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Hemodynamics and prostacyclin - A prospective cohort study

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Laser Speckle Contrast Imaging-based diagnosis of severe mesenteric traction syndrome: Hemodynamics and prostacyclin - A prospective cohort study

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ABSTRACT

Brief abstract: Today, the diagnosis and grading of mesenteric traction syndrome relies on a subjective assessment of facial flushing. However, this method has several limitations. In this study, Laser Speckle Contrast Imaging and a predefined cut-off value are assessed and validated for the objective identification of severe mesenteric traction syndrome.

Background: Severe mesenteric traction syndrome (MTS) is associated with increased postoperative morbidity. The diagnosis is based on an assessment of the developed facial flushing. Today this is performed subjectively, as no objective method exists. One possible objective method is Laser Speckle Contrast Imaging (LSCI), which has been used to show significantly higher facial skin blood flow in patients developing severe MTS. Using these data, a cut-off value has been identified. This study aimed to validate our predefined LSCI cut-off value for identifying severe MTS.

Methods: A prospective cohort study was performed on patients planned for open esophagectomy or pancreatic surgery from March 2021 to April 2022. All patients underwent continuous measurement of forehead skin blood flow using LSCI during the first hour of surgery. Using the predefined cut-off value, the severity of MTS was graded. In addition, blood samples for prostacyclin (PGI$_2$) analysis and hemodynamics were collected at predefined time points to validate the cut-off value.

Main results: Sixty patients were included in the study. Using our predefined LSCI cut-off value, 21 (35 %) patients were identified as developing severe MTS. These patients were found to have higher concentrations of 6-Keto-PGF$_{a2}$ (p = 0.002), lower SVR (p < 0.001), lower MAP (p = 0.004), and higher CO (p < 0.001) 15 min into surgery, as compared with patients not developing severe MTS.

Conclusion: This study validated our LSCI cut-off value for the objective identification of severe MTS patients as this group developed increased concentrations of PGI$_2$ and more pronounced hemodynamic alterations compared with patients not developing severe MTS.

Abbreviations: CO, Cardiac Output; HR, Heart Rate; LSCI, Laser Speckle Contrast Imaging; MAP, Mean Arterial Pressure; MTS, Mesenteric Traction Syndrome; PGI$_2$, Prostacyclin; qMSTS, quantified severe Mesenteric Traction Syndrome; SVR, Systemic Vascular Resistance.

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1. Introduction

Mesenteric traction syndrome (MTS) is defined by the occurrence of hypotension, tachycardia, and facial flushing early during major abdominal surgery (Olsen et al., 2022a; Krohn et al., 2014; Olsen et al., 2022b; Olsen et al., 2022c). This response is caused by a release of prostacyclin (PGI₂) (Myers et al., 1994; Myers et al., 1988; Buecher et al., 2006) as part of a defense mechanism against the development of splanchnic hypoperfusion/ischemia (Myers et al., 1988; Brinkmann et al., 1999; Reed et al., 1989; Reed et al., 1990), which possibly can occur during the initial manipulation of the abdominal viscera and mesenteric traction early in the surgical procedure. The release of PGI₂ is thought to play an essential role in maintaining the intestinal mucosal barrier during surgery (Brinkmann et al., 1999; Brinkmann et al., 1996). However, the potent vasodilator PGI₂ may also cause an inappropriate systemic hemodynamic dysfunction, ranging from a mild transient decrease in blood pressure to the development of marked hypotension, counteracted by increased heart rate and cardiac output due to increased endogenous vasopressor release (Brinkmann et al., 1996).

MTS is very common during major open abdominal surgery, with a reported prevalence of 70 % (Olsen et al., 2022c). Furthermore, approximately 35 % of patients develop severe MTS. These patients have the highest levels of PGI₂ and develop severe hemodynamic alterations resulting in the need for fluid and vasopressor interventions (Brinkmann et al., 1999; Brinkmann et al., 1998; Brinkmann et al., 1997; Brinkmann et al., 1996; Seltzer et al., 1988; Ambrus et al., 2017). However, the development of MTS, and especially of severe MTS, also affect the postoperative period, as recent studies have shown that the development of severe MTS is associated with increased postoperative morbidity, increased risk of severe postoperative complications, and an increased length of stay (Ambrus et al., 2017; Olsen et al., 2020; Olsen et al., 2021). This has since been shown to be due to an increased surgical stress response, seen as increased levels of CRP and IL6 (Olsen et al., 2021; Strandby et al., 2021), as well as increased endothelial dysfunction postoperatively (Olsen et al., 2021).

Today, the diagnosis of MTS is based on a subjective assessment of facial flushing. This method divides MTS into three levels of severity: no MTS, moderate MTS, and severe MTS (Koyama et al., 1995; Nomura et al., 2010). Nevertheless, this method has limitations. Firstly, the subjective assessment of flushing can be difficult and almost impossible in some patient groups, such as patients with darker skin color, anemic patients, and patients with a natural redness (Olsen et al., 2022a; Alexis et al., 2019). Furthermore, the method may be associated with high levels of observer variability, affecting the quality and comparability of different MTS studies. Therefore, there is a need for an objective method for identifying MTS, and especially severe MTS (Olsen et al., 2022a; Olsen et al., 2022c).

One possible approach to the objective diagnosis of severe MTS could be to quantify facial flushing. Multiple methods could possibly be used for this approach, such as Laser Speckle Contrast Imaging (LSCI), Laser Doppler Flowmetry, optical coherence tomography, and remote photoplethysmography (Low et al., 2020; Lai et al., 2022). However, only LSCI has been examined previously in patients developing MTS, showing intriguing results. LSCI is a real-time non-invasive, non-contact method for quantifying perfusion and so could be used to quantify facial flushing (Ambrus et al., 2016). LSCI is already used for perfusion assessment in several medical specialties (Heeman et al., 2019; Iredahl et al., 2015; Miller et al., 2022; Boss and Dunn, 2010) and has previously been used to quantify facial flushing in patients developing MTS (Ring et al., 2018; Zaar et al., 2014). One study found a significant difference in facial skin perfusion between patients developing severe MTS and patients developing moderate/no MTS using LSCI (Ring et al., 2018). The data from that study was used to identify a cut-off value for the detection of severe MTS. However, this new cut-off value has not yet been validated.

This study aimed to validate our predefined LSCI cut-off value for detecting severe MTS in a new cohort, using the intraoperative levels of PGI₂ and the hemodynamics as references.

2. Methods

The study adhered to the STROBE guidelines for observational studies.

2.1. Study design

This study was a prospective cohort study approved by the Scientific-Ethical Committees (H-20058773), Capital Region, Copenhagen, and registered at clinicaltrials.gov (NCT04796493). The cohort consisted of patients planned for open esophagectomy or open pancreatic surgery (Whipple procedure/total pancreateoduodenectomy). Verbal and written informed consent was obtained before the enrollment of patients.

2.2. Outcomes

The primary outcome was validating our predefined cut-off value for the objective detection of qsMTS using the levels of PGI₂ and hemodynamics.

The secondary outcome was to assess the correlation between facial skin blood flow and PGI₂ and hemodynamics 15 min into the surgical procedure.

2.3. Patients

Patients planned for open esophagectomy, or open pancreatic surgery were included in this study. Patients were still included even if they only received an explorative laparotomy due to the findings of disseminated disease during surgery. The exclusion criteria were patients under the age of 18 and patients having received oral or intravenous cortico-steroid or NSAID <24 h prior to the surgical procedure. However, patients planned for open pancreatic surgery were allowed to be administered 20 mg dexamethasone shortly following induction without being excluded, as it is standard treatment at our center. All included patients received standard-of-care surgery at our institution from March 2021 to April 2022.

2.4. Anesthesia

All patients underwent standard-of-care anesthesia. Anesthesia was induced with a bolus of intravenous propofol (1.5–2 mg/kg), remifentanil (0.5 μg/kg), and cisatracurium (0.1 mg/kg), or suxamethason (1 mg/kg). Tracheal intubation followed guidelines, and ventilation was set with 5 cm H₂O PEEP and a maximum pressure of 30 cm H₂O (usually below 20 cm H₂O). Anesthesia was maintained with the continuous infusion of intravenous propofol (5–10 mg/kg/h), remifentanil (1.75–2.25 mg/h), and cisatracurium with a target Train of Four response of 0 %. Norepinephrine infusion was initiated following induction of anesthesia with the goal of maintaining a mean arterial pressure (MAP) > 65 mm Hg. All patients received continuous fluid therapy consisting of the infusion of Ringers lactate (1 ml/kg/h) throughout the surgical procedure. Furthermore, patients undergoing pancreatic surgery underwent goal-directed fluid therapy (GDFT) by standardized stroke volume (SV) optimization after induction prior to the first incision, thereby ensuring hemodynamic stability prior to the start of the surgical procedure. GDFT consisted of the infusion of 250 ml of human albumin 5 %, and in the case of an increase of SV > 10 %, a new bolus of 250 ml of human albumin was administered until the maximum SV (SV set point) was reached. SV optimization was repeated if SV decreased >10 %. The maximum total dosage of human albumin 5 % was 25 ml/kg, and if surpassed, additional SV optimization was performed using fresh frozen plasma.

All patients received a thoracic epidural catheter placed at the Th8–10, and placement was confirmed by administering 3 ml lidocaine.
2 % with 5 μg adrenaline. Epidural analgesia was started following induction of anesthesia by the administration of 15 mg + 15 mg of bupivacaine and followed by the continuous infusion of bupivacaine/morphine (2.5 mg + 50 μg/ml) at 5 ml/h, as well as a repeated bolus of 15 mg bupivacaine every hour of the surgical procedure. The epidural has not been found to increase the incidence of severe MTS but has been found to be associated with a more pronounced hemodynamic response in patients developing severe MTS (Strandby et al., 2021).

According to local guidelines and as part of an enhanced recovery pathway at our center, a single dose of 20 mg of intravenous dexmedetomidine was administered to all patients planned for pancreatic surgery following induction in an attempt to attenuate postoperative pain (Steinhorsdottir et al., 2021a), nausea (De Oliveira et al., 2013), and surgical stress (de la Motte et al., 2014; Steinthorsdottir et al., 2021b). Patients undergoing esophageal surgery did not receive any corticosteroids.

2.5. Blood samples

Blood samples for determining the levels of plasma-6-keto-PGF$_{1α}$ (a stable metabolite of PGI$_2$) were collected and analyzed at: A: baseline (after induction of anesthesia), B: 15 min into surgery, and C: by 60 min. 6-Keto-PGF$_{1α}$ was determined by enzyme-linked immunosorbent assay (ADl-900-004, Enzo Life Science, Lörrach, DE (Podgorska et al., 2017; Dam et al., 2021)) according to the manufacturer’s instructions.

2.6. Hemodynamic variables

The hemodynamic variables of systemic vascular resistance (SVR), MAP, heart rate (HR), and cardiac output (CO) were measured continuously during surgery using modified pulse contour analysis (Nexfin®, BMEYE B.V., Amsterdam, NL or LiDCO™, Massimo, UK) via an arterial catheter in the radial artery if no contraindications of the procedure were present. Hemodynamics was noted at baseline, 15 min, 30 min, 45 min, and 60 min into surgery as a 30 s mean value.

2.7. Laser Speckle Contrast Imaging

Facial skin blood flow was measured during the first hour of surgery on the forehead of all patients using LSCI (MoorFLPI, Moor Instruments LTD., Axminster, UK). The LSCI apparatus underwent factory service and the calibration was controlled prior to the inclusion of the first patient, ensuring comparable measurements in all included patients. LSCI measures superficial blood flow in real-time in a non-contact fashion. During the measurements, the device was placed at a distance of 25 cm perpendicular to the targeted tissue surface. Analysis of facial blood flow was performed posthoc using MoorFLPI Review (Vs 4.0, Moor Instruments LTD). A region of interest of approximately 2–4 cm$^2$ was defined in the forehead just above the glabella, at a level just above the eyebrows. Facial blood flow was assessed at the same intervals as hemodynamics as a 30s mean value and averaged within the selected ROI.

In short, LSCI works by illuminating a surface with a laser. The contact with the surface will lead to the scattering of the laser, and reflection back to a photodetector. This will create and scatter pattern of the examined area. Movement in the investigated area, for instance, superficial blood flow will lead to fluctuations in the scatter pattern. These fluctuations can then be quantified and analyzed as perfusion units or flux. This value can then be used as a marker of skin blood flow or skin perfusion (Heeman et al., 2019; Boas and Dunn, 2010).

2.8. MTS severity

Facial flushing during surgery was used as a surrogate marker of MTS severity (Nomura et al., 2010) and was quantified using LSCI. The previous study showed that LSCI could distinguish severe MTS from moderate and no MTS (Ring et al., 2018) and was used to create a receiver operating characteristic curve (ROC). The ROC used facial blood flow levels just above glabella 15 min into the surgery to distinguish severe MTS from moderate or no MTS. The ROC had an area under the curve of 0.891 (p < 0.001). Using the ROC, the optimal cut-off value was found to be 425 flux with a sensitivity of 90.9 % and a specificity of 80.6 %, with subjective assessment used as the reference standard. Patients with a facial blood flow above 425 flux 15 min into surgery were therefore defined as having developed quantified severe MTS (qsMTS). In contrast, patients with a value below were not defined as having developed quantified severe MTS (−qsMTS).

2.9. Statistics

The statistical analysis was performed with IBM statistics (SPSS, Version 22.0, Chicago, IL, USA) and graphs constructed in GraphPad Prism (Version 8.0.2, GraphPad Software, San Diego, CA, USA).

A sample size calculation based on the data from the prior study assessing LSCI in patients developing MTS (Olsen et al., 2020) was performed, evaluating how many patients would be required to identify a significant difference in 6-Keto-PGF$_{1α}$ between patients developing severe MTS and patients not developing severe MTS. The power calculation assumed that 35 % of patients undergoing major open esophageal or pancreatic surgery developed severe MTS (Olsen et al., 2022c). The power calculation showed the requirement of 60 patients, 21 with qsMTS, and 39 without qsMTS, to identify a difference in 6-Keto-PGF$_{1α}$ (α: 0.05, power: 80 %).

Patients were allocated into two groups: qsMTS or −qsMTS, using our LSCI cut-off value.

Data were tested for normal distribution using the Shapiro-Wilk test. Intergroup differences between qsMTS and −qsMTS were assessed by an independent sample t-test for normally distributed data, Mann-Whitney U test for non-normally distributed data, and x$^2$-test or Fischer’s exact test for categorical data. Correlations were analyzed as a Pearson correlation coefficient. Due to multiple testing of five hemodynamic and biochemical markers, a Bonferroni correction was made. A p-value <0.01 was considered statistically significant when assessing the difference in levels 6-Keto-PGF$_{1α}$, SVR, MAP, HR, and CO between patients developing qsMTS and not developing qsMTS. No correction was done when assessing facial skin blood flow, as this was part of the definition for qsMTS. A p-value<0.05 was considered significant for the analysis of skin blood flow and the Pearson correlation analysis. Data are presented as either count (%), mean (SD), or median (IQR).

3. Results

A total of 60 patients were included in the final analysis. Patients were scheduled for open esophagectomy (n = 28) or Whipples procedure (n = 32). Patients ended up undergoing open esophagectomy (n = 22), Whipples procedure (n = 18), total pancreatectomy (n = 7), or explorative laparotomy (n = 13). Using the calculated cut-off value, it was found that 21 of 60 patients (35 %) developed qsMTS. Baseline characteristics are shown in Table 1.

3.1. LSCI and qsMTS

Patients characterized as developing qsMTS using our LSCI cut-off value for facial skin blood flow 15 min into surgery were found to have increased facial skin blood flow in the forehead 30 min (p < 0.001, Fig. 1), 45 min (p < 0.001), and 60 min into surgery (p < 0.001) as compared with patients characterized as not developing qsMTS by the LSCI cut-off value. See Supplementary Table 1 for exact values.

3.2. 6-Keto-PGF$_{1α}$

Patients with qsMTS had almost three times higher levels of 6-Keto-
PGF\(_{1\alpha}\) after 15 min of surgery (p = 0.002, Fig. 2). No difference was identified in the levels of 6-Keto-PGF\(_{1\alpha}\) at baseline nor after 60 min of surgery. See Supplementary Table 2 for exact values.

3.3. Hemodynamics

Patients characterized as developing qsMTS also had lower levels of SVR 15 min (p < 0.001, Fig. 2) and 30 min (p = 0.002) into surgery. In addition, patients developing qsMTS also had a lower MAP (p = 0.004) 15 min into the surgical procedure. Lastly, patients characterized as developing qsMTS by LSCI had a significantly higher CO 15 min (p < 0.001) and 30 min (p = 0.004) when compared with patients not developing qsMTS. See Supplementary Table 3 for exact values.

3.4. Correlation of facial blood flow with PGI\(_2\) and hemodynamics

Facial skin blood flow levels measured by LSCI 15 min into surgery were found to be correlated with the levels of 6-Keto-PGF\(_{1\alpha}\) 15 min into the surgical procedure (r = 0.462, p < 0.001). Furthermore, facial skin blood flow 15 min into the surgery was also inversely correlated with SVR after 15 min of surgery (r = −0.575, p < 0.001, Fig. 3), as well as MAP at 15 min into surgery (r = −0.346, p = 0.007). Lastly, facial skin blood flow levels 15 min into the surgery were also found to be correlated with HR (r = 0.304, p = 0.019) and CO (r = 0.531, p < 0.001) 15 min into surgery.

4. Discussion

This study found that patients characterized as developing qsMTS by LSCI developed higher levels of facial skin perfusion during the first hour of surgery. Furthermore, these patients developed significantly higher levels of 6-Keto-PGF\(_{1\alpha}\) as a sign of increased levels of PGI\(_2\). Moreover, they had significantly lower SVR and MAP and higher CO during the first hour of surgery. Lastly, levels of facial skin blood flow, measured with LSCI 15 min into surgery, correlated significantly with the
Facial skin blood flow 30, 45, and 60 min into the surgery was significantly higher in patients with qsMTS. This finding is in line with the only other study examining LSCI for detecting MTS. It found that patients with severe MTS, using a subjective assessment of facial flushing, had higher levels of facial skin flow 15 and 60 min into surgery, with no measurements in between (Ring et al., 2018). Therefore, it would be expected that facial skin blood flow would also be increased 30 and 45 min into surgery, as identified in our study. Due to the natural course of the MTS response is known to peak around 15 to 20 min into surgery and then slowly normalize during the next 1 to 2 h due to endogenic and exogenic countermeasures (Ambrus et al., 2017; Olsen et al., 2020; Strandby et al., 2021; Brinkmann et al., 1998).

Using our LSCI cut-off value, 35 % of patients were identified as developing qsMTS. This incidence compares well with the existing literature on MTS, as studies report incidences of severe MTS varying from 23 to 54 % (Ambrus et al., 2017; Nomura et al., 2010; Brinkmann et al., 1994; Gottlieb et al., 1989; Hudson et al., 1990), while a recent systematic review found an incidence of 35 % (Olsen et al., 2022c). Patients characterized as having developed qsMTS were found to have increased levels of PGI\(_2\) 15 min into surgery. This is in line with the existing literature on the syndrome, which all found increased levels of PGI\(_2\) in patients developing severe MTS (Olsen et al., 2022b; Ambrus et al., 2017; Olsen et al., 2020; Olsen et al., 2021; Nomura et al., 2010). However, the existing studies vary on whether only SVR is decreased or if MAP and HR also are affected in patients developing severe MTS. The missing effect on MAP and HR may be explained by an increased endogenous vasopressor response (Brinkmann et al., 1998) and increased exogenous vasopressor administration from the anesthesia in patients developing severe MTS (Ambrus et al., 2017; Olsen et al., 2020). Both compensate the SVR drop, thereby protecting against the hypotension and limiting the reactive tachycardia. This might also explain why this study found no increased HR in patients developing qsMTS.

Lastly, facial skin blood flow 15 min into surgery correlated significantly with the hemodynamics 15 min into surgery. This has never been examined before, but the results were expected judging from the existing literature, as LSCI quantifies the degree of facial flushing, which is known to correlate with the degree of hemodynamic alterations in patients developing MTS (Ambrus et al., 2017; Strandby et al., 2021; Takada et al., 2013; Takahashi et al., 2017; Takahashi et al., 2016). When reviewing the results of the study, our LSCI qsMTS cut-off value divides patients into two phenotypically different groups. The two groups differ significantly concerning facial perfusion, PGI\(_2\), and hemodynamics, some of the key characteristics of MTS. Furthermore, the differences between the two groups are in line with the differences identified between patients subjectively identified as developing severe MTS or not developing severe MTS. From these findings, it is reasonable to conclude that this study validates our predefined LSCI cut-off value for objective identification of qsMTS. This marks the first time in the literature that an objective method for diagnosing severe MTS has been validated.
This new objective method may not have any immediate clinical impact. It does, however, solve a big limitation of previously published research on MTS; the subjective assessment and differing criteria of MTS (Olsen et al., 2022c). This objective method will improve the diagnostics of MTS in future research, thereby increasing both the comparability and the quality of future studies. Also, it should improve comparability between future studies, as it standardizes the diagnosis and lowers the observer variability. Moreover, it forms an important basis for future studies examining potential interventions and their possible attenuation on the intraoperative and postoperative adverse effects of developing severe MTS. All this could potentially lead to improvements in both short-term morbidity and long-term mortality after open major abdominal oncological surgery. However, this objective method is not yet applicable in the clinical setting, as no efficient treatment of the syndrome has been identified and validated in the literature (Olsen et al., 2022a; Olsen et al., 2022c). As such this validated objective approach will primarily impact and improve the future research at this point of time.

This study had some limitations. Firstly, the study was an observational single-center study, including two different surgical procedures and anesthetic protocols, potentially increasing the risk of selection bias. However, no differences in the planned or performed surgical procedure nor in the anesthetic protocol were found between patients developing severe MTS and patients not developing it, lowering the risk of selection bias. Furthermore, patients planned for Whipples procedure received 20 mg of dexamethasone, which is a powerful anti-inflammatory drug, and therefore could impact the degree of MTS developed. However, no differences were found in the incidence of severe MTS and corticosteroid administration, and a recent review did not find that corticosteroids lowered the incidence of severe MTS (Olsen et al., 2022c). All patients received continuous treatment against the development as well as attenuating the developed hypotension, which impacts SVR, MAP, and HR. Still, a significant difference was found in most hemodynamic variables, even though it is known from the literature that patients developing severe MTS receive more vasopressor therapy (Olsen et al., 2022c; Olsen et al., 2020). This study did not exclude patients undergoing an explorative laparotomy. Yet, these patients received the same initial surgical procedure as patients who received the planned surgical procedure. Also, the incidence of qsMTS was comparable between patients undergoing an explorative laparotomy and patients receiving the planned surgical procedure. Furthermore, differences in patient skin tones could have impacted the results, as, at least to our knowledge, the impact of skin tone on LSCI measured skin blood flow has been published. Yet, one study has examined the impact of skin tone in flow phantoms, as well as in vivo using speckleplethysmography (Rice et al., 2020), a method closely related to LSCI. This study did not identify any significant effect of increasing skin tone on skin blood flow. As such, we believe our findings to be valid in patients with different skin tones. Lastly, no fiducial markers were used for the ROI analysis in different time points, as such we cannot be secure that the same area was used as ROI at all times. However, the LSCI has a laser pointer to ensure optimal, and consistent distance to the area of interest at all times. This was combined with a clear definition of the targeted ROI, which had to be the area, around 2–4 cm² just above the glabella at a level just above the eyebrows. As such, we believe the impact of this to be negligible. Yet it would be reasonable to use a fiducial marker for future studies.

Lastly, this study has some strengths as it, to our knowledge, is the first study to examine and validate an objective method for the identification of qsMTS. Furthermore, it comprises an almost complete dataset of 60 patients undergoing major open abdominal surgery.

5. Conclusion

In this study, we validated a cut-off value for facial skin flow just
above the glabella measured using LSCI of 425 flux for the objective identification of severe MTS. This cut-off value was validated by the finding that patients developing qsMTS showed increased levels of PGII and increased alterations in SVR, MAP, and CO compared with patients not developing it. This new objective method will lead to improved diagnostics of severe MTS. This will improve the quality of future research on the syndrome, enabling larger multi-center studies by standardizing the diagnosis and lowering the interobserver variability. The post-operative impact of qsMTS must be examined in future studies.

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Ethical approval
All procedures performed in the study were in accordance with the ethical standards of the institutional and national research committees and approved by the national ethical committee.

Informed consent
Verbal and written informed consent was obtained from all individual participants included in the study.

CRediT authorship contribution statement
• Study conception and design: AAO, MBS, LBS, MPA
• Acquisition of data: AAO, SB, DRB, MS, EKA, JPG, MBS, LBS, MPA
• Analysis and interpretation of data: AAO, JPG, MBS, LBS, MPA
• Drafting of the manuscript: AAO
• Critical revision and final approval of the manuscript: AAO, SB, DRB, MS, EKA, JPG, LBS, MPA.

Conflict of interest
All authors declare that they have no conflict of interest.

Data availability
The authors do not have permission to share data.

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