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Research Article

Long-term clinical outcome after anterior cervical discectomy with polymethylmethacrylate (PMMA) as intervertebral spacer: A propensity score matched analysis

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ABSTRACT

Background: For single-level cervical degenerative disorders, an anterior cervical discectomy (ACD) is often performed with interposition of an intervertebral spacer. Most surgeons prefer a cage or arthroplasty, although superiority in comparison with other types of spacers, or leaving out a spacer, still has never been proven. Polymethylmethacrylate (PMMA) is a cost-friendly spacer with reported clinical outcome similar to other spacers. Therefore, the aim of this study was to assess long-term clinical outcome of ACD with PMMA as a spacer compared with ACD with a cage or without a spacer.

Methods: A retrospective cohort study among patients with cervical degenerative disorders requiring a single-level ACD was performed in two hospitals in the Netherlands. Subgroups were made for PMMA, cage and no spacer. The primary outcome measure was the Neck Disability Index, secondary outcome measures were complication and reoperation rates, quality of life, workability and the need of additional treatments (e.g. physiotherapy, selective nerve root block, spinal cord stimulation). A 1:1 propensity score matching was performed that adjusted for age, gender, body mass index, comorbidities, duration and type of symptoms, and level of surgery.

Results: A total of 241 patients were included in the study, with a median follow-up of 9.4 years. Propensity score matching revealed no statistically significant differences in all clinical outcome parameters between all subgroups. Complications, reoperations and the need for additional treatments were similarly distributed as well. A sensitivity analysis in which multiple PMMA patients were implemented (1: many matching) demonstrated equal results.

Conclusions: No differences in long-term clinical outcome were demonstrated between ACD with PMMA compared to ACD with cage, or without any intervertebral spacer. Complication and reoperation rates were equal among the matched cohorts. In conclusion, PMMA is an effective, safe and cost-friendly alternative with equal long-term clinical outcome compared to other surgical techniques for cervical degenerative disorders.

1. Background

For single-level cervical degenerative disorders, an anterior cervical discectomy (ACD[1]) is often performed with interposition of an intervertebral spacer [1,2]. Historically, autologous bone graft from the iliac crest was initially used as spacer [3–5]. Because of frequent donor site

Abbreviations: ACD, Anterior Cervical Discectomy; BMI, Body Mass Index; EQ-5D-5L, EuroQol 5 Dimensions 5 Level Survey; MH, Martini Hospital; NDI, Neck Disability Index; PMMA, Polymethylmethacrylate; RCT, Randomized Controlled Trial; SD, Standard Deviation; UMCG, University Medical Center Groningen.

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morbidity, there are currently multiple alternatives such as different types of cages, bone allograft, disc arthroplasty or the polymer polymethylmethacrylate (PMMA). The ACD without the application of an intervertebral spacer is also a well-known alternative that goes back to the 1960s and is still being used in spinal surgical praxis [6,7]. Although none of the different techniques has proven to be superior with regards to clinical outcome, cages and arthroplasty are most frequently used nowadays [8–14]. A disadvantage of the use of these type of intervertebral spacers are the associated costs. As cost-effectiveness plays an increasing role in current health care [15,16], it is questionable whether the use of costly spacers is justified when there are possible lower cost alternatives with equal clinical outcome.

PMMA seems to be a cost-friendly alternative to a cage or arthroplasty, although cost-effectiveness studies are lacking. The short-term clinical outcome of PMMA is equal to other techniques [9,10,12,17–19]. However, among surgeons, the reported low rate of intervertebral bony fusion and the possibility of graft migration is often considered a major drawback, but evidence for a correlation between radiological fusion and clinical outcome is absent [11,12,17,18,20].

No long-term outcome is reported where PMMA is compared to different types of spacers. Therefore, the objective of the current study was to investigate the long-term clinical outcome of ACD with PMMA as an intervertebral spacer compared to ACD with a cage, and ACD without spacer.

2. Methods

2.1. Study design

A retrospective cohort study was performed among patients with cervical degenerative disorders requiring single-level ACD between 2007 and 2012 in two Dutch hospitals (University Medical Center Groningen (UMCG) and Martini Hospital (MH). Both hospitals are main regional referral centers, with experienced neurosurgical teams regarding cervical spine surgery. The UMCG is a regional teaching hospital. The study was conducted in accordance with the Helsinki declaration. The ethical medical committees of both hospitals granted a waiver for this study. Guidelines for reporting observational studies and propensity score matched analyses were used in the preparation of this manuscript [21,22].

2.2. Participants

All patients that underwent ACD were retrieved by searching the electronic patient records on surgical treatment code. Patients were deemed eligible to participate if they presented with single-level radiculopathy, myelopathy or both, based on cervical degenerative disorders. Exclusion criteria were prior cervical surgery, (congenital) deformities of the spine, morbid obesity (body mass index (BMI) > 40), osteoporosis and chronic use of corticosteroids. Subgroups were made for patients who received PMMA as intervertebral spacer (PMMA), a cage (cage) or no spacer at all (ACD).

2.3. Recruitment and data collection

Patients eligible for participation received information about the study and an informed consent form. Upon returning a signed informed consent form, patients were included and received a link to a web-based questionnaire. Medical records were reviewed to extract patient demographics, medical history and clinical data. Comorbidities were classified in subgroups according to etiology (e.g. pulmonary, cardiovascular) and a sum score of the amount of comorbidities per patient was used for comparison between groups.

2.4. Surgical techniques

The surgeries in the UMCG were exclusively ACD with PMMA, while the MH performed all three types of surgery (PMMA, cage or ACD). The choice for PMMA in the UMCG was based on the equivalent clinical outcome and economic advantages compared to cages, and the surgeons preference to use an intervertebral spacer. The choice of spacer in the MH was subject to surgeons' preference, with the introduction of cages in 2010.

A total of 18 different neurosurgeons were involved in the study. A right-sided or contra-lateral Smith-Robinson approach was used to reach the anterior vertebral column [3]. Distraction screws were placed and a complete discectomy was performed. In the case of ACD, no intervertebral spacer was applied. When a cage was placed, a stand-alone titanium or polyethyletherketone cage (from various distributors) was used. For application of PMMA, a piece of hemostatic cellulose (Surgicel, Johnson & Johnson) was placed against the spinal cord to avoid thermal damage. Time was taken to ensure that the PMMA had the right viscosity to avoid leakage into the neural foramina. After complete hardening of the PMMA, the distraction screws were removed. Procedures and policies during hospital admission and regular follow-up (one visit to the outpatient clinic six weeks after surgery) were similar in both centers. Postoperatively, no neck collars were used.

2.5. Outcome assessment

The primary outcome was the Dutch language version of the Neck Disability Index (NDI), a patient-reported outcome measure that aims to objectify the neck-pain related disability [23,24]. It consists of 10 questions to be scored from 0 to 5, the sum of which can be doubled to get a disability score from 0 to 100, with 0 meaning no disability and 100 meaning total disability.

Secondary outcomes were quality of life using the EuroQol 5 Dimensions 5 Level Survey (EQ-5D-5L) [25,26] and the Work Ability Index single-item [27,28], an index comparing current ability to work to lifetime best, on a scale from 1 to 10.

Furthermore, the questionnaire included a general improvement scale similar to the Odom criteria [29], and questions about the nature of pre-operative symptoms, complications and postoperative complaints, such as dysphagia and hoarseness. Reoperations at index-level and adjacent levels were questioned, and checked in the medical file. Lastly, additional treatments for pain (e.g. pain medication, physiotherapy, selective nerve root blocks, spinal cord stimulation) were also queried.

2.6. Statistical analysis

All statistical analyses were performed using SPSS version 23 (IBM Corporation, 2015). Descriptive data was presented as mean with standard deviation or percentage of patients. Statistically significant differences between the different subgroups were tested with Pearson's Chi-square tests for categorical and Kruskal-Wallis tests for continuous data. A Kaplan-Meier graph was used to visualize time to reoperation.

Due to the retrospective nature of our study, we chose to compare the data of the different surgical techniques with a propensity score matching method to adjust for possible confounders and to balance the baseline characteristics of the different subgroups, in order to mimic a randomized controlled study design [30].

For the propensity score matching, associations of clinical relevant covariates with the outcome parameters and the different types of spacers were evaluated to select possible confounders. A propensity score was estimated by making a logistic regression model for the subgroups PMMA versus cage, and for PMMA versus ACD separately.

Balance between groups was analyzed for all covariates by conducting logistic regression with the type of spacer as dependent with, and without the propensity score as factor.

Patients were manually paired using the method of the nearest

neighbor without replacement with a maximal 5% difference in propensity score. Subsequently, baseline demographics of the matched groups and outcome parameters were analyzed with statistical tests adequate for paired data (paired *t*-tests for continuous normally distributed data, Wilcoxon signed rank test for categorical or ordinal data, and McNemar's test for dichotomous variables). A sensitivity analysis was performed by executing a weighted propensity matched analysis with multiple PMMA cases for each cage or ACD case (1:n matching). A standard significance level of 0.05 was used.

3. Results

Of the 332 eligible patients (106 UMCG, 226 MH), 241 patients gave informed consent and returned the questionnaires (response rate of 73%). Median follow-up time was 9.4 years with an interquartile range from 8.0 to 11.3 years. Baseline characteristics before propensity score matching indicated no statistically significant differences between the subgroups, except for age at time of surgery. Clinical characteristics are specified in Table 1.

3.1. Clinical outcome in the unmatched cohorts

Patient reported outcomes before propensity score matching are presented in Table 2. Complications occurred in 4.6% and reoperations in 9.1% of all cases. One or more non-surgical additional treatments for recurring or persistent pain were necessary in 38% of cases. Patient-reported temporary dysphagia and/or hoarseness were reported in 16–32% of cases. Details regarding complications, reoperations and additional treatments are specified in Table 3 and Fig. 1.

3.2. Propensity score matching

A propensity score model was made for the subgroups PMMA versus cage and PMMA versus ACD, including age, gender, BMI, sum of comorbidities, type of complaints (radiculopathy or myelopathy), duration of complaints and level of surgery (C5-6, C6-7 or other). Analysis of the balance between groups among the covariates demonstrated an improved balance among all parameters with the propensity score as factor (Supplementary material A). All cage (n = 37) and ACD (n = 32) patients could be matched within the 5% difference margin. Baseline characteristics after propensity score matching are presented in Table 4.

Table 1
Baseline characteristics of the unmatched cohorts.

	PMMA	Cage	ACD	p-value
Number of patients	171	37	32	
Female (%)	49	65	53	0.22
Age at operation (mean ± SD)	48.7 ± 9.0	53.3 ± 8.7	50.3 ± 10.4	0.02*
BMI (mean ± SD)	26.2 ± 4.4	25.7 ± 4.2	27.1 ± 4.6	0.53
No. of comorbidities (mean ± SD)	0.4 ± 0.7	0.6 ± 0.8	0.6 ± 0.9	0.34
Active smokers (%)	41	32	41	0.63
Duration of complaints (%)				
0–6 months	35	30	41	
6–12 months	29	19	44	
12–18 months	18	24	6	
> 18 months	18	27	9	0.11
Classification of symptoms (%)				
Radiculopathy	77	70	94	
Myelopathy	23	30	6	0.05
Level of surgery (%)				
C3-C4 or C4-C5	8	16	3	
C5-C6	49	57	44	
C6-C7	42	27	53	0.13

*Age in cage group was higher compared to the PMMA group with a statistical significance of p = 0.02.
ACD = anterior cervical discectomy without intervertebral spacer, BMI = body mass index, Cage = anterior cervical discectomy with cage as intervertebral spacer, No. = number, PMMA = anterior cervical discectomy with polymethylmethacrylate as intervertebral spacer, SD = standard deviation.

Table 2
Patient reported outcomes of the unmatched cohorts.

	PMMA	Cage	ACD	p-value
Number of patients	171	37	32	
Neck Disability Index (mean ± SD)	17.9 ± 16.6	15.4 ± 16.2	14.8 ± 15.7	0.44
EQ-5D-5L (mean ± SD)	0.81 ± 0.17	0.82 ± 0.17	0.81 ± 0.19	0.78
Work Ability Index (mean ± SD)	7.0 ± 2.2	7.5 ± 2.0	7.3 ± 2.1	0.35
Improved patients (%)*	77	81	84	0.56

*According to the 'excellent' and 'good' categories of the Odom criteria.
ACD = anterior cervical discectomy without intervertebral spacer, Cage = anterior cervical discectomy with cage as intervertebral spacer, EQ-5D-5L = EuroQol 5 Dimensions 5 Level Survey, PMMA = anterior cervical discectomy with polymethylmethacrylate as intervertebral spacer, SD = standard deviation.

Table 3
Complications, reoperations and additional treatments in the unmatched cohorts.

		PMMA	Cage	ACD
		n = 171	n = 37	n = 32
Registered complications (number (%))	**Total**	**7 (4)**	**2 (5)**	**2 (6)**
	Hemorrhage	3 (2)		
	Hoarseness*	2 (1)		
	Horner's syndrome	1 (1)		
	Dysphagia	1(1)		
	Recurrent nerve palsy		1 (3)	
	Septic shock		1 (3)	
	C5 palsy			1 (3)
	Other**			1 (3)
Reoperations (number (%))	**Total**	**15 (9)**	**3 (8)**	**4 (12.5)**
	Index level	3 (2)	1 (3)	1 (3)
	Adjacent level	12 (7)	2 (5)	3 (9)
Patient reported (temporary) (number (%))	Dysphagia	37 (20)	10 (32)	8 (25)
	Hoarseness	28 (16)	10 (30)	5 (16)
Additional treatments (number (%))	Pain medication	28 (16)	5 (14)	5 (16)
	Selective nerve root block	7 (4)	1 (3)	
	Spinal cord stimulation	1 (1)		
	Physiotherapy	51 (30)	11 (30)	9 (28)
	Multidisciplinary treatment	4 (2)		

*Severe hoarseness without recurrent nerve palsy on examination. **Readmission due to severe pain at one side of the body (contralateral of initial symptoms), no radiological explanation for complaints, improved conservatively with pain medication.
ACD = anterior cervical discectomy without intervertebral spacer, Cage = anterior cervical discectomy with cage as intervertebral spacer, PMMA = anterior cervical discectomy with polymethylmethacrylate as intervertebral spacer.

3.3. Clinical outcome after propensity score matching

Patient reported outcomes did not demonstrate a statistically significant difference between groups (Table 5). A 'good' or 'excellent' score on the general improvement scale was present in 78% versus 81%

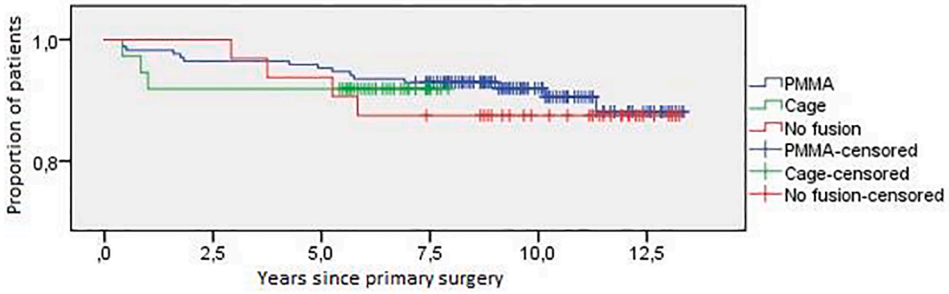

Fig. 1. Time-to-event for reoperation after primary surgery.

Table 4
Baseline characteristics in the matched cohorts.

	PMMA	Cage	p-value	PMMA	ACD	p-value
	n = 37	n = 37		n = 32	n = 32	
Female (%)	62	65	1.00	56	53	1.00
Age at operation (mean ± SD)	53.9 ± 9.0	53.3 ± 8.7	0.77	51.2 ± 9.3	50.3 ± 10.4	0.68
BMI (mean ± SD)	25.8 ± 4.1	25.7 ± 4.2	0.98	26.2 ± 4.0	27.1 ± 4.6	0.49
Comorbidities (mean ± SD)	0.5 ± 0.6	0.6 ± 0.8	0.33	0.5 ± 0.8	0.6 ± 0.9	0.37
Active smokers (%)	27	32	0.79	47	41	0.73
Duration of complaints (%)						
0–6 months	41	30		47	41	
6–12 months	8	19		41	44	
12–18 months	24	24		9	6	
>18 months	27	27	0.75	3	9	0.49
Classification of symptoms (%)						
Radiculopathy	68	70		94	94	
Myelopathy	32	30	1.00	6	6	1.00
Level of surgery (%)						
C3-4 or C4-5	14	16		0	3	
C5-6	54	57		41	44	
C6-7	32	27	0.54	59	53	0.41

ACD = anterior cervical discectomy without intervertebral spacer, BMI = body mass index, Cage = anterior cervical discectomy with cage as intervertebral spacer, PMMA = anterior cervical discectomy with polymethylmethacrylate as intervertebral spacer, SD = standard deviation.

Table 5
Paired differences patient reported outcomes after propensity score matching.

	Mean PMMA	Mean control	Mean difference	p - value
Neck Disability Index (0–100) (mean ± SD)				
PMMA – Cage	16.2 ± 15.7	15.4 ± 16.2	0.41 ± 22.91	0.92
PMMA – ACD	16.6 ± 16.1	13.9 ± 15.9	2.75 ± 24.49	0.53
EQ-5D-5L (-1.0 – 1.0) (mean ± SD)				
PMMA – Cage	0.81 ± 0.14	0.82 ± 0.17	−0.01 ± 0.22	0.85
PMMA – ACD	0.83 ± 0.17	0.82 ± 0.19	0.01 ± 0.29	0.85
Work Ability Index (1–10) (mean ± SD)				
PMMA - Cage	6.8 ± 2.2	7.5 ± 2.0	−0.76 ± 2.83	0.11
PMMA – ACD	7.4 ± 2.1	7.4 ± 2.1	0.00 ± 3.25	1.00

ACD = anterior cervical discectomy without intervertebral spacer, Cage = anterior cervical discectomy with cage as intervertebral spacer, EQ-5D-5L = EuroQol 5 Dimensions 5 Level Survey, PMMA = anterior cervical discectomy with polymethylmethacrylate as intervertebral spacer, SD = standard deviation.

of cases for PMMA compared to the cage subgroup (p = 0.94), and 84% versus 88% for PMMA versus ACD respectively (p = 0.55). Complications, reoperations and the need for additional pain treatments were equally distributed among the matched subgroups (p-values ≥ 0.38), as well as reported hoarseness or dysphagia (p-values ≥ 0.77) (Supplementary material B).

3.4. Sensitivity analysis

A weighted propensity matched analysis with multiple PMMA patients matched to each cage or ACD patient (n = 163 and n = 162 respectively), did not demonstrate any statistically significant differences between subgroups either, indicating that it is not likely that the 1:1 matching introduced selection bias.

4. Discussion

The results of this study demonstrate no statistically significant differences in long-term clinical outcome of PMMA as intervertebral spacer compared to ACD with cage or without spacer. This is the first study, to our knowledge, that compared long-term clinical outcome of PMMA to other spacers with a propensity score matching method. Long-term clinical outcome for PMMA was studied in three retrospective cohort studies, with varying success rates ('excellent' or 'good' according to the Odom criteria) of 66%, 78% and 94%, in which our findings (77% in the unmatched PMMA cohort) fit well [8,19,20]. The small randomized controlled trials (RCTs) that were conducted on the subject only had a short follow-up period of 6–24 months [10,12,17,18]. None of the RCTs reported statistically significant differences in clinical outcome between PMMA and other spacers studied.

Complications were present in 4% of the PMMA cohort, which is slightly lower than reported in other long-term studies (5,2% of 249 patients [8], and 6,5% of 124 patients [19]). A reoperation rate of 8,8% was present in the PMMA subgroup, of which 1,8% at index level over a 10-year period. This is in line with other available long-term studies (9,6% [8] and 7,1% [19]).

The rationale that is often brought up in the literature for the use of an intervertebral cage, is the aim to accomplish bony fusion of the adjacent vertebral bodies. For this reason, PMMA is frequently deemed unsuitable due to the reported low rates of fusion [8,10–12,17,18,20,31,32]. However, PMMA has been used for multiple decades [17,33,34] and a clinical inferiority compared to other types of spacers has never been demonstrated. Our present study neither demonstrates long-term clinical differences for PMMA compared to the other surgical techniques. If bony fusion after ACD would be clinically relevant (due to symptomatic pseudarthrosis or graft migration), a higher rate of reoperation would be expected. In critique, as we only investigated the clinical outcome from the patient's perspective and we did not perform a radiological analysis on our cohort of patients, we can only assume that there is no correlation between radiological fusion and clinical outcome based on the high similarity of clinical parameters among the subgroups and the earlier reported fusion rates of PMMA [8,10–12,17,18,20,31,32].

Interestingly, a relatively high amount of our patients (38%) received one or more additional non-surgical treatments for pain after

surgery, most often physiotherapy (29%). In the Netherlands, no standard physiotherapy program is offered after cervical spine surgery. Where there are multiple trials and even a Cochrane review about rehabilitation after lumbar discectomy, evidence for optimal rehabilitation after cervical discectomy is lacking [35]. Also, the need for other additional treatments after surgery, such as selective nerve root blocks or spinal cord stimulation, is not described in other long-term studies regarding cervical discectomies in general.

Although there were, with the exception of age, no statistical baseline differences between the groups, confounders could play a role in the outcome of the retrospective cohorts. The aim of propensity score matching is to minimalize these confounders, although this method does not guarantee that all confounders are adjusted for. For instance, not all techniques were performed in both hospitals and therefore it was not possible to adjust for the different medical centers. This could lead to bias regarding the baseline patient population or the clinical results due to different surgical teams. As patient characteristics were adjusted for in the propensity score model, and clinical results demonstrated a high similarity among groups, we do not assume this limitation has led to the introduction of relevant bias. Furthermore, due to the retrospective nature of the study, we did not have baseline scores of the patient reported outcomes. Therefore, we were not able to calculate improvement scores, and consecutively could not distinguish clinically relevant changes. As the minimal clinically important difference for the NDI is 17.3% and for the EQ-5D-5L 0.24 quality-adjusted life years [36], we could argue that the long-term results between the different subgroups were not clinically significant. Also, recall bias could have influenced the results of the patient reported complications such as dysphagia and hoarseness. Another limitation is the difference in sample size between the subgroups. Due to the relatively small sample size of the ACD and cage group, it is possible that our findings did not reach enough power to find statistically significant differences. However, the small intergroup differences in all outcome parameters did not indicate that there is an underlying trend that we have overlooked. The difference in sample sizes could also have introduced bias at the moment of constructing the matched pairs. To evaluate the robustness of our results, we therefore performed the additional analysis with multiple matched PMMA controls. This analysis demonstrated equal results compared to the 1:1 matched cohorts.

Current research on cervical degenerative disorders is focusing, mostly due to industry-driven research, on the difference between arthroplasty and fusion with a cage or allograft, in which arthroplasty demonstrates promising results [14]. However, there is still no evidence that a cage or arthroplasty is clinically or regarding cost-effectiveness, superior to other types of spacers [37–43]. There is long and wide experience with the use of PMMA as intervertebral spacer, and it has demonstrated to be straight forward and safe. The costs of the material are considerably lower than cages or arthroplasty [40,44].

Especially in an era where the costs of healthcare are rising uncontrolled, the favoring of expensive implants over much cheaper alternatives with equal clinical outcome cannot hold. In this light, also ACD without intervertebral spacer is an alternative that is worth considering with probably even lower (direct) costs than PMMA, and a comparable clinical outcome to ACD with intervertebral spacers. Future research should therefore be aimed towards a cost-effectiveness approach and, in our opinion, with less focus on the achievement of radiological fusion.

In summary, PMMA demonstrates to be an effective, safe and cost-friendly alternative to intervertebral cages or no spacer, with equal clinical outcome over a near 10-year period. Although PMMA is, in general, not favored among surgeons, it therefore could be considered when choosing from the wide variety of intervertebral spacers.

5. Conclusion

No statistically significant differences in long-term clinical outcome were demonstrated between ACD with PMMA as spacer, compared to ACD with cage or without any intervertebral spacer. Complication and reoperation rates were equal among the matched cohorts and in line with reported rates in current literature.

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7. Ethical standards

The Medical Ethical Committee of the University Medical Center Groningen granted a waiver for this study.

Author contributions

AB, RS, JMAK, MR and RG initiated and conceptualized the study. AB, MC and JK collected the study data. AB, MC and JMAK analyzed and interpreted the data. Drafting of the manuscript was done by AB and MC. Revision of the manuscript was performed by JMAK, RS, MR, JK and RG. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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