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The Clearance of Midazolam and Metabolites during Continuous Renal Replacement Therapy in Critically Ill Patients with COVID-19

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Keywords
Critically ill patients · Drug blood level · Renal replacement therapy · Drug elimination routes · Midazolam

Abstract

Introduction: Midazolam-based continuous intravenous sedation in patients admitted to the intensive care unit (ICU) was a necessity during the COVID-19 pandemic. However, benzodiazepine-based sedation is associated with a high incidence of benzodiazepine-related delirium and additional days on mechanical ventilation. Due to the requirement of high midazolam doses in combination with the impaired renal clearance (CL) of the pharmacological active metabolite 1-OH-midazolam-glucuronide (10% compared to midazolam), ICU patients with COVID-19 and continuous renal replacement therapy (CRRT) were at risk of unintended prolonged sedation. Several CRRT-related factors may have influenced the delivered CL of midazolam and its metabolites. Therefore, the aim of the study was to identify and describe these CRRT-related factors. ***Methods:*** Pre-filter blood samples and ultrafiltrate samples were collected simultaneously. Midazolam, 1-OH-midazolam, and 1-OH-midazolam-glucuronide plasma samples were analyzed using an UPLC-MS/MS method. The prescribed CRRT dose was corrected for downtime and filter integrity using the urea ratio (urea concentration in effluent/urea concentration plasma). CL of midazolam and its metabolites were calculated with the delivered CRRT dose (corrected for downtime and saturation coefficient [SD]). ***Results:*** Three patients on continuous venovenous hemodialysis (CVVHD) and 2 patients on continuous venovenous hemodiafiltration (CVVHDF) were included. Midazolam, 1-OH-midazolam, and 1-OH-midazolam-glucuronide concentrations were 2,849 (0–6,700) µg/L, 153 (0–295) µg/L, and 27,297 (1,727–39,000) µg/L, respectively. The SD was 0.03 (0.02–0.03) for midazolam, 0.05 (0.05–0.06) for 1-OH-midazolam, and 0.33 (0.23–0.43) for 1-OH-midazolam-glucuronide. The delivered CRRT CL was 1.4 (0–1.7) mL/min for midazolam, 2.7 (0–3.5) mL/min for 1-OH-midazolam, and 15.7 (4.0–27.7) mL/min for 1-OH-midazolam-glucuronide. ***Conclusions:*** Midazolam and 1-OH-midazolam were not removed during CVVHD and CVVHDF. However, 1-OH-midazolam-glucuronide was removed reasonably, approximately up to 43%. CRRT modality, filter integrity, and downtime affect this removal. These data imply a personalized titration of midazolam in critically ill patients with renal failure and awareness for the additional sedative effects of its active metabolites.

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Introduction

Benzodiazepine-based continuous intravenous sedation in patients admitted to the intensive care unit (ICU) was a necessity during the coronavirus disease 2019 (COVID-19) pandemic [1–3]. Several studies reported high midazolam requirements in critically ill COVID-19 patients, possibly due to agitation, increased patient ventilator dyssynchrony, and challenging mechanical ventilation in prone position and ARDS [1, 3, 4]. However, benzodiazepine-based continuous sedation in critically ill COVID-19 patients is associated with a high incidence of benzodiazepine-related delirium and additional days on mechanical ventilation [5].

Midazolam is metabolized by CYP3A enzymes to form 1-OH-midazolam mainly and to a smaller extend 4-OH-midazolam. After hydroxylation, 1-OH-midazolam is subsequently metabolized to 1-OH-midazolam-glucuronide as its major metabolite, which is renally excreted. Previous research showed that 1-OH-midazolam and 1-OH-midazolam-glucuronide have sedative potency compared to midazolam of 60–80% and 10%, respectively and may therefore be responsible for unexpected prolonged sedative effects when used in patients with renal failure [6, 7].

Around a third of the COVID-ARDS patients admitted to the ICU developed acute kidney injury (AKI), of whom 14.3% required continuous renal replacement therapy (CRRT) [8, 9]. In these specific patients, especially in the ventilator-weaning phase of the disease, the risk of unintended and unwanted accumulation of midazolam and its metabolites in COVID-ARDS patients is augmented. Because 1-OH-midazolam-glucuronide possess only 10% of the sedative potency compared to midazolam, it is often overlooked as a possible contributor to unexplained persistent low consciousness states in ICU patients. If 1-OH-midazolam-glucuronide is accumulated in high concentrations, it can significantly contribute to the observed prolonged sedation effects [4, 7, 10].

Clearance (CL) data of midazolam and its metabolites during CRRT are limited. We anticipated that several factors related to the technical aspects of the extracorporeal system may influence the delivered CL of midazolam and its metabolites. First, the choice of the dose intensity in terms of the prescribed CRRT dose in mL/kg/h; second, the actual day-to-day downtime of the CRRT circuit (delivered CRRT dose mL/kg/h), due to virus associated hypercoagulability, premature clotting of the membrane resulted in frequent premature termination of the circuit with a significant effect on the delivered CRRT dose [11]; third, filter patency issues due to "second membrane" development, especially in diffusive modalities; lastly, the differences in midmolecular CL between CRRT modalities, convective versus diffusive-related CLs (continuous venovenous hemodialysis [CVVHD] vs continuous venovenous hemodiafiltration [CVVHDF]) [12].

In this case series, patients who were suspected for unintended prolonged sedative effects, we intended to describe the effect of the 4 above mentioned CRRT-related technical factors. We anticipated their influence on CL of midazolam and its metabolites with possible prolonged sedative effects in this series of CRRT requiring COVID-ARDS patients admitted to our ICU.

Materials and Methods

In April 2020 during the first COVID-19 wave, we identified 5 adult patients with CRRT requiring AKI and COVID-ARDS who received midazolam at our tertiary ICU of Erasmus MC University Medical Center (Rotterdam, the Netherlands). The medical research Ethics Committee approved the study and waived informed consent (MEC 2020-0381).

All patients were initially ventilated in prone position, and therefore sedated to RASS-5 as per protocol with midazolam (loading dose, followed by a continuous infusion of 0.05–0.2 mg/kg/h) and sufentanil (0.3–0.7 μg/kg/h) infusion and neuromuscular blockade if needed. Initiation and adjustment of CRRT was at the discretion of the attending physician according to local clinical practice with an initial prescription of 30 mL/kg/h. The daily delivered CRRT dose was calculated by correction for the circuit downtime. Filter patency was objectified with the urea ratio (concentration urea effluent/concentration urea plasma) and subsequently applied as an additional correction on the delivered CRRT dose.

First choice CRRT modality was citrate-based CVVHD using multiFiltratePRO (Fresenius Medical Care) with an Ultraflux AV1000s filter (Polysulfone, Fresenius Medical Care) and 1.8 m^2 membrane surface area. Patients with bodyweight >110 kg were treated with citrate based CVVHDF.

Data were extracted from the electronic medical records, including patient characteristics, midazolam treatment, Sequential Organ Failure Assessment (SOFA) score, and CRRT modalities. Pre-filter blood samples and effluent samples were collected simultaneously for determination of midazolam, its metabolites, and urea concentrations. Midazolam, 1-OH-midazolam, and 1-OH-midazolam-glucuronide plasma samples were analyzed by means of an FDA-validated method using ultra-performance liquid chromatography-tandem mass spectrometry. The limits of quantification of the method were 2–2,400 μg/L for midazolam, 3–2,300 μg/L for 1-OH-midazolam, and 10–3,000 μg/L for 1-OH-midazolam-glucuronide. If concentrations exceeded the upper limit of quantification, the calibration curve was used to extrapolate those concentrations.

CVVHD (CL_{CVVHD})- and CVVHDF (CL_{CVVHD})-related midazolam CL was calculated from the saturation coefficient (SD). An addition of both the sieving coefficient and the SD in CVVHDF

leads to an overestimation of the total CL [12, 13]. Therefore, during CVVHDF is the SD the diafiltration equivalent of the sieving coefficient. The SD is calculated as follows [14]: $SD = [Midazolam_{dialysate\ or\ ultrafiltrate}]/[Midazolam_{plasma}]$.

Next, the following equations were used to calculate the extracorporeal CL over 24 h:

$$CL_{CVVHD(F)} = (\text{prescribed CRRT dose} * \text{bodyweight} * SD)/60$$

$$CL_{CVVHD(F)} = (\text{delivered CRRT dose} * \text{bodyweight} * SD)/60$$

Here, the prescribed CRRT dose was determined using the set total effluent flow of the dialysis machine and corrected for the weight of the patient (sum dialysate, substitute, and ultrafiltrate). The delivered CRRT dose was calculated using the prescribed CRRT dose with correction for downtime of the therapy. All CRRT dosages were expressed as mL/kg/h and CL in mL/min. All data are presented as mean with range.

Finally, a PubMed search was conducted in April 2023 using the keywords "midazolam" and "renal replacement therapy." Relevant English language studies in adult patients were discussed in the manuscript.

Results

Five COVID-ARDS patients with CRRT requiring AKI were included in this case description during the first COVID-19 wave in April 2020 (age 61.4 [34–75] years; weight 105 [80–150] kg; SOFA score 10 [5–16]). Patient characteristics are presented in Table 1. Three patients received CVVHD-CiCa and 2 patients received CVVHDF-CiCa. The prescribed CRRT dose was 30.8 (27.5–34.7) mL/kg/h. The delivered CRRT dose was 26.6 (10.3–33.3) mL/kg/h and the additionally corrected delivered CRRT dose using urea ratio was 22.4 (8.8–29.3) mL/kg/h. One patient had a severe filter patency problem within 9 h after initiation of the circuit; the urea ratio was 0.53.

Midazolam, 1-OH-midazolam, and 1-OH-midazolam-glucuronide concentrations were 2,849 (0–6,700) μg/L, 153 (0–295) μg/L, and 27,297 (1,727–39,000) μg/L, respectively. The SD was 0.03 (0.02–0.03) for midazolam, 0.05 (0.05–0.06) for 1-OH-midazolam, and 0.33 (0.23–0.43) for 1-OH-midazolam-glucuronide. The delivered CRRT CL was 1.4 (0–1.7) mL/min (due to cessation of the midazolam infusion), 2.7 (0–3.5) mL/min for 1-OH-midazolam, and 15.7 (4.0–27.7) mL/min for 1-OH-midazolam-glucuronide. The PubMed search yielded 4 studies describing the midazolam CL characteristics in critically ill patients with CRRT, including 1 other study in COVID-ARDS patients [15], 1 study in patients with cardiological pathology [16], and 2 studies of patients with multiple organ dysfunction syndrome [17, 18]. These studies concerned 13 CVVH patients, 12 CVVHDF patients, and 4 CVVHD patients. The effluent flow and blood flow ranged from 1,000 mL/h to 2,000 mL/h and 50–180 mL/min, respectively. The plasma concentrations ranged from below of quantification to 3,285 μg/L for midazolam, below of quantification to 410 μg/L for 1-OH-midazolam, 66–2,745 μg/L for midazolam-glucuronide, and 76–19,945 μg/L for 1-OH-midazolam-glucuronide. The characteristics of the 4 previous studies are presented in Table 2.

Discussion

In this case series, we assessed CRRT-related factors that may have influenced CL of midazolam and its metabolites. The midazolam and 1-OH-midazolam SDs are very low, which emphasizes that CRRT-related CL of these compounds irrespective of the CRRT modality is unlikely. However, 1-OH-midazalom-glucuronide has an acceptable SD, which enhances its CRRT-related CL. Despite the difference in molecular weight and therefore probably no one-to-one relationship, the SD changes in concordance with the changes in urea ratio, which implies that filter patency issues drastically interfere with the true delivered mass removal of the molecule (patient 1 vs. patient 2). Moreover, when downtime was taken into account, a major decrease was observed in the delivered CRRT CL (patient 4 4 mL/min vs. patient 5 14.1 mL/min, whereby patient 4 had a downtime period of 15 h due to catheter malfunction). Furthermore, adding convective CL to the system adds up for the delivered CRRT dose. Patient 2 versus 3, with almost identical urea ratios, a CL showed a significant increase in CL of 27.7 mL/min and 17.7 mL/min, respectively. When patients 1, 4, and 5 had better filter patency and/or no downtime period, this will give proportionally a similar increased convective-related CL when comparing CVVHD versus CVVHDF. Also, the obtained previous literature showed a significant difference between diffusive-related CL and diffusive combined with convective-related CL. In summary, these are modifiable factors that can be addressed in a situation where unwanted prolonged unconsciousness interferes with the clinical trajectory of the patient.

The literature of CRRT-related midazolam CL in critically ill patients is limited. The previous studies showed a large variability in sieving coefficients/SDs and CRRT-related CL of midazolam and its metabolites. This variability can possibly be explained by the previously mentioned CRRT-related factors that could influence the actual delivered CRRT CL. However, of the four studies found, none provided information about effects of downtime and/or filter patency. Furthermore, only prescribed CRRT doses with effluent volumes were reported [15–18].

Table 1. Patient characteristics and clinical data of midazolam and CRRT therapy

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Total
	CVVHDF	CVVHDF	CVVHD	CVVHD	CVVHD	
Demographics						
Gender	M	M	M	F	M	
Age, years	34	64	72	62	75	61.4 (34–75)
Weight, kg	121	150	85	80	89	105 (80–150)
SOFA score from date sampling day midazolam	10	9	16	5	10	10 (5–16)
CRRT						
Type of CRRT	CVVHDF-CiCa	CVVHDF-CiCa	CVVHD-CiCa	CVVHD-CiCa	CVVHD-CiCa	
Type of filter	Ultraflux AV1000s	Ultraflux AV1000s	Ultraflux AV1000s	Ultraflux AV1000s	Ultraflux AV1000s	
Blood flow rate, mL/min	140	160	130	110	130	134 (110–160)
Dialysate flow rate, mL/h	2,800	3,200	2,600	2,200	2,600	2,680 (2,200–3,200)
Substitution, mL/h	1,400	1,600	n.a.	n.a.	n.a.	1,500 (1,400–1,600)
Prescribed renal dose, mL/kg/h	34.7	32	30.6	27.5	29.2	30.8 (27.5–34.7)
Delivered renal dose, downtime corrected, mL/kg/h	33.3	30.7	29.3	10.3	29.2	26.6 (10,3–33.3)
Corrected delivered renal dose, using urea ratio, mL/kg/h	17.6	28.2	29.3	8.8	28.3	22.4 (8.8–29.3)
Urea ratio	0.53	0.92	1.0	0.85	0.97	0.85 (0.53–1.0)
Midazolam						
Infusion rate, mg/h	20	25	10	0	30	17 (0–30)
Dose, mg/kg/h	0.14	0.17	0.12	n.a.	0.34	0.19 (0.12–0.34)
Plasma concentration, µg/L						
Midazolam	3,650	660	1,016	n.a.	6,070	2,849 (0–6,070
1-OH-midazolam	97	43	178	n.a.	295	153 (0–295)
1-OH-midazolam-glucuronide	39,000	21,630	37,490	1,727	36,640	27,297 (1,727–39,000)
Total sum	7,627	2,857	4,907	173	9,970	5,106 (173–9,970)
SD						
Midazolam	0.02	0.02	0.03	n.a.	0.03	0.03 (0.02–0.03)
1-OH-midazolam	0.05	n.a.	0.06	n.a.	0.05	0.05 (0.05–0.06)
1-OH-midazolam-glucuronide	0.23	0.36	0.43	0.29	0.32	0.33 (0.23–0.43)
Midazolam CL by, mL/min						
Prescribed renal dose	1.7	1.7	1.3	n.a.	1.1	1.5 (0–1.7)
Delivered renal dose	1.7	1.6	1.2	n.a.	1.1	1.4 (0–1.7)
1-OH-midazolam CL by, mL/min						
Prescribed renal dose	3.6	n.a.	2.4	n.a.	2.2	2.7 (0–3.6)
Delivered renal dose	3.5	n.a.	2.3	n.a.	2.2	2.7 (0–3.5)
1-OH-midazolam-glucuronide CL by, mL/min						
Prescribed renal dose	15.8	28.9	18.5	10.7	14.1	17.6 (10.7–28.9)
Delivered renal dose	15.1	27.7	17.7	4.0	14.1	15.7 (4–27.7)

Total data are presented as mean with range. All renal doses and associated calculated CL are over the last 24 h. Numbers are rounded to 2 decimal places. CiCa, calcium citrate; CL, clearance; CRRT, continuous renal replacement therapy; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous haemodiafiltration; N.a., not applicable; SD, saturation coefficient; SOFA score, sequential organ failure assessment score.

Table 2. Literature summary of midazolam CL in critically ill adult patients with CRRT

Source	Patients	Type CRRT	Plasma concentration, µg/L	Sieving/SD	CL by CRRT, mL/min
Shudofsky et al. [15]	*N* = 3	CVVH-CiCa Blood flow 180 mL/min Ultrafiltrate flow 50 mL/min Pre-filter flow 1,920 mL/h Post-filter flow 1,600 mL/h AN69 membrane	Midazolam: 15–917 1-OH-midazolam: 6–399 Midazolam-gluc: 66–2,745	Midazolam: 0.02 1-OH-midazolam: 0.05–0.07 Midazolam-gluc: 0.30–0.60	Midazolam: 1.33–1.50 1-OH-midazolam: 3.67–4.67 Midazolam-gluc: 5–10
Bolon et al. [16]	*N* = 4	CVVHD (anticoagulant unknown) Blood flow 50–80 mL/min Dialysate flow 1,000 mL/h Polyacrylonitrile membrane	Midazolam[a]: 10–330 1-OH-midazolam[a]: n.a. 1-OH-midazolam-gluc[a]: 80–1,700	Midazolam: 0.007–0.24 1-OH-midazolam: n.a. –0.008 1-OH-midazolam-gluc: 0.38–0.61	Midazolam: 0.13–4.7 1-OH-midazolam: n.a. – 0.14 1-OH-midazolam-gluc: 7.8–9.5
Swart et al. [18]	*N* = 10	CVVH (anticoagulant unknown) Blood flow 180 mL/min Pre- or post-filter 2,000 mL/h Cellulose triacetate membrane	Midazolam: 0–3,285 1-OH-midazolam: 0–410 1-OH-midazolam-gluc: 77–19,945	Midazolam: 0.02–0.1 1-OH-midazolam: 0.08–0.09 1-OH-midazolam-gluc: 0.34–0.52	Midazolam[b]: 0.92 1-OH-midazolam: Not known 1-OH-midazolam-gluc[b]: 14.5
Tsubo et al. [17]	*N* = 12	CVVHDF-heparin Blood flow 70 mL/min Dialysate flow 500 mL/h Post-filter flow 1,000 mL/h Polyacrylonitrile membrane	Midazolam 1,069±697 No information of metabolites	Not known	Midazolam: −1.3±5.9 No information of metabolites

CiCa, calcium citrate; CRRT, continuous renal replacement therapy; CVVHD, continuous venovenous hemodialysis; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; Gluc, glucuronide; N.a., not applicable; SD, saturation coefficient; SOFA score, sequential organ failure assessment score. [a]An approximate concentration since data are only showed as figure. [b]CLs based on study population estimates.

The CL of midazolam in our study was similar to the findings from Shudofsky et al. [15], Swart et al. [18], and Bolon and colleagues, [16] found higher midazolam CLs, which are probably the result of a higher Sc of midazolam up to 0.24. In addition, it was found that the CL of 1-OH-midazolam in Shudofsky et al. [15] was broadly in line with our results. Bolon and colleagues, [16] showed a much lower and an undeterminable CL of 1-OH-midazolam, possibly caused by a much lower midazolam dose of 0.05 mg/kg/h. Moreover, our prescribed CRRT dose CL of 1-OH-midazolam-glucuronide was similar to the reported CL by Shudofsky and colleagues. When we correct for downtime of the CRRT and/or take filter patency into account, a much lower SD and therefore a much lower CL was achieved. The studies from Bolon et al. [16] and Swart et al. [18] reported lower CL as well, which are probably attributed to the differences in prescribed CRRT dosages.

With regard to the CRRT modality, our increased CL of 1-OH-midazolam with a convective modality (CVVHDF) was in line with the higher convective-related CL (CVVH) reported by Shudofsky et al. (30.8–34 mL/min) versus the diffusive related CL (CVVHD) reported by Bolon et al. (7.8–9.5 mL/min) [15, 16]. Our case series emphasizes that the CL of target compounds in the blood depends on the delivered CRRT dose, on the SD of the molecule in the applied membrane and the variability of the SD in relation to the addition of convective mass transfer and filter patency issues ("second membrane") expressed and monitored by the urea ratio.

Hopefully, this case series brings more awareness for personalized titration and evaluation of midazolam in critically ill patients and more specific COVID-ARDS patients with CRRT requiring AKI. Prolonged unconsciousness states in these patients can be possibly due to the presence of the unexpected metabolite 1-OH-midazolam-glucuronide. Oversedation should be avoided to enhance the process of weaning from the ventilator. Since 1-OH-midazolam-glucuronide is only partly removed by CRRT, our study implies that the use of midazolam during CRRT should lead to incentives to decrease midazolam dosage as much as feasible to mitigate adverse consequences of oversedation. Moreover, in case of oversedation, CVVHDF can be considered instead of CVVHD as the addition of convective mass transfer results in an almost twice higher delivered CRRT CL. Furthermore, in this study, we used the urea ratio for the calculation of actual delivered CRRT dose, which is an adequate marker for filter patency during CRRT [19, 20]. We observed a clear concordance between the urea ratio and a reduced CL of 1-OH-midazolam-glucuronide. Therefore, in absence of a dedicated midazolam analysis in terms of therapeutic drug monitoring, a urea ratio is an easy method to estimate a possible reduced CL of 1-OH-midazolam-glucuronide during CRRT. A frequent assessment of the delivered CRRT dose is also recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Despite this recommendation, the literature on urea ratio-based filter patency correction is limited.

Finally, in case of oversedation, one should consider to perform therapeutic drug monitoring. We found plasma concentrations of 27,297 (1,727–39,000) μg/L for 1-OH-midazolam-glucuronide and a total sum plasma concentration of 5,106 (173–9,970) μg/L for midazolam and metabolites. This appears to be high compared to previous studies [15–18]. Despite the potency of only 10% for 1-OH-midazolam-glucuronide, plasma concentration up to 39,000 μg/L as found in our study can contribute significantly to a prolonged sedation effect. In addition, there seems to be a correlation between midazolam plasma concentrations and the degree of sedation [21, 22]. For example, Nies et al. [22] observed in a non-COVID-ARDS ICU population, a median midazolam concentration of roughly 1,500 μg/L for RASS-5. However, since there is a large interpatient variability in plasma concentrations of midazolam and metabolites, it is difficult to formulate a target concentration for a particular degree of sedation.

Some limitations of this study should be noted. First, we studied a small cohort of patients, in which the CRRT-related factors that could influence CRRT CL of midazolam and metabolites could not be compared in all patients. However, we were still able to provide important insights into these various CRRT-related factors. Second, due to the observational method, we did not correlate the CL of midazolam and metabolites with the previous reported risk of delirium, prolonged coma, and increased ICU length of stay.

Conclusions

Midazolam and 1-OH-midazolam are not removed efficiently by CRRT and 1-OH-midazolam-glucuronide approximately up to 43%. CRRT modality, filter patency, and downtime of the CRRT circuit affect the CL of the pharmacological active metabolite 1-OH-midazolam-glucuronide. Our results can help in more personalized titration of midazolam in COVID-ARDS patients with CRRT, mainly to avoid oversedation.

Statement of Ethics

The Medical Research Ethics Committee of Erasmus MC University Medical Center, Rotterdam, the Netherlands, approved the study and waived informed consent (approval number MEC 2020-0381).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.J.V., H.R.H.G., H.E., and N.G.N.H. contributed to the study conception and design. Material preparation, data collection, data analyses were performed by T.J.L.S., L.B., and A.J.V. The manuscript was written by T.J.L.S., and all authors (L.B., A.J.V., H.R.H.G., D.A.M.P.J., B.C.P., N.G.M.H., and H.E.) commented on previous versions of the manuscript. All authors (T.J.L.S., L.B., A.J.V., H.R.H.G., D.A.M.P.J., B.C.P., N.G.M.H., and H.E.) read and approved the final manuscript.

Data Availability Statement

All data analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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