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Real world outcomes of patients with endometrial cancer from a South African radiation oncology unit

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Background: Endometrial cancer adds significantly to the burden placed on the South African health care system with GLOBOCON 2020 cancer statistics ranking it as the 5th most frequently diagnosed cancer in South African women.

Aim: A retrospective audit to assess real-world clinical outcomes in women with endometrial carcinoma that received radiation as a treatment modality.

Setting: A radiation oncology unit at a public tertiary hospital in the Johannesburg area, Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in South Africa.

Methods: Medical records between 2010 and 2020 were evaluated for patients who received either combination external beam (EBRT) and vaginal brachytherapy (VBT) or VBT alone. Overall survival rates (OS) and progression-free survival (PFS) were assessed.

Results: One hundred and two patients were analysed. Demographic profiles were 76,5% black people, 18.6% white people, 3.9% asian people and 1% mixed race. Median age was 66 years (range: 64 years–67 years). Type 1 histology in 70%. OS at 5-year was 61.75% and at 10-year was 40% with stage and histological type being significant contributors. Statisical significance in survival occurred with a combination of LVSI with greater than 50 % myometrial invasion ($P = 0.038$) and a combination of greater than 50% myometrial invasion with positive margins ($P = 0.032$). Radiation treatment was completed in 102 (100%) of the patients.

Conclusion: Real world outcomes of overall survival rates of endometrial carcinoma are lower than projected in our developing country, although contributory high risk factors play a role in keeping with international literature and historic landmark trials.

Contribution: This study contributes to the growing body of research on endometrial cancer outcomes in low- and middle-income countries (LMICs).

Keywords: radiation; endometrial cancer; inoperable; surgery; external beam radiation; high dose brachytherapy; vaginal brachytherapy; South Africa.

Introduction

Endometrial carcinoma has a significant global burden impact, being ranked as the 6th most common female cancer worldwide. GLOBOCON (Global Cancer Statistics) for 2020 assigns South African females a cumulative incidence of 0.97 for developing uterine cancer and ranks endometrial cancer as the 5th most common female cancer in South Africa with the fastest increasing incidence rate noted in Asia and South Africa since 1990.[1] The incidence rate has more than doubled over a 10-year period from 1998 to 2008 with obesity and diabetes having been suggested as causal reasons for this trend.[2] Being a developing country, the patient population faces resource constraints and cannot always access world standard care for endometrial cancer. According to the South African National Cancer Registry figures, the cumulative lifetime incidence risk of uterine cancer in the female population is 0.71.[3]

Historically, Bokman divided endometrial cancer into two broad histological subtypes: Type 1 and Type 2 based on endocrine and metabolic influences.[4,5] Type 1 is of endometroid (adenocarcinoma) histology and accounts for 80% of tumours, with oestrogen responsiveness and has a favourable prognosis. In American studies, these tumours were most noted in the white population.[4,5,6] Type 2 tumours account for 20% of endometrial cancers, are fast-growing tumours and include serous, papillary, clear cell, squamous, mesonephric, transitional cell, undifferentiated and carcinosarcoma. Type 2 differs in natural history and disease course. It is not associated with

oestrogen stimulation, is fast growing and tends to have an endometrial intraepithelial carcinoma as a precursor lesion. Because of the aggressive nature of Type 2 cancer, extrauterine spread often results with a poorer prognosis independent of stage.[7] This classification is currently being reviewed based on molecular phenotypes. The advent of tumour genomic atlas now defines endometrial cancer as 4 specific subtypes namely: DNA polymerase ε (POLE, ultra-mutated), microsatellite instability (MSI, hypermutated), copy number high, and copy number low. Association with hereditary syndromes such as Lynch and Cowden syndrome are also being assessed.[8] This has prognostic and predictive implications and will pave the way for targeted chemo-immunotherapy strategies.

Surgery plays a pivotal role in the management of endometrial carcinoma. Radiation is a consideration in early stages, locally advanced stage, and in the metastatic setting. External beam radiation therapy (EBRT) and vaginal brachytherapy (VBT) are the two forms of radiation therapy that can be administered in the treatment of endometrial cancer. Currently, adjuvant radiation treatment strategies are determined by the FIGO (International Federation of Gynecology and Obstetrics) stage and the grade of the patient along with other adverse high-risk factors.[9] The beneficial role of VBT alone or combined EBRT and VBT as treatment radiation modalities is also being assessed worldwide.[10,11]

Materials and methods

Patient selection and work-up

Medical records of 102 patients who have undergone EBRT and VBT between 01 January 2010, and 31 December 2020, were evaluated, with a follow-up duration of 13 years until 20 July 2023. All patients with histological confirmation of endometrial cancer who were treated in the Department of Radiation Oncology at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) were included. Patients were graded as FIGO stage 1–4, grade 1–3 using the binary 2009 FIGO staging as well as the revised version in 2017, as the study overlapped the staging revision periods.[12] Recently, a revised 2023 staging was released but was not used in our study as it was not within the study's time frame.[13] Patients who received chemotherapy instead of radiation exclusively, carcinosarcoma, and FIGO stage 1 patients that underwent observation were excluded from the research.

Data collection

A data collection sheet was utilised that assessed various clinical and demographic data. Treatment regimens as well as adverse events from these modalities were documented. Pathology reports for surgical resections that were in the files were assessed for high-risk factors (lymph vascular stromal invasion [LVSI], >50% myometrial invasion and positive resection margins). Post treatment follow-up patients were documented as being disease-free on clinical examination or disease progression. Disease progression according to biopsy proven recurrence and radiological evidence as well as date, and site of relapses on restaging was recorded. Progression-free survival was calculated. Data on living status of patients were obtained from the South African identity document services for OS calculations.

Surgery

A multidisciplinary team of surgeons and radiation oncologists evaluated patients prior to treatment. Clinical assessment, histology and baseline imaging by computerised axial tomography (CT) scanning, abdominal sonar and chest x-ray validated stage at diagnosis. Resectable patients underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH & BSO) and peritoneal fluid was collected for cytology. Lymph node dissection was seldom conducted at our facility. Patients commenced radiation therapy 4–6 weeks following surgery.

Radiation

In the adjuvant setting, patients were risk stratified using the National Comprehensive Cancer Network (NCCN) risk stratification system and GOG 99 trial.[14,15] Patients with intermediate-risk group were offered either VBT alone or EBRT combined with VBT based on stage, grade, age and LVSI. All stage 1 high-risk patients underwent surgery and received adjuvant EBRT (utilising 2D technique) combined with VBT. Stage 2 endometrial cancer received combined EBRT with VBT in the adjuvant setting. Stages 3 and 4A or those early stage deemed medically inoperable endometrial cancer, received EBRT combined with VBT. Stage 4B disease received palliative EBRT.

Radiation technique for external beam radiation

After CT simulation, a four-field box technique was utilised. Borders delineated were as follows: superior border mid-L5 vertebral body, lateral border was 2 cm beyond the border of the bony pelvis, and inferior border was the bottom of the ischial tuberosity. Radiation energy utilised was either a Cobalt 60 machine or Linac machine at either 6 MV, 15 MV or 18 MV energies. The most common fractionation scheme used for EBRT was 48Gy in 2Gy per daily fraction. Local recurrent disease that did not receive prior radiation was given combined EBRT 48Gy in 2Gy per daily fractions with VBT. Palliative EBRT dose of 20Gy in 4Gy per daily fractions were given to patients who received prior radiation or with incurable disease.

Radiation technique for vaginal brachytherapy

Vaginal cylinders were used to target the upper third of the vagina to include the vaginal mucosa of the vaginal cuff which is a common site for recurrence. The resulting mean target length was 4 cm–5 cm. The prescription point was 0.5 cm from the surface of the applicator with a dose gradient from the applicator surface (140% – 160%) to the dose at 5 mm tissue depth (100%). The dose used at our institution was 21Gy in 7GY per weekly fraction when VBT was used either as a sole radiation modality or in combination with EBRT for FIGO stage 1. The dose for VBT was adjusted to 15Gy in 5Gy per

weekly if microscopic disease was present at margins or 20Gy in 5Gy per weekly fractions if macroscopic disease was present. Clear margins were given 10Gy in 5Gy per weekly fractions.

Surveillance and follow up

Patients on radiation were monitored weekly at the clinic to assess tolerance to treatment. Patients received surveillance upon completion and were counselled about vaginal dilation, late adverse events, infertility and survivorship programmes. The first follow-up date was 6 weeks, thereafter 3–4 monthly. Patients with a suspicious lesion on the vault underwent a confirmation biopsy and was subsequently restaged with imaging to confirm the recurrence.

Statistical analysis

Data analysis was conducted using Stata statistical software, and a *p*-value less than 0.05 was deemed statistically significant. Frequency distribution tables and measures of central tendency were used to present descriptive statistics. The Chi-square and Fischer Exact tests were used to assess association between categorical variables. Analysis of variance (ANOVA) and independent samples *t* tests were used to compare mean differences for continuous variables. Kaplan-Meier curves were used to estimate the survival function (probability that a subject will survive up to time t) for censored data.

Ethical consideration

Ethical approval for the study was received from the Human Research Ethics Committee at the University of Witwatersrand in writing on 26 May 2023 (No.M230553). No patient identifiers were used, and all patients were given a unique study number. This study was a human study.

Results

Patient and tumour characteristics are presented in Table 1. A total of 102 patients that received radiation during the study period were analysed. The median age of patients was 66 years (range: 64 years–67 years). Racial distribution included black people (76.5%; *n* = 78), white people (18.6%; *n* = 19), Asian people (3.9%; *n* = 4), and mixed race (1%; *n* = 1). When assessing the variables of HIV and diabetes, it was difficult to draw a conclusion as the status of majority of the patients was unknown. However, 65.7% (*n* = 67) were HIV-negative and 21.6% (*n* = 22) were diabetic. A significant number of patients were hypertensive (60.8%; *n* = 62). The commonest stage of presentation in order of frequency was stage 1 (47%; *n* = 48), stage 3 (28.4%; *n* = 29), stage 2 (21.5%; *n* = 22), and stage 4 (2.9%; *n* = 3). Kaplan-Meier projected estimate shows a high survival rate in order of frequency from stage 4 to stage 1 (Figure 1).

The most common histological subtype was type 1 (71.6%; *n* = 71) with type 2 comprising of 25.5% (*n* = 26). An equal number of patients between type 1 and type 2 diseases presented with extrauterine disease (*n* = 29 each). Serous carcinoma comprised of 29.5% (*n* = 23) in our majority black population.

Surgical resection was performed in 86% (*n* = 86) of our patients for majority type 1 histology subtype (75%; *n* = 66) versus type 2 histology subtype (22.7%; *n* = 20). Majority of patients who underwent surgery were stage one patients (52.3%; *n* = 46). Vaginal brachytherapy was used as a sole

TABLE 1: Patient and tumour characteristics.

Characteristic	Frequency	%
Age (Mean) in years	65.95 (64.01 – 67.87)	-
Race		
Black people	78	76.5
White people	19	18.6
Asian people	4	3.9
Mixed race	1	1
HIV status		
Positive	2	2
Negative	67	65.7
Unknown	33	67.6
Hypertension positive		
Yes	62	60.8
No	1	1
Unknown	39	38.2
Diabetes mellitus positive		
Yes	22	21.5
No	1	1
Unknown	79	77.5
Histological type		
Type 1	73	71.5
Type 2	29	28.4
Operability		
Operable	88	86.2
Inoperable	14	13.7
FIGO stage		
1	48	47
2	22	21.5
3	29	28.4
4	3	2.9
EBRT dose and fractionation		
48Gy/2Gy dly	48	47
50.4Gy/1.8Gy dly	1	1
50Gy/2Gy dly	7	6.9
42.5Gy/2.5Gy dly	2	2.0
46Gy/2Gy dly	1	1.0
50.4Gy/2.1Gy dly	1	1.0
40Gy/2.5Gy dly	3	2.9
40.5Gy/2.5Gy dly	1	1
30Gy/3Gy dly	1	1
No EBRT received	37	36.2
Brachytherapy dose and fractionation		
15Gy/5Gy wkly	50	49
21Gy/7Gy wkly	40	39.2
24Gy/3Gy wkly	1	1
18Gy/9Gy wkly	4	3.9
10Gy/5Gy wkly	3	2.9
14Gy/7Gy wkly	1	1
36Gy/9Gy wkly	1	1
18Gy/9Gy wkly	1	1
10Gy stat	1	1

EBRT, External beam radiation therapy.

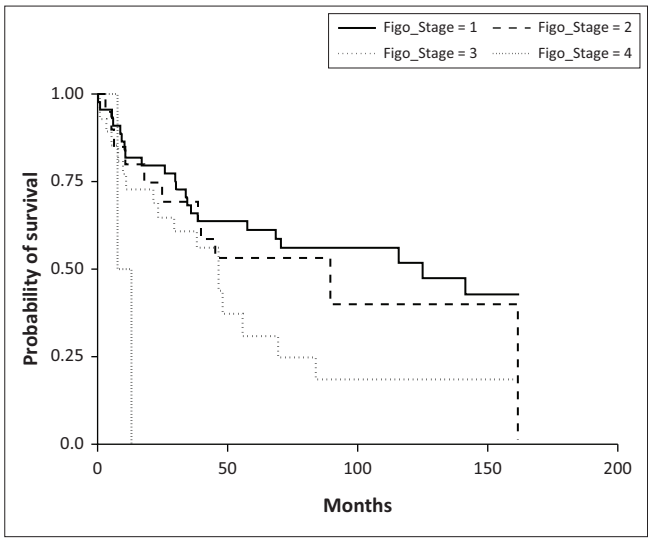

FIGURE 1: Stage analysis stage 1/2/3/4 on survival-comprehensive-Kaplan-Meier projected estimate shows a higher survival rate in months for patients in order of frequency from FIGO stage 4 to stage 1.

radiation modality in the adjuvant setting for 68.5% (n = 33) of patients with stage 1 disease, while a combination of EBRT and VBT was administered to 32.1% (n = 15) of patients with stage 1 disease in the adjuvant setting. In stage two, 90.9% (n = 20) of patients received combination EBRT and VBT, while 9.09% (n = 2) received VBT alone. Patients in stage 3 received only combination EBRT and VBT (44.6%; n = 29). In stage four, 3.1% (n = 2) of patients received combined EBRT and VBT and 3% (n = 1) of patients received VBT alone.

The most frequently prescribed VBT regimen was 15Gy in 5Gy per weekly fractions (49%; n = 50) and the most prescribed EBRT dose was 48Gy in 2Gy per daily fractions (46%; n = 47). Radiation treatment was completed in 102 (100%) of the patients.

The adverse events to radiation that the patients experienced are listed in order of frequency with radiation dermatitis (20.6%) being the most common, followed by vaginal stenosis (18.6%), radiation cystitis (2.0%), radiation colitis (2.0%), radiation proctitis (2.0%) and vesicovaginal fistula (VVF) (2.0%). There was no rectovaginal fistula reported (RVF) (0.0%).

The mean OS was 36.16 months (standard deviation [s.d.] 34.46; confidence interval [CI] 19.03–53.30) and progression-free survival post radiation was 16.47 months (s.d. 17.40; CI 7.82–25.12) reflected in Table 2.

The 5-year OS of our patient population as per Table 3 was 61.75%. The 10-year survival is 40.0%. Stage had the greatest influence on survival rates (Figure 1). Patients with stage 1 disease had a 5-year OS of 70.0%, followed by stage 2 (61.9%), stage 3 (51.7%) and stage 4 (0.0%). Average survival in months was 34.46 (95% CI 19.03–53.30). The shortest progression-free survival was observed in patients with grade 3 histology

TABLE 2: Survival analysis: Mean overall survival and progression-free survival post radiation.

Variable	Mean	s.d.	95% CI
Overall Survival (months)	36.16	34.46	19.03–53.30
Progression-free survival (months)	16.47	17.40	7.82–25.12

s.d., standard deviation; CI, confidence interval.

(mean 13.5 months) and was followed by irresectable disease (mean 13.9 months) and by patients with grade 3 histology. An analysis of other clinicopathological factors was done and no statistical significance on survival could be ascertained from solitary high-risk factors such as positive margins, LVSI, and >50% myometrial invasion of tumour. However, an ANOVA test between subjects effects revealed that the most statistically significant variable that resulted in a difference in survival rate were two combinations. One being the presence of LVSI and >50% myometrial invasion (p = 0.038) and the second was the combination of >50% myometrial invasion and positive margins (p = 0.032) (Table 4).

Discussion

Endometrial carcinoma is of concern because of the rising increase in South Africa with factors like diabetes and obesity being implicated. In our study, no significant association between endometrial cancer and risk factors such as diabetes and hypertension could be identified. The majority of our patients were HIV negative with an HIV positivity rate of 2%. Our patient population is in keeping globally with the mean range for age of presentation between 55 years and 60 years of life.[16]

Type 1 endometrial cancers were most prevalent, and aligns with international statistics comprising of an 80% incidence of type 1 and 20% incidence of type 2. We noted that there was no difference between the incidence of extrauterine disease between type 1 and type 2 histology (n = 23) by virtue of clinical and radiological staging. However, a significantly larger number of patients with type 1 histology underwent a surgical resection as compared to patients that had type 2 histology [Type 1 disease (75%; n = 66) versus type 2 disease (22.7%; n = 20)].

A TAH & BSO with peritoneal fluid was collected for cytology. Current recommendations include pathologic nodal assessment for uterine-confined endometrial cancer, which aids both stage and adjuvant therapy.[17] However, prophylactic nodal dissection is associated with significant lymph oedema and hence seldom done. If final pathology shows a non-invasive endometrioid histology, nodal assessment can be eliminated. The NCCN sentinel lymph node (SLN) algorithm is recommended if sentinel node mapping is utilised. The department has adopted external beam to prophylactically address high risk of nodal disease in patients with adverse histological features. Sentinel lymph node availability and more so SLN ultra-staging is limited at our institution. Nodal evaluation in theatre and frozen sections can be considered currently as an approach in our gynaecology oncology department.

TABLE 3: Overall survival at 5 years and 10 years.

Overall survival	%	FIGO STAGE											
		1			2			3			4		
		%	months	s.d.	%	months	s.d.	%	months	s.d.	%	months	s.d.
5 years	61.75	70	69.56	34.16	60	53	44.53	51.7	40.4	44.37	0	7.35	5.71
10 years*	40	-	-	-	-	-	-	-	-	-	-	-	-

s.d., standard deviation.

*Because of low 10 years overall survival, OS per FIGO stage was not projected.

TABLE 4: ANOVA test of the between subjects effects.

Source	Mean square	*F*-value	*P*-value
> 50% myometrial invasion	7083.4	3.5	0.068
LVSI	2455.2	1.2	0.278
Margin involved	5.4	0.003	0.959
> 50% myometrial invasion*LVSI	9928.8	4.8	0.038
> 50% myometrial invasion*Margin involved	0	0	0.032

ANOVA, analysis of variance; LVSI, lymph vascular stromal invasion; *F*-value, the ratio of the between-group variance to the within-group variance; *P*-value, determine statistical significance of the differences between means.

*ANOVA test between subjects' statistical significance and OS ($p < 0.05$).

Majority of patients with stage 1 intermediate-risk disease received VBT as a radiotherapy modality in the adjuvant setting and combined with EBRT if they were categorised as high risk. Majority of patients with stage 2–4 disease received a combination of EBRT and VBT. The PORTEC-1, GOG-99, GOG 249 and PORTEC-2[18,19,20,21,22] trials explore the benefits of radiation (EBRT or VBT) as the recommended adjuvant treatment in patients with high-intermediate risk factors and form the basis of supporting evidence to use radiation in early-stage high-intermediate risk groups. PORTEC-2 emphasises that VBT can successfully decrease vaginal vault recurrence rate in early-stage low risk patients.[22]

The recommended dose of EBRT should be between 45Gy and 50.4Gy in 1.8Gy–2Gy per daily fraction.[23] At our institution, a variety of dose ranges were adopted from 48Gy–50.4Gy in 1.8Gy–2Gy per daily fractions. Doses included hypofractionation 40Gy–42.5Gy in 2.5Gy per daily fractionations.

The recommended dose for VBT was 21GY in 7Gy per weekly fractions and the prescription point used was of 0.5 cm from the vaginal cylinder, in keeping with the ABS (American Brachytherapy Association) guidelines.[24] Patients with microscopic invasion or positive margins were given brachytherapy of 15Gy in 5Gy per weekly fractions. Radiation treatment was completed in 102 (100%) of the patients.

The most prevalent early adverse event seen was radiation dermatitis in our study population. Late adverse events in order of the most to the least prevalent was vaginal stenosis, radiation cystitis radiation colitis, radiation proctitis and vesicovaginal fistula (VVF). Poor patient follow-up is attributed to low VVF and RVF rates considering 2D techniques were administered as the EBRT technique of choice. The toxicity profile experienced using 2D techniques is significantly higher than more conformal techniques.[25,26] A move to more conformal techniques such as IMRT and VMAT are the preferred modality of choice to limit the toxicity targeted to the vault or whole vagina with a resulting mean target length of 4 cm–5 cm by 2D techniques, which would result in the above adverse events. Our department commenced more conformal techniques outside the study time. Because of this being in development, we do not have comparative data.

The 5-year OS in our patient population is 61.7%. When comparing this to the SEER 5-year data relative survival rates (surveillance, epidemiology, and end results in the United States), the SEER data for localised disease were 96%, for regional disease 72% and 20% for distant disease. The SEER mean OS for all combined stages of SEER is 84%.[27]

The limitations of our study included the lack of surveillance being offered as an adjuvant treatment option for stage 1A/B, GOG low risk patients; hence, comparisons could not be made in this subgroup of patients. A secondary limitation includes adverse events being poorly graded, and patients with late adverse events were possibly lost to follow-up or died prior to reporting the late adverse event. No concurrent chemotherapy was prescribed at radiation oncology and those with metastatic disease were referred to the medical oncology department.

Landmark trials for endometrial cancer projected higher OS rates and progression-free survival than our statistics[15] but we have taken into account selection bias of patients in these trials and have accounted for the first world setting these trials were conducted in. Our real-world data results are attributed to multiple factors.

In a developing country, patients are of poorer general condition with treatment delays and resource constraints. The average life span of a South African women is 65.0 years versus an American women whose average life span is 79.1 years.[27] The shorter lifespan of our population group could contribute to a lower 5-year survival in our elderly female population. It should be noted that in the context of average survival of a South African women being lower, this does not necessarily translate to a poor outcome in our patient population. The scope of the problem is attributed to the paucity of cancer registries in many developing countries. Health inequity is experienced by many women in developing countries, and lack of access to screening and treatment because of discriminatory beliefs and practices could contribute to the lower-than-expected survival rates.[28]

Stage is the most important contributor to survival. Our study kept with the trend that the mean survival in months was lower as one progresses higher into the stage of the disease. An assessment of other solitary high-risk factors that

can affect OS and recurrence, such as positive margins, LVSI and >50% myometrial invasion of the tumour was assessed in our study. A combination of LVSI and >50% myometrial invasion (p = 0.032) as well as the combination of >50% myometrial invasion and a positive margin were found to be statistically significant variables that resulted in a difference in survival. This aligns with the Aalders Norway trial that highlighted LVSI and >50% myometrial involvement as a subgroup that benefited the most from the addition of EBRT to VBT in the adjuvant setting.[29]

Relapse rates in our population are slightly lower than 18% globally.[30] Factors that have statistically contributed to a decrease in progression-free survival included patients with grade 3 disease that had the shortest progression-free survival. The aggressive nature of grade 3 disease accounts for this and classifies patients into a high-risk category. There were also a significant number of patients who presented with serous carcinoma being the predominate histological subtype of type 2 disease. This has also been supported in the Aalders Norway trial as a consideration for the addition and benefit of EBRT to VBT in the adjuvant setting.[29]

Conclusion

We conclude that our patient profile and demographics are in keeping with world population statistics. Being a developing country, we have sufficiently adopted the recommended dose of adjuvant and definitive radiotherapy. Overall survival was lower than projected in international data.[31] with high-risk factors (LVSI positive, >50% myometrial involvement, positive margins) in combination having a contributary detrimental effect on the South African survival rates for endometrial cancer.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

N.M. conceived and designed the study, collected data from the medical files, captured the data on an electronic platform, analysed the data, and took the lead in writing the article. The supervisors, P.B., D.R. and D.T. provided relevant feedback by assessing the data, guiding the author by appraising intellectual content, and restructuring the article. The author and the co-authors granted approval of the final version to be published.

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Data availability

The data that support the findings of this study are available from the corresponding author, N.M., upon reasonable request.

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