

# A Retrospective Cohort Study on the Impact of Oxytocin and Carbetocin on Trend of Blood Transfusion Needs Following Caesarean Delivery

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## Abstract

**Objective:** To analyze the 10-year impact of carbetocin and oxytocin on trend of blood transfusion needs during Caesarean, in University of Port Harcourt Teaching Hospital (UPTH). **Design:** Retrospective 10-year analysis. **Subjects:** 5,684 women who had Caesarean. **Methods:** Ethical clearance secured, a ten-year analysis of all Caesarean-related blood loss and transfusions was conducted from 1st January, 2015 to 31st December, 2024. Data were obtained from Obstetric theatre, Recovery room, Postnatal ward, Intensive care unit, and Obstetric Anaesthesia Unit records in UPTH. **Results:** Out of 5684 Caesarean 3427 had oxytocin and 2257 received carbetocin for third stage management. Mean blood loss [range: 699.2 (207.7) - 706.9 (218.1) versus 437.2 (112.8) - 576.7 (167.1)], proportion (%) of parturients who had blood loss >1000ml (range: 4.5 – 6.9 versus 0.0 – 3.6), needed transfusion (range: 4.1 – 7.7 versus 1.1 – 2.9), and required additional uterotonic (42.95 versus 9.39) were greater with oxytocin compared to carbetocin. With carbetocin fewer parturients experienced bradycardia (2) and hypotension (33) compared to 9 and 550 respectively, following oxytocin administration. **Conclusion:** There was greater reduction in Caesarean-related blood loss, transfusion, additional uterotonic use, bradycardia and hypotension, with carbetocin administration compared to oxytocin.

**Keywords:** *Caesarean, Carbetocin, Oxytocin, Transfusion Needs.*

## Introduction

Severe obstetric haemorrhage is the ranking cause of maternal mortality in sub-Saharan Africa, according the World Health Organisation (WHO), and a major contributor to postpartum hysterectomy <sup>[1,2]</sup>. Approximately 140,000 women worldwide die of severe postpartum bleeding every year and uterine atony has been identified as the most frequent cause, being responsible for about 80% of cases <sup>[3,4]</sup>. Blood loss during Caesarean is to be expected, however, this is considered excessive and dangerous to the parturient hence occasioning the need for transfusion, if the volume lost is >1000ml <sup>[5]</sup>.

Uterotonics are important drugs administered with the delivery of the foetus to enhance myometrial contraction and reduce the likelihood of excessive postpartum bleeding. Slow intravenous injection of 5 International Units (IU) of oxytocin is currently recommended in the United Kingdom for all Caesarean sections, but the use of additional oxytocic medication to arrest bleeding is common, or prophylactically if there are risk factors for postpartum haemorrhage <sup>[6]</sup>.

Oxytocin is currently the uterotonic of first choice. It has been proven to decrease the incidence of postpartum haemorrhage (PPH) by 40% and consequently transfusion need, as well as documented to have a rapid onset of action with a good safety profile. A disadvantage of oxytocin is its short half-life of 4-10 minutes, regularly requiring a continuous intravenous infusion or repeated intramuscular injections <sup>[7,8]</sup>. Carbetocin, a long-acting oxytocin analogue, is indicated for the prevention of uterine atony during Caesarean delivery, under regional or general anaesthesia. It is a long-acting synthetic oxytocin analogue, structurally 1-deamino-1- monocarbo-(2-o-Methyltyrosine)-oxytocin, which was first described in 1987. It has a half-life of 40 minutes (about 4-10 times longer than oxytocin) and uterine contractions occur in less than two minutes after intravenous administration of an optimal dose of 100ug <sup>[9]</sup>. In UPTH, carbetocin succeeded oxytocin as the uterotonic of choice for Caesarean delivery from 2020 till date, as a hospital policy. The aim of this study, therefore, was to retrospectively analyze the trend in postpartum blood loss and transfusion needs of parturients who received single dose intravenous 100µg of carbetocin, or single dose intravenous 5 IU of

oxytocin, as uterotonic during Caesarean section over 10 years, in UPTH, Port Harcourt, Nigeria.

### Materials and Method

Institutional ethical clearance was secured for a retrospective cohort study of patients who underwent Caesarean deliveries in the University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria. A ten-year review of all Caesarean deliveries was carried out from 1st January, 2015 to 31st December, 2024. Data of all blood loss and transfusions in parturients during or following Caesarean was obtained from the Obstetric theatre, Recovery room, Postnatal ward and Intensive care unit Registers, as well as from the records of the Obstetric Anaesthesia Unit of the University of Port Harcourt Teaching Hospital. Also, any additional use of uterotonic and the type were noted. Cases of ruptured uterus, Caesarean hysterectomy, coagulopathy and known history of bleeding diathesis were excluded from the survey. All data were handled confidentially, and presented in tables and figures.

### Results

A total of 5684 Caesarean deliveries were recorded within the 10-year period of survey, with 3594 (63.2%) done as emergencies and 2090 (36.8%) as electives. The mean values in age (years), weight

(kg), height (m) and BMI (kg/m<sup>2</sup>) of the parturients were 32.3 (8.7), 82.2 (7.8), 160.4 (6.5) and 31.9 (3.7), which had the respective ranges of 16 – 47 years, 69 – 98 kg, 1.48 – 1.75m and 24.1 – 42.0 kg/m<sup>2</sup> (Table 1).

There was remarkable decline in the observed mean amount of blood loss (in ml) during Caesarean from 2015 to 2024. While the recorded mean blood loss with the use of oxytocin had a range of 699.2 (207.7) - 706.9 (218.1), the range was 437.2 (112.8) - 576.7 (167.1) amongst parturients who received carbetocin (Figure 1.1). As observed also, the proportions (%) of parturients who had blood loss > 1,000ml and needed transfusion during Caesarean were greater following intravenous oxytocin administration, from 2015 to 2019, compared to those given carbetocin from 2020 to 2024. Remarkably, while blood loss in excess of 1000ml was recorded yearly within the 5-year period when oxytocin was used, for two consecutive years (2022 and 2023) the corresponding proportions were 0.0 when carbetocin was the uterotonic of choice (Figure 1.2).

Far less number of patients (only 212) required additional use of uterotonics with the administration of carbetocin for third stage management (Table 2); in contrast, 1472 patients required additional uterotonic use following oxytocin administration.

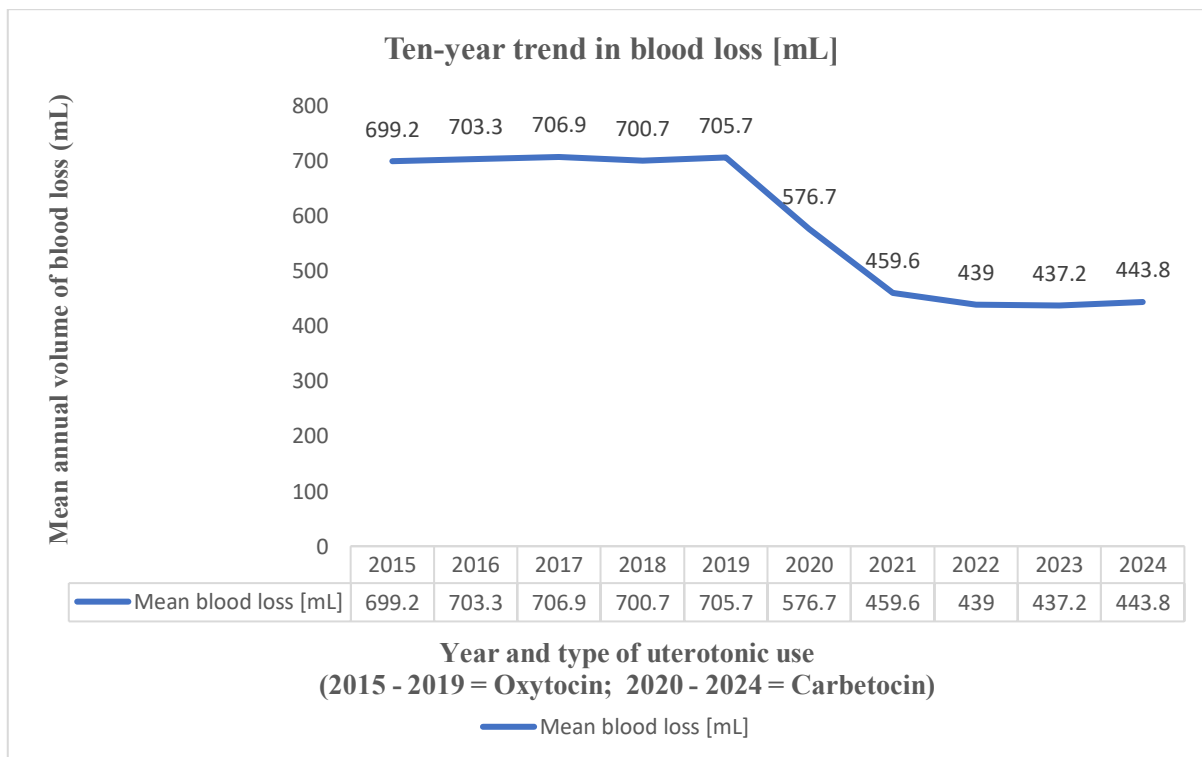
Fewer women had bradycardia (2) and hypotension (33) with the use of carbetocin, compared to the corresponding values of 9 and 550, recorded amongst those who received oxytocin (Table 3).

**Table 1: Distribution of demographic features of parturients across the groups in the ten-year period.**

Parameter	Range	Mean (SD)	N (%)
Age (years)	16 – 47	32.3 (8.7)	
Weight (kg)	69 – 98	82.2 (7.8)	
Height (m)	1.48 -1.75	160.4 (6.5)	
BMI (kg/m <sup>2</sup> )	24.1 – 42.0	31.9 (3.7)	
<b>Caesarean Deliveries</b>			
Elective			2090 (36.8)
Emergency			3594 (63.2)
<b>Total</b>			<b>5684 (100.0)</b>

Data are expressed as number (N), percentage (%), mean (SD)

BMI = Body mass Index



**Figure 1.1**

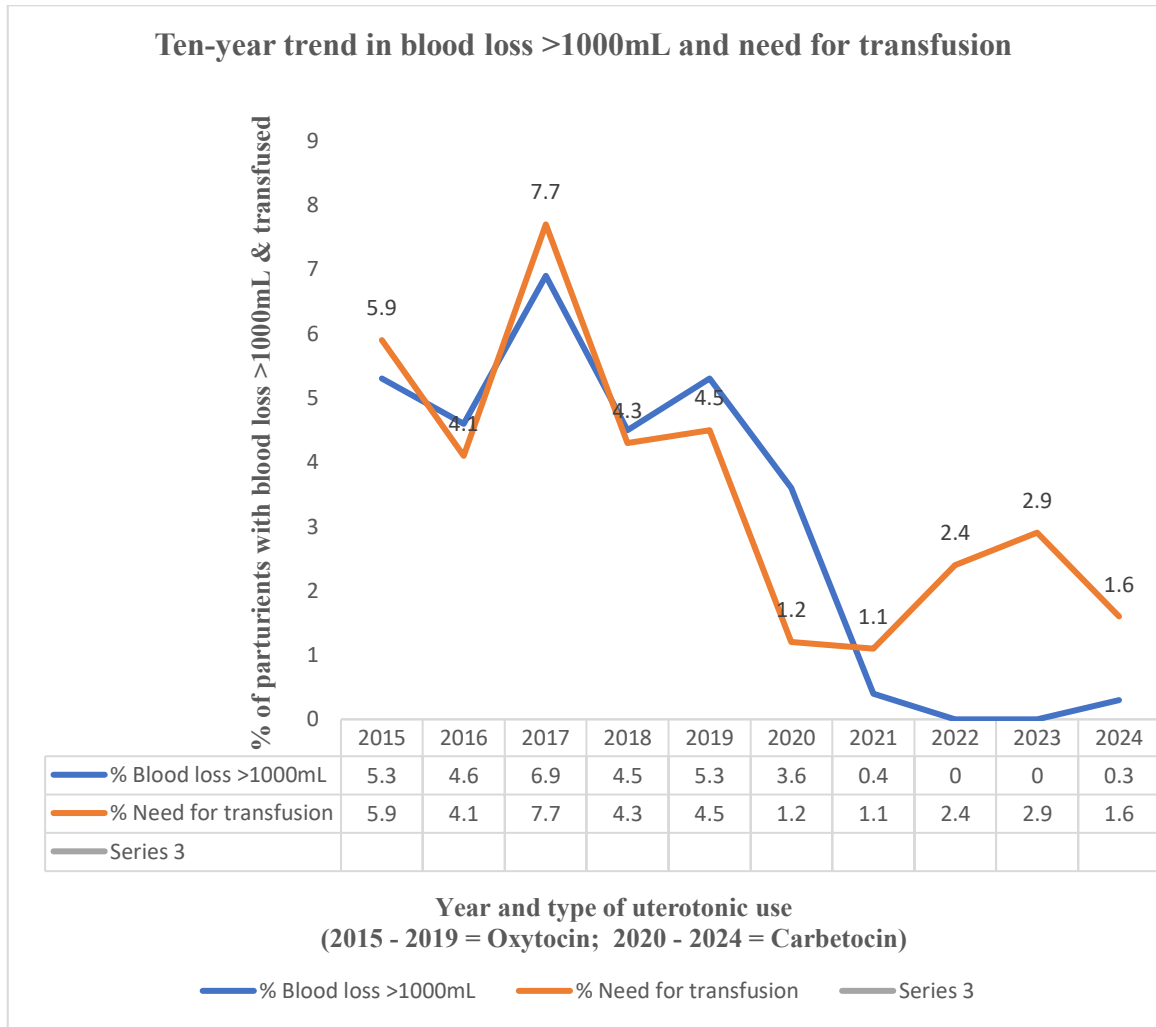


Figure 1.2

Table 2: Need for additional uterotonic administration at Caesarean over ten years

Year	Caesarean Delivery (N)	Additional Uterotonic Need (N)	%	Type of Uterotonic Used
2015	676	337	49.85	Oxytocin
2016	709	309	43.58	Oxytocin
2017	698	275	39.40	Oxytocin
2018	717	310	43.24	Oxytocin
2019	627	241	38.44	Oxytocin
2020	496	145	29.23	Carbetocin
2021	474	43	9.07	Carbetocin
2022	424	9	2.12	Carbetocin
2023	477	9	1.89	Carbetocin
2024	386	6	1.55	Carbetocin

Data are expressed as number (N) and percentage (%)

Table 3: Intraoperative complications over the ten-year period

Year	Caesarean Delivery	Hypotension N (%)	Bradycardia N (%)	Type of Uterotonic Used
2015	676	108 (15.98)	9 (1.33)	Oxytocin
2016	709	109 (15.37)	0 (0.0)	Oxytocin
2017	698	115 (16.48)	0 (0.0)	Oxytocin
2018	717	109(15.20)	0 (0.0)	Oxytocin
2019	627	109 (17.38)	0 (0.0)	Oxytocin
2020	496	14 (2.82)	2 (0.40)	Carbetocin
2021	474	6 (1.26)	0 (0.0)	Carbetocin
2022	424	5 (1.18)	0 (0.0)	Carbetocin
2023	477	3 (0.63)	0 (0.0)	Carbetocin
2024	386	5 (1.30)	0 (0.0)	Carbetocin

Data are expressed as number (N) and percentage (%)

## Discussion

The retrospective cohort survey revealed an actual amount of blood loss, proportion of parturients who had blood loss >1000ml and needed blood transfusion, as well as the requirement for additional use of uterotonics that were much less with the use of carbetocin in comparison to oxytocin during Caesarean; also, a greater proportion of parturients had bradycardia and hypotension resulting from the use of oxytocin than from carbetocin.

Over the 10-year period in this survey, the finding of much less amount of blood loss amongst the carbetocin-treated, relative to the oxytocin-treated parturients, depicts a superiority in the efficacy of carbetocin to oxytocin. Inferentially, the degree of sustained adequacy of uterine contraction achieved was greater with carbetocin, than with oxytocin administration. In their study comparing the efficacy and safety of carbetocin with those of oxytocin infusion in women with twin pregnancy undergoing elective Caesarean, Seow *et al.*<sup>[10]</sup> found carbetocin more effective than oxytocin in reducing actual blood loss, attributing this efficacy to induced stronger uterine contractions. Another study<sup>[11]</sup> equated the efficacy of a single intravenous 100µg of carbetocin to a 16-hour continuous oxytocin infusion. Although haemoglobin estimations before and after Caesarean were not included in this survey, in their systematic review and meta-analysis of randomized trials comparing carbetocin with oxytocin in preventing PPH after Caesarean, Maged *et al.*<sup>[12]</sup> had shown an association of lower fall in haemoglobin concentration with a corresponding lower need for blood transfusion amongst the women given carbetocin, compared to oxytocin.

The observed annual proportions of parturients who had blood loss >1000ml and required transfusion, in this analysis, being greater with oxytocin administration, relative to carbetocin, further depicts the superior uterotonic efficacy of carbetocin to oxytocin, corroborating the earlier observation by Seow *et al.*<sup>[10]</sup>. Correspondingly, the need for transfusion was comparatively much less with carbetocin than oxytocin as choice of uterotonic. Again, in their meta-analysis of seven randomized controlled trials of Caesarean deliveries comparing carbetocin with oxytocin in 2012 women, Voon *et al.*<sup>[13]</sup> had documented the finding of a significant reduction in transfusion when carbetocin rather than oxytocin was used (RR 0.31; 95% CI 0.15 to 0.64; p=0.002).

Clinically, the need for transfusion bears a direct correlation with amount of blood loss, and the latter varies directly with the duration of haemorrhage. Following intravenous carbetocin, that uterine contraction occurs within 1 - 2 minutes, with sustained tetanicity for 6 minutes, succeeded by 60 minutes of rhythmic contractions of higher amplitude and frequency than those induced by oxytocin had been observed, together with a half-life of 40 minutes which is about 4 - 10 times that of oxytocin<sup>[9,14]</sup>. By possessing such combination of pharmacological properties, carbetocin had been described as a hybrid drug exhibiting the safety and tolerability profile of oxytocin and the sustained uterotonic activity of parenteral ergot alkaloids<sup>[15]</sup>. The peculiar therapeutic effects of carbetocin are the result of synthetically achieved structural modification, involving deamination and substitution of a Sulphur atom, eventually conferring heat-stability and a resistance to rapid plasma enzymatic cleavage, in contrast with the parent drug - oxytocin<sup>[16]</sup>.

In this retrospective survey, there was an observation of much less additional uterotonic use during Caesarean following

carbetocin administration, compared to oxytocin. This observation agrees with the finding by Onwochei *et al.*<sup>[17]</sup>, that carbetocin decreased the need for additional uterotonic administration for the control of PPH by 53%, relative to oxytocin (OR 0.47; 95% CI 0.34 to 0.64; p<0.001; I<sup>2</sup>=63.5), as well as supports Maged *et al.*<sup>[12]</sup>. The combined documentations from meta-analyses by Maged *et al.*<sup>[12]</sup> and Onwochei *et al.*<sup>[17]</sup>, lend empirical evidence to the greater efficacy of carbetocin than oxytocin in decreasing blood loss, transfusion need and additional uterotonic use during Caesarean delivery, as similarly observed in this survey.

An association of a significantly greater reduction in blood pressure with oxytocin compared to carbetocin had been reported<sup>[8]</sup>. In this survey, similarly, there was more hypotension in association with oxytocin use, compared to carbetocin; bradycardia, though minimal in the two groups, was also more with oxytocin. The mechanisms leading to the occurrence of hypotension and bradycardia, in association with oxytocin and carbetocin administrations, have been linked to the presence of oxytocin receptors in the right atrium, whose interaction with the agonists activate negative inotropicity and chronotropicity via atrial natriuretic peptide (ANP) mediated release of cyclic guanosine monophosphate; however, these actions can be antagonized with atropine<sup>[18]</sup>. Although yet to be fully elucidated, it is likely that carbetocin, compared to oxytocin, exhibits less pharmacological agonism at its atrial oxytocin receptor site, hence, the observed associated milder haemodynamic changes.

From an economic stand-point, carbetocin is about 100 times more costly to procure than oxytocin; however, this apparent drawback to its use during Caesarean in low- and middle-income countries, becomes really insignificant when reappraised against the background of facts of critical importance: (a) the prevalence of high maternal mortality in some regions of the globe, especially sub-Saharan Africa, where excessive bleeding from uterine atony is the leading cause, (b) the high cost and attendant risks of multiple transfusions that become necessitated with the occurrence of severe PPH, (c) the need to achieve reduction in maternal mortality rate globally to <70 per 100,000 live births, and less than twice the global target in any country, by 2030, and (d) the pricelessness of a parturient's life in the event of mortality from severe PPH. In this regard, the preferential choice of a safe and more potent uterotonic, such as carbetocin, as first line drug during Caesarean is judicious and warranted. Occurring at Caesarean, excessive bleeding is a grave complication, with a global record as the ranking complication out of the 5 top causes of maternal mortality; this obstetric emergency not only poses a nightmare to the attending perioperative team, but also occasions major psychological distress for the parturient who is awake under regional anaesthesia, and for the circle of relatives who bear the pressure of the triad of emotional burden, unanticipated funding need and demand for providing more units of blood/blood products for life-saving transfusion. Of the multifactorial entities reported to have an established aetiological association with the occurrence of severe haemorrhage at Caesarean, uterine atony is the most common, accountable for 70% of cases of PPH<sup>[19,20]</sup>.

By definition, uterine atony is the absence of adequate myometrial contraction in response to endogenous oxytocin released during labour<sup>[19]</sup>. Excessive bleeding ensues because placental expulsion leaves disrupted uterine spiral arteries which, due to their characterizing anatomy of absence of any musculature, fail to

contract, hence, making postpartum haemostasis dependent on mechanical compression by myometrial contraction [19]. Thus, the adequacy of myometrial contraction is the critical denominator in limiting blood loss and transfusion need; however, this is negatively impacted by uterine muscle severance during Caesarean. That Caesarean section is a risk factor for PPH, responsible for about 30% of cases, had been documented by Jansen *et al.* [21]; thus, an active interventional management aimed at preventing excessive haemorrhage is warranted. Recognizing this necessity, the WHO had since 2007 endorsed its support for the recommendation on active management of the third stage of Labour (AMTSL) as a critical intervention for PPH prevention [22]; again, in 2012 the WHO, following the empirical findings of its multi-centred clinical trial [23], identified and endorsed the timely administration of an effective uterotonic as the most important integral component of AMTSL, for all births, upholding same 2012 recommendation with a renewed endorsement in 2018 [24,25].

Importantly, certain physiological and anatomical changes in pregnancy predispose the parturient to significant blood loss and consequent transfusion, in the event of uterine atony at Caesarean; the changes are cascaded by initiation of maternal-embryo cross-talk between immune cell receptors, extravillous trophoblasts and uterine spiral arteriolar endothelial cells, following implantation of the zygote: a) 10-fold increase in uterine blood flow to  $\geq 600\text{ml/minute}$  at term., b) hyper-coagulability state, c) uterine expansion, with resultant significant stretching and thinning of myometrial fibres, and d) angiogenesis with expansive remodelling of uterine spiral arteries, involving loss of musculature, autonomic innervation and consequent vasodilation [26-28]. While intended for favourable foetal development and parturition, these modifications, however, predispose to life-threatening haemorrhage, in the event that haemostatic mechanisms become dysregulated [29]. Clinically, blood loss at Caesarean is inevitable; therefore, timely active intervention with high efficacy uterotonic, to ensure sustained adequate myometrial contraction, is key in achieving the goal of minimizing haemorrhage.

This retrospective study could have been tainted with some limitations. Firstly, the quantity of transfusion might not have been properly recorded. Secondly, due to the mixture of liquor amnii with blood during Caesarean, accurate estimation of volume of pure blood loss might have been rendered relatively difficult by swab count. Thirdly, being a retrospective study, haemoglobin values before and after Caesarean, that would have served as useful indices for accurate estimation of blood loss, were difficult to capture.

In conclusion, carbetocin demonstrated greater efficacy than oxytocin in reducing blood loss, occurrence of PPH, transfusion need, and additional uterotonic use during Caesarean, with very minimal hypotension and bradycardia.

## Declarations

## Ethical approval

Granted by the University of Port Harcourt Teaching Hospital Research Ethics Committee (Ethical Clearance Reference: UPTH/ADM/90/S.11/VOL.XI/2023)

## Acknowledgements

The authors are grateful for the assistance given by Matron Amonia Wokoma, Matron Gideon Krama and Mr. Robert Milverton.

## Funding

No funding from any individual or organization.

## Conflict of interest

None

## Authors' Roles

ATA: Final intellectual content development, manuscript preparation, final version approval and corresponding author.

FH: Data acquisition, initial intellectual content development and integrity appraisal.

SFO: Initial study conception, study design and critical reviewing author

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