ill can reach as high as 20–30% (5). Although not fully elucidated, propofol-associated pancreatitis in the absence of hypertriglyceridemia has also been reported, raising suspicion for additional mechanisms of injury (6).

Patients with acute respiratory distress syndrome (ARDS) often require high dosages of sedatives, including propofol to improve ventilator synchrony and oxygenation (7–9). This exposure potentially increases the risk of medication side effects. An additional recommendation for treatment of severe ARDS is the utilization of neuromuscular blocking agents (NMBA) to facilitate lung protective ventilation, in which deep sedation is required prior to initiation and throughout the duration of neuromuscular blockade (10, 11).

Given that elevated inflammatory markers mimicking a hemophagocytic lymphohistiocytosis-like syndrome are frequently present in coronavirus disease 2019 (COVID-19) infection, it is unknown if patients with COVID-19-associated ARDS receiving propofol are more likely to experience hypertriglyceridemia than patients with non-COVID ARDS (12, 13). The development of hypertriglyceridemia precludes further utilization of propofol and often requires the use of less desirable sedative agents, such as benzodiazepines, which are associated with worse clinical outcomes (14, 15). We hypothesized that patients with COVID-19-associated ARDS would develop a higher incidence of hypertriglyceridemia than their non-COVID-19 counterparts. Accordingly, we compared these two groups of patients in terms of severity of illness, propofol utilization, and development of hypertriglyceridemia.

**MATERIALS AND METHODS**

This prospective observational study was approved by the University of Michigan’s Institutional Review Board (IRB) with a waiver of informed consent (HUM00179997). From the date of IRB approval on April 7, 2020, to May 15, 2020, all consecutive patients requiring mechanical ventilation in the regional infectious containment unit (RICU) and medical ICU (MICU) were screened for study inclusion. The end date for study enrollment corresponded with the transition of University of Michigan’s RICU from an intensive care and intensivist-only unit to a mixed-acuity unit.

Patients 18 years old or older, with either COVID-19- or non-COVID-19-associated ARDS requiring at least 24 hours of propofol infusion at 20 µg/kg/min, were eligible for inclusion. Patients receiving mechanical ventilation at an outside facility for greater than 48 hours prior to transfer were excluded. Additional exclusion criteria included treatment with extracorporeal membrane oxygenation, history of pancreatitis, baseline triglyceride level of 300 mg/dL or greater, prisoners, and pregnancy. Baseline triglyceride level was defined as the lowest documented triglyceride level within 6 months prior to, and up to 24 hours after, the start of propofol infusion. Patients included in the study only received propofol formulated in a standard 10% lipid emulsion.

Baseline information regarding age, sex, weight, height, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, baseline comorbidities, and laboratory data including daily serum triglyceride levels, liver-associated enzymes, and available inflammatory markers were recorded. Receipt of continuous NMBA and daily propofol usage was also measured. Medications administered during the study period with the actual or potential ability to influence serum triglyceride levels or for treatment of COVID-19 were collected and included tocilizumab, corticosteroids (defined as any amount above a patient’s baseline), remdesivir, statins, heparin infusion, and insulin infusion. Based on historical discontinuation threshold for propofol at the study site, hypertriglyceridemia was defined as a serum triglyceride concentration of 500 mg/dL or greater. The National Cholesterol Educational Program Adult Treatment Panel III defines this triglyceride concentration as “severely elevated” (16). Due to an early perceived increase in the frequency of hypertriglyceridemia and an attempt to preserve the use of propofol, the recommended institutional discontinuation threshold was increased to 750 mg/dL during the COVID-19 pandemic. Once this threshold was met, an alternative sedative was initiated and propofol was weaned off as rapidly as tolerated. Except for those requiring deep sedation (i.e., NMBA use or ventilator desynchrony), maintaining a light level of sedation with daily spontaneous awakening trials is considered standard of care at the study institution. Additionally, the frequency of monitoring serum triglyceride levels for all patients receiving propofol increased compared with historical practice. Data were collected for up to 7 days after propofol initiation at the study institution. COVID-19 status was defined based on hospital diagnosis, utilizing a reverse-transcriptase polymerase chain reaction positive severe acute respiratory syndrome coronavirus-2 test.

The primary outcome measure for this study was the incidence of hypertriglyceridemia between patients with COVID-19- versus non-COVID-19-associated ARDS. Secondary endpoints included time to development of triglyceride levels of 500 mg/dL, 750 mg/dL, and development of acute pancreatitis, which was defined based on current American Gastroenterological Association acute pancreatitis guidelines of at least two of the following: characteristic abdominal pain, amylase or lipase greater than three times the upper limit of normal, and radiographic evidence of pancreatitis (18). Propofol-related infusion syndrome (PRIS) was screened for by review of daily progress notes.

We examined the data using descriptive measures, reporting as median and interquartile range (IQR) or counts and percentages. Statistical tests included Fisher exact test for categorical data and the Mann-Whitney U test for continuous data. Kaplan-Meier curves were constructed to compare the time to development of hypertriglyceridemia between groups during the 7-day study period and were analyzed with the log-rank test. Patient survival times were censored if propofol was discontinued or if they had not reached an event (i.e., development of hypertriglyceridemia) prior to day 7. We performed a Firth logistic regression due to the small sample size to examine the association of COVID-19 positive status and total propofol receipt on the development of hypertriglyceridemia. Because of potential confounding due to the differences in total propofol dose, we conducted a sensitivity
analysis by balancing data between groups using propensity score (PS) matching. We used nearest neighbor matching and logistic regression to create the distance measure with the R package MatchIt (R Foundation for Statistical Computing, Vienna, Austria) (19, 20). We then compared propofol dose using standardized differences with the stddiff package. A standardized difference of less than 0.1 designated a small difference between the treatment groups for binary variables and a difference of less than 0.2 was considered small for continuous variables, even if the p value was significant (21, 22). Due to the sample size, only propofol administration until reaching a triglyceride level of 500 µg/dL was matched on and included along with COVID-19 status in each regression performed. Statistical analyses were completed using R statistical software (Version 3.6.3, 2020).

RESULTS
A flow diagram is presented in Figure 1. Of 120 consecutively screened, mechanically ventilated patients admitted to the RICU or MICU during the screening period, 50 were eligible and enrolled. The median age was 64.5 years (IQR, 59–69 yr), with 56% men. Median APACHE II and SOFA scores within the first 24 hours of mechanical ventilation were 35.5 (IQR, 30.2–41) and 8 (IQR, 6–9), respectively, with a PaO₂/FIO₂ ratio of 130.5 (IQR, 94.5–193.8). Baseline demographics between the COVID-19 and non-COVID-19 cohorts were well matched apart from a higher weight, body mass index, and prevalence of coronary artery disease in the COVID-19 patients, and a higher prevalence of chronic obstructive pulmonary disease in non-COVID-19 patients (Table 1). Those in the COVID-19 cohort had a numerically higher peak serum ferritin during the study period, but this did not reach statistical significance (p = 0.292). However, C-reactive protein (CRP; p = 0.002), aspartate transaminase (p = 0.005), pro-calcitonin (p = 0.031), and baseline triglyceride level (p = 0.004) were statistically higher in those with COVID-19 ARDS (Table 1). Other peak serum inflammatory markers were similar between groups (Table 1).

A description of potentially interacting medication is listed in Table 1. No patients included in the study received hydroxychloroquine, lopinavir-ritonavir, antiretroviral, or fibrate therapy. Patients were enrolled in this study prior to the widespread adoption of corticosteroid therapy for treatment of COVID-19-associated ARDS; the primary indication for corticosteroid use in the study was as adjunct therapy for shock. Additionally, no patients received IV lipid emulsion therapy or hyperalimentation. Three patients in the COVID-19 cohort were randomized and enrolled into a double-blinded study comparing sarilumab versus placebo.

Propofol Utilization and Hypertriglyceridemia
Table 2 lists propofol utilization and clinical outcomes in the study cohort. Propofol utilization was significantly higher in the COVID-19 cohort versus non-COVID-19 cohort, both in terms of total propofol dose during the 7-day study period (median, 5,512.2 mg [IQR, 3,405.5–6,845.5 mg] vs 4,013.0 mg [IQR, 2,075.2–4,893.2 mg]; p = 0.008) and propofol dose until reaching a triglyceride level of 500 mg/dL (median, 5,436.0 mg [IQR, 3,405.5–6,845.5 mg] mg vs 4,229.0 mg [IQR, 2,083.4–4,972.1 mg]; p = 0.027). However, there was no difference in maximum propofol rate (median, 50.0 µg/kg/min [IQR, 32.5–67.5 µg/kg/min] vs 50.0 µg/kg/min [IQR, 40.0–60.0 µg/kg/min], respectively; p = 0.913). Subjects with COVID-19-associated ARDS experienced a higher rate of hypertriglyceridemia (triglyceride 500 mg/dL) than non-COVID-19-associated ARDS (9 [33.3%] vs 1 [4.3%]; p = 0.014). Six patients (22.2%) in the COVID-19 cohort experienced a triglyceride level greater than 750 µg/dL, compared with none in the non-COVID-19-associated ARDS group (p = 0.025). One COVID-19 ARDS patient experienced a triglyceride level greater than 1,000 mg/dL. Median time to development of hypertriglyceridemia for all patients, regardless of COVID-19 status, was 3.0 days (IQR, 1.7–5.2 d). Time to development of a serum triglyceride level of 750 mg/dL (n = 6) was a median of 3.6 days (IQR, 1.9–5.7 d). There was no difference between groups in time to hypertriglyceridemia (Fig. 2) (p = 0.063).

Regression Analysis
Due to the significant difference in propofol utilization between the two groups, a logistic regression was performed to account for the difference in propofol dose until reaching a triglyceride level of 500 µg/dL. After this adjustment for propofol administration, there was a significant difference in the development of hypertriglyceridemia between the COVID-19- and the non-COVID-
19-associated ARDS (odds ratio [OR], 5.97; 95% CI, 1.16–59.57; \( p = 0.031 \)). A PS matching was also separately performed as a sensitivity analysis to adjust for the baseline differences in propofol administration. Prior to matching, the standardized difference of propofol dose until reaching a triglyceride level of 500 mg/dL between the COVID-19 and non-COVID-19 groups was 0.52. After matching, the standardized difference was reduced to 0.33. The resulting COVID-19 and non-COVID-19 cohorts’ propofol doses were balanced according to the Mann-Whitney \( U \) test (median 5,159.0 mg [IQR, 3,059.8–5,790.5 mg] vs 4,229.0 mg [2,083.4–4,972.1 mg]; \( p = 0.095 \)). This analysis produced 23 matched pairs in each cohort (Table S1, http://links.lww.com/CCX/A461). A logistic regression was performed with the PS-matched patients, which resulted in a statistically significant increase in the development of hypertriglyceridemia in those with COVID-19-associated ARDS (OR, 8.64; 95% CI, 1.27–149.12; \( p = 0.025 \)).

### Additional Outcomes

When examining all patients who became hypertriglyceridemic (triglyceride 500 mg/dL; \( n = 10 \)), regardless of COVID-19 status...
Tables S2 and S3, http://links.lww.com/CCX/A461), those with hypertriglyceridemia had a higher weight (median 104 kg [IQR, 91.8–126.8 kg] vs 81.2 kg [IQR, 66.9–91.7 kg]; *p* = 0.005), more continuous NMBA use (6 [60%] vs 7 [17.5%]; *p* = 0.012), lower median PaO2/FiO2 ratio at baseline (94 [IQR, 82.8–101.1] vs 149.5 [IQR, 104.1–201.0]; *p* = 0.01), a higher baseline triglyceride level (204.5 µg/dL [IQR, 153.8–252.0 µg/dL] vs 153.5 µg/dL [IQR, 76.5–198.0 µg/dL]; *p* = 0.022), and more total propofol exposure (median, 6,845.5 mg [IQR, 5,247.3–8,408.8 mg] vs 4,052.5 mg [IQR, 2,616.4–5,377.5 mg]; *p* = 0.002). In a safety analysis, peak serum lipase was not different in those with triglyceride levels greater than 500 mg/dL (*p* = 0.545), nor in the six patients with triglyceride levels greater than 750 mg/dL (*p* = 0.545), when compared with those who maintained normal triglyceride levels. No cases of suspected or confirmed pancreatitis or PRIS were noted in any patient in the study.

**DISCUSSION**

Propofol is a commonly used sedative agent for mechanically ventilated patients with ARDS, and those with COVID-19-associated ARDS in this study were treated with a high cumulative dose of this medication in the first 7 days of intubation. Patients with COVID-19-associated ARDS experienced a higher rate of serum triglyceride elevation than those with non-COVID-19 ARDS, and this

| Variable | Overall (n = 50) | COVID-19 Positive (n = 27) | COVID-19 Negative (n = 23) | *p* |
|----------|----------------|---------------------------|--------------------------|-----|
| Propofol dose until triglyceride 500 mg/dL reached (mg)* | 4,653.0 (2,818.0–5,864.2) | 5,436.0 (3,405.5–6,845.5) | 4,229.0 (2,083.4–4,972.1) | 0.027 |
| Cumulative 7-d propofol dose (mg) | 4,520.0 (2,803.0–5,938.0) | 5,643.0 (3,405.5–7,732.0) | 4,229.0 (2,083.4–4,972.1) | 0.008 |
| Maximum propofol rate (µg/kg/min) | 50.0 (36.2–68.8) | 50.0 (32.5–67.5) | 50.0 (40.0–60.0) | 0.193 |
| Propofol rate at time of triglyceride 500 mg/dL (µg/kg/min, n = 10) | 47.5 (36.2–60.0) | 50.0 (40.0–60.0) | 20.0 (20.0–20.0) | 0.161 |
| Serum peak triglyceride (mg/dL) | 234.0 (136.2–385.8) | 354.0 (222.0–693.5) | 126.0 (78.0–260.5) | < 0.001 |
| Delta triglyceride (peak minus baseline; mg/dL) | 78.0 (8.2–194.0) | 156.0 (53.5–492.0) | 12.0 (0–95.0) | < 0.001 |
| Hypertiglyceridemia (triglyceride > 500 mg/dL) | 10 (20%) | 9 (33.3%) | 1 (4.3%) | 0.014 |
| Hypertiglyceridemia (triglyceride > 750 mg/dL) | 6 (12%) | 6 (22.2%) | 0 (0%) | 0.025 |

COVID-19 = coronavirus disease 2019.

*Propofol dose until triglyceride 500 µg/dL reached or propofol stopped, whichever occurs sooner.
Data are reported as median (interquartile range) or n (%), as appropriate.
remained true after adjustment for propofol exposure. Patients with COVID-19-associated ARDS receiving propofol should have their serum triglyceride levels monitored frequently.

In an early study describing the frequency of hypertriglyceridemia associated with propofol, Devlin et al (4) examined 159 patients receiving at least 24 hours of propofol at any rate and demonstrated an 18% incidence of hypertriglyceridemia, defined as a triglyceride level greater than 400 mg/dL. Notably, they demonstrated six of the 21 patients with hypertriglyceridemia developed a triglyceride level greater than 1,000 mg/dL. Three patients in the study cohort developed acute pancreatitis. Patients in this study received a wide range of cumulative propofol doses before development of hypertriglyceridemia (median, 15,032 mg [range, 3,638–235,110] mg). In a Swiss study of 220 critically ill patients (23), hypertriglyceridemia (defined as a triglyceride greater than 2 mmol/L or approximately 177 mg/dL) was common (45%), with intake of propofol and lipids ($r^2 = 0.28$ and 0.26, respectively) having the highest correlation with serum triglyceride levels, followed by inflammation (CRP; $r^2 = 0.18$). The authors stated the median dose of propofol associated with hypertriglyceridemia was 2.04 mg/kg/hr after a median of 4 days with “higher-dose” propofol (roughly estimated to 16,470 mg given our study’s median weight of 84.1 kg—no weight was provided in the Swiss study). Notably, the frequency of severe hypertriglyceridemia in the Swiss study (defined as triglyceride greater than 5 mmol/L or approximately 442 mg/dL) was only 4.5%, similar to the non-COVID-19 cohort in present study. Both the Devlin and Swiss studies demonstrated larger doses of propofol administered prior to the development of hypertriglyceridemia (at a lower triglyceride threshold) than the present study’s approximate dose of 6,800 mg.

The implications of the findings of our study are two-fold. First, we found that patients with COVID-19-associated ARDS received high amounts of sedation during the first 7 days of mechanical ventilation compared with non-COVID-19 ARDS, despite similar baseline characteristics such as APACHE II, SOFA, and Pao2/Fio2 ratios. This finding has been suggested, but not yet well documented throughout the COVID-19 epidemic and hospitals have faced critical drug shortages of sedative medications due to not only the surge of patients, but the increased amounts of sedatives used when receiving mechanical ventilation (24, 25). Second, patients with COVID-19-associated ARDS who receive propofol experience hypertriglyceridemia, a medication-limiting side effect, to a larger degree than similar non-COVID-19 patients. Although there is continued uncertainty regarding the role of a “cytokine storm” in COVID-19-associated ARDS versus non-COVID-19-associated ARDS (26), the development of hypertriglyceridemia may signify extrapulmonary involvement of the virus in the gastrointestinal system, similar to what has been demonstrated in other organs (27–30). The direct or even perhaps indirect role that COVID-19 plays in hindering the metabolism or utilization of triglyceride molecules, which leads to accumulation, is unknown.

Although this study used a triglyceride threshold of 500 mg/dL, seven of the 27 COVID-19 patients included also experienced a triglyceride level of 750 mg/dL, although no patients developed pancreatitis. The development of hypertriglyceridemia, defined at an institutional level, precludes further use of propofol and often requires utilization of alternative sedative agents. In select patients who do not require deep sedation and develop propofol-associated hypertriglyceridemia, dexmedetomidine may be a useful alternative agent. For patients requiring moderate-to-deep levels of sedation, or for those requiring continuous NMBA, midazolam or lorazepam are often used. These agents have been associated with an increase in adverse effects including oversedation, increased delirium, and prolonged mechanical ventilation (14). Avoidance of propofol can also lead to utilization of “salvage” therapeutic agents for sedation such as ketamine or phenobarbital, which lack robust efficacy and safety data (31–33). Unfortunately, compliance with current standards of ICU care including daily spontaneous awakening trials and maintenance of light levels of sedation that may mitigate these adverse effects are likely abandoned in the care of COVID-19-associated ARDS patients as a result of stressed healthcare providers and health-system census surges, as well as the guise of avoidance of self-extubation and reducing healthcare provider exposure (34).

Although this study is strengthened by its prospective design with stringent inclusion and exclusion criteria, it is limited by its small sample size. We attempted to adjust for this by utilizing a Firth logistic regression analysis that is often preferred in the case of smaller sample sizes or rare events. Baseline characteristics and severity of illness scores were well matched between the groups, indicating that patients were relatively similar. Differences in the primary outcomes were statistically significant in all analyses performed; however, likely due to our limited sample size, wide CIs are seen. We chose to only examine the effect of propofol exposure on the risk of hypertriglyceridemia development within the first 7 days of mechanical ventilation. There is the possibility that hypertriglyceridemia may have developed outside of this 7-day period; however, it is unlikely a significant number of patients developed this side effect past that time. We demonstrated that the majority of patients’ time to development of triglyceride levels of 500 and 750 mg/dL was less than 6 days. Additionally, the study by Devlin et al (4) demonstrated that hypertriglyceridemia developed a median of 54 hours from the start of propofol (IQR not provided). Time to peak triglyceride level in the Swiss study was a median of 4 days (IQR, 2–6 d) (23). Despite multiple adjustments for differences in baseline characteristics, there remains the possibility that patients with COVID-19-associated ARDS required more sedation with propofol, which led to an increased incidence of hypertriglyceridemia, irrespective of COVID-19 status. This, however, is less likely when these results are compared with previously published literature. Further large studies are likely still needed to clarify this difference. In addition to a robust description of baseline criteria for patients in this study, we collected and attempted to account for actual or potential triglyceride-altering medications; however, it is unknown the magnitude of effect other therapies may have had on the outcome of this study. Delivery of enteral nutrition was protocolized across the two patient units in the study and theoretically should not differ between the patient groups in this study. Larger studies are needed to examine the impact of additional risk factors and mitigation strategies for hypertriglyceridemia. Finally, after conclusion of the study, there
was an anecdotal increase of hypertriglyceridemia monitoring for COVID-19 patients receiving propofol therapy at the study site based on these data (i.e., every 48 hr while on propofol therapy). Further exploration in larger populations is needed to solidify recommendations for monitoring and determine if monitoring frequency and serum triglyceride thresholds for propofol discontinuation affect clinical outcomes.

CONCLUSIONS
Patients with COVID-19-associated ARDS experienced a higher rate of propofol-associated hypertriglyceridemia than non-COVID-19-associated ARDS patients, even after accounting for differences in propofol administration. Further studies are needed to determine an exact mechanism and potential mitigation strategies for this phenomenon.

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