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Factors involved in endoscopists' choice for prophylactic clipping after colorectal endoscopic mucosal resection: a discrete choice experiment

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ABSTRACT

Background: Delayed bleeding (DB) occurs in ~10% after colorectal EMR. Prophylactic clipping (PC) was reported to significantly decrease DB-rate in proximal lesions ≥2 cm.

Objective: Our aim was to determine which predefined variables contribute to using PC in clinical practice.

Methods: We performed an international discrete choice experiment (DCE) among ~500 endoscopists. Relevant variables for PC use were selected by EMR experts: previous DB, anticoagulants, polyp size, morphology, location, intraprocedural bleeding and visible vessel(s). Respondents answered case scenarios with various variable combinations, each time choosing only one scenario for PC, or the 'none' option. Part-worth utilities and importance weights were calculated using HB regression. Subsequently, a predictive model was created to calculate the likelihood of endoscopists choosing PC in any given case.

Results: The survey was completed by 190 EMR endoscopists from 17 countries. In total, 8% would never use PC, whereas 30.9% never chose the 'none' option. All variables except polyp type were significant in decision-making for PC ($p < .01$). The most important factor was anticoagulant use, accounting for 22.5% in decision-making. Polyps <2 cm were considered eligible for PC by 14% in the presence of high-weighing factors such as anticoagulant use. No significant differences were found between high and low-to-moderately experienced endoscopists.

Conclusions: PC after EMR is often considered useful by endoscopists, usually based on risk factors for DB. Anticoagulant use was the most important factor in decision-making for PC, independent of endoscopist experience. Although not considered cost-effective, one in seven endoscopists chose PC for adenomas <2 cm.

Introduction

Endoscopic mucosal resection (EMR) allows resection of large (≥20 mm) colorectal polyps while protecting the underlying submucosa. The most frequent complication after colorectal EMR is delayed bleeding (DB), occurring in approximately 7% after EMR of large polyps, with 2–3% occurring in the distal and 10–12.3% in the proximal colon [1]. Risk factors include

polyp size, location in the proximal colon, intraprocedural bleeding (IPB) and restart of antithrombotic medication within seven days [1–3]. Prophylactically closing the resection defect with endoclips is hypothesized to prevent DB. Two recent randomized studies demonstrated that prophylactic clipping (PC) reduces DB after colorectal EMR of large proximal nonpedunculated polyps, and polyps with a substantial

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DB risk (GSEED-RE score ≥6) [4,5]. However, PC for polyps ≥2 cm was not cost-effective in an economic modelling study [6]. Furthermore, PC has not been effective in reducing the rate of DB after polypectomy of small polyps or polyps ≥1 cm [7,8].

Until the value of PC in preventing DB is more clarified, the clinical implementation of PC remains subject to variation. Guidelines advice against PC for small lesions, but leave room for PC for proximal lesions ≥2 cm [9–11]. Insight in the decision-making for PC in every-day practice could lead to targeted strategies to improve future guideline implementation. The aim of this study is to identify factors that influence the decision-making process by endoscopists to use PC after EMR.

Methods

Study design

We conducted an international discrete choice experiment (DCE) among endoscopists who regularly perform EMR procedures [12]. DCE is a questionnaire method that is commonly used in decision-making/preference studies [13]. Respondents are presented with cases assembled from pre-defined variables (attributes) with different options (levels) in order to estimate quantifiable preferences. Every respondent is asked to complete a number of tasks in which three cases (concepts) are presented. The objective of each task is to select the case in which they would apply PC, if they could select only one case. By forcing the respondents to make this choice, the group preference for attributes and changes in attribute levels can be measured, also when they are equally (un)important. This allowed us to gain insight in the individual weight of the various factors in decision-making for PC. Additionally, if respondents preferred not to use PC in any case, a 'none' option was available. Therefore, this DCE design closely imitated and represented real-world practice.

Attributes and levels

The following attributes and levels were used: previous episode of DB after polypectomy, continued anticoagulant use (No; anticoagulants including coumarin derivatives, NOACs or heparin; platelet aggregation inhibitors including aspirin, clopidogrel, dipyridamole or a combination of these drugs), polyp size (<2 cm; ≥2 cm), polyp location (proximal; distal), polyp morphology (flat; sessile; mixed type), IPB (yes, treated with coagulation; yes, treated with clip; no) and visible vessels in a dry EMR defect (yes; no). In accordance with DCE design guidelines, these variables were selected from a broad range of known risk factors for DB by an EMR expert panel (EG, PD, LM, PS) [1,2,12]. As the external validity of a DCE depends for a large part on the studied attributes, this was done with special emphasis on relevance for clinical practice. The selected variables were evaluated on relevance and clarity by two independent endoscopists who were representative of the target population (see Supplementary Table 1 for attribute definitions).

Survey design

The survey was built in Sawtooth Software's Lighthouse Studio. We allowed only binary or triple outcome levels for each attribute. This design is relatively balanced and orthogonal, which increases the efficiency of the DCE. Figure 1 shows a screenshot from a random task in the DCE.

In addition to these DCE tasks, recipients were asked to fill out the following individual variables: gender, country, years of experience, estimated total number of EMR's performed and employment in an academic, peripheral and/or teaching hospital.

A final survey-check was performed by two investigators (EvG, PD), focusing on inconsistencies and comprehensibility.

Study population

The survey was hosted online and a link was sent to 483 gastroenterologists from the Dutch Association for Gastroenterology in November–December 2018. The number of endoscopists performing EMRs among the invitees was unknown, but the invitation clearly explained the target group for the survey. Subsequently, 68 international EMR-specialists were identified by their participation in EMR guideline committees or publications on EMR/PC and were invited to participate. People were invited to forward the survey to other EMR colleagues.

As no medical data were involved in this DCE, medical ethical approval was not required according to Dutch

Figure 1. Screenshot of a survey question from our DCE.

legislation. Nonetheless, all survey responds were anonymous and untraceable to individual participants. Informed consent was given implicitly by filling out the complete questionnaire.

Sample size

The equation for the minimum sample size for conjoint analysis (n) according to Johnson

$$N > 500c/(t \cdot a)$$

was used. Our recipients were invited to complete $t = 10$ tasks with an average $a = 3$ alternatives (not including the none-concept) and ≤ 3 levels ($c = 3 \times 3 = 9$). Based on these parameters, a sample size of 150 can be considered sufficient. Each case in the survey included all seven attributes (a full profile design). As a low response rate was anticipated, the questionnaire was designed to be completed within limited time.

Analysis plan

The primary outcome was endoscopists' preference for factors in decision-making for PC. The analyses were performed in Lighthouse Studio (Sawtooth Software, North Orem, UT). Hierarchical Bayes regression was used to calculate individual part-worth utility scores per variable (REF-HB). Negative utilities do not trigger gastroenterologists to make a decision, compared to positive utilities that do influence decision-making. Next, importance scores per attribute were derived by subtracting the part-worth utilities for the most and least important level of each attribute. To calculate the likelihood that endoscopists would use PC in any given situation, we used the following model (REF):

$$P = 1/(1 - e^{-(V + \varepsilon)})$$

where P is the chance that PC would be used by the endoscopists in any given case, and V is the total utility of that case derived from the added part-worth utilities of the variables calculated by a logit analysis. The 95% confidence intervals (CIs) of P were calculated for each case in the model using 95% CI $= V \pm 1.96\varepsilon$.

Secondarily, comparative analysis between subgroups was performed in SPSS v. 25 (IBM Corp., Armonk, NY). Skewness of the data was analyzed for each attribute. Student's t-test for unpaired data was used for the comparative analyses between highly and low-to-moderately experienced EMR endoscopists. High experience was defined as ≥ 120 EMRs performed in a lifetime [14].

Results

Between November 2018 and March 2019, 294 respondents replied to the DCE. A total of 199 EMR endoscopists fully completed all tasks, yielding a response rate of 36%. Nine respondents were removed from the dataset based on information in the remarks section reflecting misinterpretation of survey instructions.

The majority of these 190 respondents was male and 61% worked in The Netherlands (see Figure 2). Baseline characteristics are shown in Table 1 and were compared between Dutch endoscopists ($N = 116$) and other nationalities ($n = 74$) (see Supplementary Table 2). A total of 20.7% of Dutch responders worked in academic hospitals or tertiary referral centers, compared to 83.8% in the other countries.

Primary outcome

Significant importance scores were found for all attributes except polyp morphology, meaning that these attributes were meaningful to endoscopists in choosing to clip or not. Overall, the 'none' option (no PC) was chosen in 27.8% of all questions. Thirteen respondents (6.8%) chose the 'none' option in all questions, whereas 59 respondents (31%) never chose this option. Utility scores were moderated for each level of the seven attributes (see Supplementary Table 3). Importance scores were computed for each attribute (see Table 2). Antithrombotic medication, especially anticoagulants such as coumarin derivatives and DOACs, was the most important factor in this study, accounting for 22.5% of decision-making. This means that within our set of attributes and levels, anticoagulants were approximately twice as important as previous DB.

Prediction model

The simulation model that we created next uses these variables to calculate the likelihood that endoscopists would use PC in any given case (see Figure 3). The reference case, in which all variables are unknown, had a 36.2% (95% CI 33.6–38.9) likelihood to be clipped prophylactically. When all variables were set to their minimal-chance levels (no previous DB, no antithrombotics, small polyp size, etc.), this decreased to 2.3% (95% CI 1.8–3.0). On the opposite, after EMR in a patient with only high-chance levels 92.5% (95% CI 90.8–93.9) of the endoscopists would choose PC.

Secondary outcome

There were no significant differences in the importance scores for each attribute between endoscopist with different experience levels (see Table 3).

Feedback from respondents

Thirty-six responders used the remarks-section of the survey. Some responders found it hard to choose one case per task. 'When there were two cases that I would be equally likely to clip, it was just a flip of the coin' one respondent wrote.

Twenty responders suggested extra attributes that they consider when choosing PC. These are summarized in Table 4.

Discussion

The key finding from this DCE is that anticoagulant medication is the most important stimulant for endoscopists to
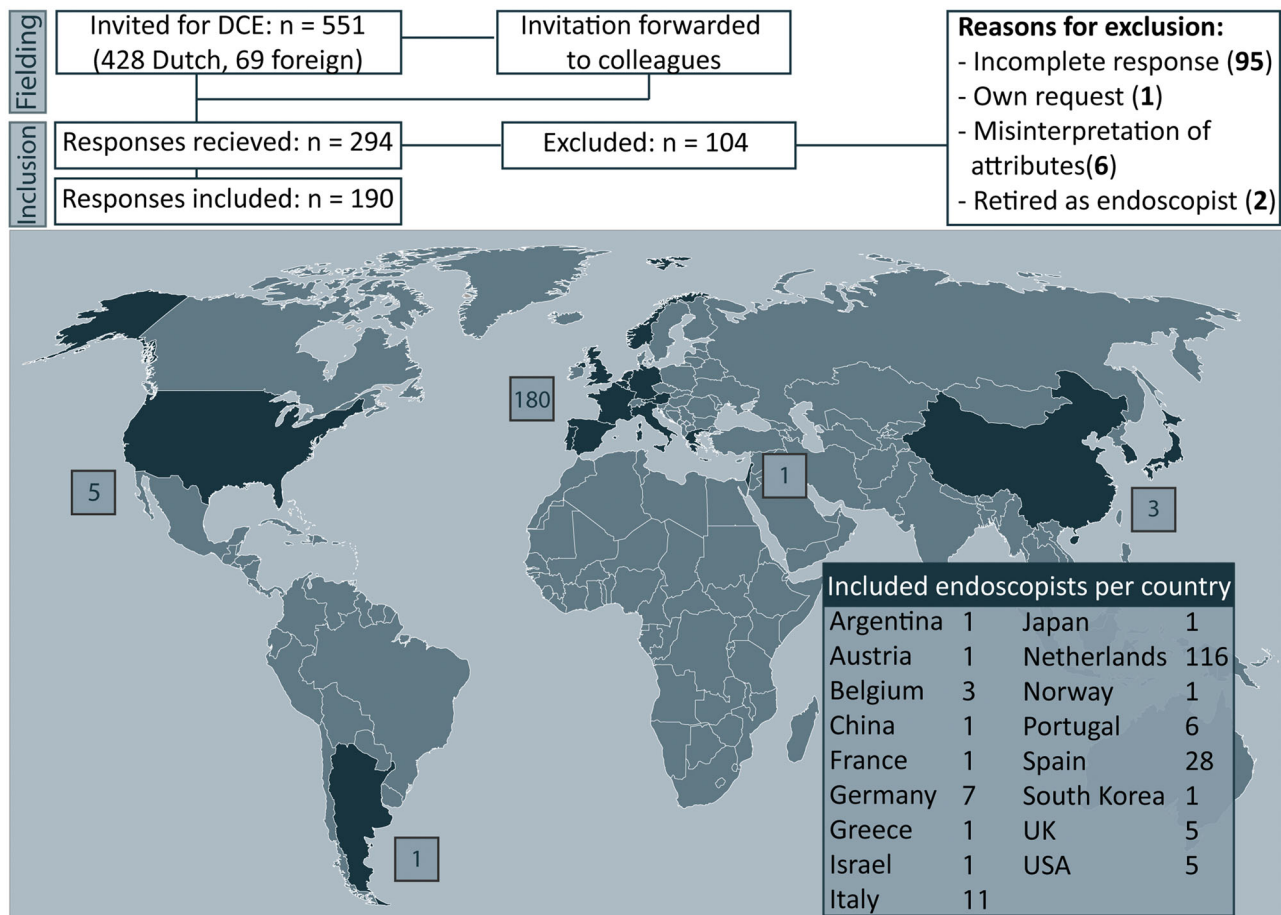
Figure 2. One hundred and ninety respondents from 17 countries.

Table 1. Baseline characteristics of 190 included responders.

Characteristics	N (%)
Male	148 (77.9)
Female	42 (22.1)
Dutch nationality	116 (61.1)
Other nationality	74 (38.9)
Academic hospital/tertiary center	86 (45.3)
Teaching/peripheral hospital	104 (54.7)
Number of years as gastroenterologist	Mean 11.5; SD 8.0; range 1–40
Lifetime amount of EMRs performed	Median 300; IQR 150–800

SD: standard deviation; IQR: interquartile range.

perform PC. Contrary to guidelines, also small polyps <2 cm are considered for PC, especially in case of high-weighing risk factors for bleeding (e.g., anticoagulant medication). These findings were independent of the endoscopist's EMR experience.

Evidence for PC

Although a majority of the EMR endoscopists in this study would use PC in the presence of risk factors for bleeding, PC after colorectal polypectomy or EMR is still controversial. A recent meta-analysis including seven RCTs with heterogeneous populations, could not demonstrate a protective effect of PC [7]. Since then, three RCTs have been published. The first study found that PC did not affect DB-rate after removal of polyps ≥1 cm [8]. In contrast to these findings, an RCT with 615 patients showed PC to be effective in proximal

adenomas ≥2 cm with an NNT of 16 [4]. Although a greater bleeding risk was seen with antithrombotic medication, the prophylactic effect of clipping was independent of this. A third RCT with 235 patients showed an effect of PC with an NNT of 14 in patients with an estimated high risk of DB (GSEED-RE score ≥6). However, this was only in case of complete closure, which was achieved in only 57% of patients in the intervention group [5]. As our DCE was conducted before the publication of these RCTs, it shows that EMR specialists were already triggered to clip post-EMR defects with a higher risk of DB, although evidence was still lacking.

Risk factors vs. factors in decision-making

Continued antithrombotic drug use, especially anticoagulants, is known to increase the risk of DB after EMR of both small and large adenomas [15–17]. Therefore, guidelines advise cessation of anticoagulants or switching to bridging therapy prior to polypectomy, with reintroduction of anticoagulant medication within 24–48 h after EMR [17–20]. However, it is still unclear to what extent these strategies are effective in lowering DB risk [21–23]. This may explain why anticoagulant medication was the strongest factor in deciding to perform PC in this study. On the other hand, we also observed a tendency for endoscopists to use PC in patients with continued platelet aggregation inhibitors. This finding was unexpected, because continued aspirin and clopidogrel

have not clearly been associated with a higher DB risk [16,24].

Few studies have investigated the correlation between IPB and clinically significant DB, but three studies reported an association [2,25]. This may be largely based on common risk factors. The notion that IPB is a risk factor is supported by this study, as IPB treated by coagulation increased the likelihood of PC. On the other hand, endoscopists were less likely to apply PC when IPB was already treated with

hemostatic clips, as they probably considered these clip(s) to have sufficiently treated the most likely source for a DB.

The importance of polyp size and proximal location is consistent with the literature [1,3,26,27]. Both are known risk factors for DB, and PC-studies often focus on high-risk patients with large proximal adenomas.

The presence of submucosal visible vessels also stimulated PC. Recently, Kim et al. concluded that cut vessels and severe coagulation injury are predictive for DB [27]. Intact visible vessels are less clearly associated with DB-rate [28,29], but ≥ 3 visible vessels in the post-EMR defect have been suggested to also increase the risk of DB [30]. Although prophylactic coagulation of visible vessels does not decrease clinically significant DB after EMR, the effect of clipping is unknown [28,31].

Lastly, previous DB was a significant factor in the decision-making for PC in our respondents. However, there is no evidence to support an association between previous DB and risk of new DB. The importance of previous DB may be confounded by variables that generally stay the same over time (e.g., co-morbidities). Nonetheless, it could also simply reflect they 'learned from the past'.

Based on the abovementioned risk factors, we created a predictive model as a visualization of current clinical practice and as a decision aiding tool. Of course, endoscopists should always consider technical feasibility before starting clip placement. The model shows that the average likelihood of any patient with large lateral spreading lesions to receive PC increases to 92.5% when all high-risk variables are present, and decreases to 2.3% when all variables are set to their minimal-risk levels. So far, this is to be expected. However, we would like to point out two interesting findings from the model. First, we see a surprisingly strong effect of withheld anticoagulants on the likelihood of PC. The smaller, but significant, increase of 5% in case of continued platelet inhibitors is also surprising, as guidelines actually advice the continuation of these drugs based on minimal effect on bleeding risk. Second, although small lesion size reduces the likelihood of PC in our model with roughly 12–15%, this still leaves adenomas <2 cm with a 24% likelihood to be closed with clips, independent of location or antithrombotics use. Small polyps with anticoagulants even have a higher likelihood to be clipped (37.2%) than large polyps without any antithrombotic medication (29.8%). This is not conform current literature and guidelines [9,10]. This finding emphasizes the need for more studies to help convince endoscopists.

Table 2. Importance scores per attribute.

Attribute	Mean, SD	Minimum–maximum	Median	IQR
Anticoagulant medication	22.50, 5.34	7.35–42.44	22.07	19.13–25.57
Intra-procedural bleeding	16.28, 7.07	1.89–40.45	15.49	11.40–20.04
Polyp size	16.21, 7.02	0.78–33.31	16.67	10.90–21.53
Location in colon	15.93, 6.50	0.69–31.94	16.28	11.76–20.68
Visible vessels	13.53, 8.43	0.03–37.01	12.46	6.31–19.52
Previous DB	10.04, 6.09	0.11–29.94	9.23	5.51–14.14
Polyp morphology	5.51, 2.96	0.43–15.06	5.08	3.35–6.83

SD: standard deviation; IQR: interquartile range.

Figure 3. Predictive model for PC. This graph shows the likelihood that an endoscopist would use PC per variable. The chance that an endoscopist would use PC on a random patient with a flat or sessile polyp (reference case) is 36.2%.

Table 3. Comparison of importance scores per attribute between endoscopists that are highly (>120 EMR procedures lifetime) and moderately experienced in EMR.

Attribute	Low/moderate experience (mean ± SD)	High experience (mean ± SD)	Mean difference (95% CI)[a]
Anticoagulant medication	21.79 ± 4.26	22.70 ± 5.61	0.91 (−0.39 to 2.75)
Intra-procedural bleeding	15.16 ± 7.01	16.59 ± 7.08	1.43 (−1.00 to 3.87)
Polyp size	15.32 ± 6.69	16.45 ± 7.12	1.15 (−1.28 to 3.57)
Location in colon	17.34 ± 7.24	15.54 ± 6.24	−1.80 (−4.04 to 0.43)
Visible vessels	14.09 ± 9.48	13.14 ± 8.10	−1.76 (−4.66 to 1.15)
Previous DB	10.19 ± 6.67	10.00 ± 5.93	−0.19 (−2.29 to 1.92)
Polyp type	5.30 ± 2.65	5.56 ± 3.05	0.26 (−0.76 to 1.28)

[a]All differences are not significant as $p > .05$ for all attributes and the confidence intervals for the mean differences all include 0.

Table 4. Suggestions for extra attributes left in the remarks-sections of the DCE.

Remark	#
Suggested extra attributes to consider	
Technical possibility of clipping (dependent on endoscope position, exact location of polyp, etc.)	4
Older age	3
Distance to hospital (out- or inpatient)	4
Targeted prophylactic clipping of a visible vessel rather than closing the whole resection plane	2
Prophylactic coagulation of visible vessels	4
Exact size of the polyp matters (e.g., a polyp of 6 cm has a higher bleeding risk than 3 cm)	3
Do you cover the eschar with a biogel?	1
Specify location not as left or right sided, but as rectum or cecum	2
People who refuse blood products due to religious principles/convictions	1

'#' is the number of times that the corresponding suggestion was made by an individual respondent in the remarks section of the survey.

Strengths

This study has several strengths. The number of respondents was high, increasing the external validity and generalizability. With 190 complete responses, we well achieved the calculated sample size of 150. Nonetheless, our efficient design was also important to optimize the precision of the estimates [32].

The survey was designed for a target population with preemptive experience in EMR, which was clearly stated in the invitation and instruction. The percentage of invited gastroenterologists that were EMR endoscopists is unknown. Therefore, the response rate of 36% is a rough estimation. The actual response rate, expressed as a percentage of EMR endoscopists that completed the survey, is likely higher, as the majority of non-responders will not have been EMR specialists. The 190 complete responses from 17 countries around the world allow us to draw solid and relevant conclusions.

Our insight in the global application of PC after EMR is further improved by the remarks-section of the survey. This was used by 36 respondents to provide explanations and suggestions in addition to their answers, or relate their experience of filling out the questionnaire.

Limitations

We realize that this study also has some limitations. First, 61% of respondents were Dutch, with a majority working in peripheral or teaching hospitals. Most of the foreign respondents worked in academic or tertiary hospitals. Although in the Netherlands, it is common practice to perform EMRs of large adenomas outside of academic hospitals, we considered EMR experience as a potential confounder. We saw no differences in importance scores between respondents with high vs. low-to-moderate experience. This seems to underline the generalizability of the results.

Second, a selection of the most relevant variables had to be made. In view of the guidelines, we chose risk factors for DB that were paramount to PC efficacy studies over some less studied attributes such as 'technical feasibility of clip closure' and 'cost of clips'. This is not to say that these factors may not play a role, but that they probably operate more on the background of the decision-making process.

Although the variables were carefully selected, the presentation of some attributes in the survey may have benefitted from more detailed explanation of the used definitions. For example, we explained that the cases should be answered from the perspective of everyday clinical practice. In daily practice, people using anticoagulants will generally be adequately bridged before the procedure to decrease the bleeding risk. Nevertheless, some respondents interpreted the variable 'use of anticoagulants' in the sense of continued, unbridged use. Although we excluded all respondents of whom we were aware of this misinterpretation from the analysis, this may have caused a slight overestimation of the part-worth utility. Nevertheless, as both bridged and unbridged patients on anticoagulants are to some degree at increased risk for bleeding compared to coagulated patients, we would expect the part-worth utility for this attribute to remain high after correction [22].

Lastly, we performed a subgroup analysis to compare outcomes in endoscopists with low vs. high experience in EMR. Expertise was self-reported by the respondents and are therefore prone to recall bias. We based thresholds for experience on previous research [14,33], and believe the rough division in experience level that we made is clinically relevant. Although we did not find any, various studies report a significant difference in EMR success rates between non-expert and expert endoscopists and advice to refer high-risk EMRs to tertiary centers [9,14]. However, consensus on a clear definition of high expertise is lacking.

Conclusions

PC after EMR is commonly considered useful by endoscopists, usually based on known risk factors for DB. Anticoagulant use was the most important factor in decision-making for PC, independent of endoscopist experience. Although not considered (cost-)effective, one in seven EMR endoscopists also use PC for adenomas <2 cm in the presence of high-weighing risk factors. These results can be used to guide future research and selective implementation of PC.

Disclosure statement

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Data availability statement

The data supporting the results and analyses presented in this paper are available via the corresponding author at reasonable request.

Author contributions

AT designed and performed the study, collected and analysed the data and wrote the paper. PD and EvG contributed to the design of the study, interpretation of the data and writing the paper. YP contributed to the analysis and interpretation of the data and reviewed the manuscript. LM and PS contributed to the design of the study and writing the paper. RMS contributed to the design of the study and reviewed the manuscript. All authors gave final approval of this version to be published.

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