Evaluation of quality of life after a transurethral resection of the prostate at the Pointe-a-Pitre clinic

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Abstract

Background: Trans-urethral resection of the prostate (TURP) remains to this day the "gold standard" for the treatment of obstructive prostatic hypertrophy and is both the surgical treatment of choice when other methods fail. Its realization can affect the urinary and sexual functions, thus causing a repercussion on the quality of life of the patient. The absence of publications in our circles aroused the interest of this study.

Aims: to assess the quality of life of patients who have benefited from an RTUP at the Pointe-a-Pitre Clinic.

Methods: Through a cross-sectional approach carried out at Pointe-a-Pitre Clinic in Kinshasa during the period from June 2017 to June 2019, the data of the 65 patients who benefited from an RTUP had been collected and then analyzed. The assessment of quality of life was assessed using the IPSS score and the factors determining poor quality of life were sought by logistic regression with the calculation of the Odds ratio. The performance of the IPSS score was evaluated by the ROC curve with the determination of the Youden index.

Results: A total of 65 patients aged on average 70.1 ± 6.3 years had benefited from a TURP, of which 90.8% were married and 81.5% were academics. Dysuria and nocturia were the main admission complaints (30.8%) and urinary incontinence (23.1%). Assessment of quality of life by the IPSS showed moderate (46.2%) to severe (21.5%) prostatic symptoms, with a considerable proportion of patients reporting an improvement in quality of life (78.5%) across the board versus only 20%, who reported poor quality of life. The factors associated with this poor quality of life were the occurrence of complications [OR: 8.2 95% CI (4.5-12.6), p <0.001] and moderate prostatic symptoms [OR: 3.5 95% CI (1.3-5.9), p = 0.002] to severe [OR: 7.5 95% CI (4.1-9.6), p = 0.001]. The ROC curve showed good performance predicting poor quality of life with an optimal score of 0.18, corresponding to a sensitivity of 88.0% and a specificity of 90.7% (Youden's index 0.607).

Conclusion: RTUP currently occupies an important place in surgical urological activities in Kinshasa. It considerably improves the urinary function of patients as well as their general quality of life, but it can nevertheless have some repercussions including disorders of the lower urinary tract (acute urinary retention, urinary incontinence), hemorrhage, urinary tract infection and erectile dysfunction.

Keywords: TURP, quality of life, assessment and CPAP.

Introduction

Transurethral resection of the prostate (TURP) was the first successful minimally invasive surgical procedure of the modern era [1]. To date, it has been the “gold standard” for the treatment of obstructive prostatic hypertrophy and is both the surgical treatment of choice when other methods fail. Prostate adenoma has increased in frequency along with life expectancy and has become the third leading cause of health expenditure in industrialized countries. Eighty percent of men are treated for prostate adenoma during their lifetime [2]. In recent years, the proportion of elderly people has increased. We are witnessing a decline in infectious pathologies; cardiovascular, respiratory and prostatic pathologies take center stage [3].
TURP for the surgical treatment of BPH is an alternative to upper adenomectomy (AVH) \(^2\), \(^3\). It has demonstrated its effectiveness and safety in use, even with anticoagulant (4-6). This is a technique that reduces the risk of bleeding, the duration of the catheterization and the average length of stay without any difference in effectiveness compared to the AVH \(^6\), \(^5\), \(^7\), \(^8\), \(^9\), \(^10\). Studies have shown a reduction in the post-operative retention rate or even overall complication \(^7\), \(^11\).

The instruments are introduced retrograde into the urethra; the prostate is removed in the form of chips which are analyzed in order to detect possible cancer. The advantages of RTUP are indisputable for the patient: it is less decapit than laparotomy performed at any age; the absence of incision, less cosmetic damage; shorter hospital stay; short survey time, postoperative comfort; lower cost (3); a rapid resumption of activities; thus the return home is made within 5 to 6 days following the surgical intervention.

However, in view of the anatomical position of the prostate and its proximity to important structures such as neurovascular bundles and internal and external urinary sphincters, these can be affected during resection. The disruption of urinary continence and sexual function will affect the patient’s quality of life with a significant psychological impact \(^4\), \(^5\). Nowadays, quality of life is at the heart of the concerns of all health professionals (doctors, nurses, rehabilitators, psychologists, etc.) who work in hospital or extra-hospital environments. In the current concept of care in industrialized countries, it is no longer enough to treat the patient medically, ad integrum recovery is the priority of all healthcare providers \(^6\).

During previous consultations, the consensus committee, under the aegis of the WHO, recommended the use of the international score for the symptomatic state of the patient (IPSS) and quality of life assessment (QOL) as the scale official body for the evaluation of the symptoms of men suffering from voiding disorders (symptoms of the lower urinary tract) and for whom an obstruction to bladder emptying is mentioned. The IPSS is based on the answer to seven \(^7\) questions assessing the severity of urinary symptoms. Responses are scored from 0 to 5. Each question allows patients to choose one of six responses that increasingly quantify the severity of the symptom. The total score can then be added from 0 to 35 points (asymptomatic to very symptomatic). The symptom score symbol is: IPSS [0-35].

The International Consensus Committee currently recommends the use of a single question to determine the impact of symptoms on the patient’s quality of life. The answers to this question range from “satisfied” to “very bored” rated from 0 to 6 points \(^8\). The symbol for the quality of life response is QDV = [0-6].

The asymptomatic state of the patient can then be summarized by IPSS = [0-35], QDV = [0-6].

Several European studies having evaluated the quality of life of patients after surgery have reached identical conclusions \(^3\), \(^4\), \(^5\), \(^6\). This is the case of a French study, which estimates that more than one million men over the age of 50 have benign prostatic hyperplasia (BPH); very rarely the life-threatening is threatened, but can affect the quality of life of patients. However, in Africa, more particularly in the DRC, RTUP has emerged since 1970, but there are very few studies that have been interested in assessing the fate of patients benefiting from this technique. However, today it seems to be performed in most hospitals in the city of Kinshasa. The purpose of this study is to assess, on the basis of scores validated by the WHO, the quality of life of patients after an RTUP at the Pointe-à-Pitre Clinic in order to contribute to the improvement of patient management.

**Methods**

**Nature, setting and period of study**

This is a cross-sectional study, which took place at the Pointe-à-Pitre Clinic, a clinic specializing in Urology and General Surgery, located in Kinshasa. It covered the period from June 2017 to June 2019, i.e. a period of 2 years.

**Population and sampling**

The outcome measure was the achievement of TURP in patients with symptomatic BPH resistant to medical treatment, complicated BPH or obstructive prostate cancer. We selected 97 files of patients having benefited from a TURP among which 65 had met the inclusion criteria.

**Data collection technique and variables of interest**

The data used in this study were collected by the systematic review of the medical records of patients who had undergone a TURP at the Pointe-à-Pitre Clinic as well as by questioning the patients during their appointments. The records of these patients were collected consecutively using a pre-established file

The TURPs were performed according to the standardized resection technique derived from the Nesbit technique \(^12\). The material used was a Storz or Olympus ch 27 resector, with bipolar current. The irrigation fluid was 0.9% saline. The shavings were systematically sent in their entirety to the pathology laboratory.

The quality of life of patients after a TURP was assessed using the IPSS score items. The quality of life questionnaires were given to patients during the preoperative and postoperative consultation. The average response time was 5-10 minutes. Each response was decoded according to the recommendation tables, then the averages of these responses were calculated for each area. This questionnaire consists of 7 items concerning urinary symptoms rated from 0 to 5 and generates a score ranging from 0 to 35, as well as a question relating to QOL. The means of the scores obtained are: 0-7 = Not very symptomatic; 8-19 = Moderately symptomatic and 20-35 = Severe symptoms.

The variables retained were; socio-demographic data (age, marital status, profession, level of education and funding for care); clinical data (admission complaints, medical and surgical history); data related to RTUP (Type of RTUP, duration of resection, duration before ablation of the probe, quality of urination after ablation of the probe, possible complications, weight of the prostate, maximum flow rate, post-voiding, postoperative, short and long term complications and type of anesthesia), paraclinical data (PSA level, ECBU, Ultrasound, Debimetry and Anatomopathology) and elements of the IPSS score.

**Data processing and analysis**

Data was entered using Microsoft Excel 2013 software and analyzes were performed using SPSS 22.0 software.

A simple descriptive analysis was performed on the entire study population. The results are expressed as the mean ± standard deviation for the quantitative variables or as a percentage with the 95% confidence interval for the qualitative variables.

Pearson's chi-square test or Fisher’s exact test was performed to compare the percentages. Student's T-test compared the means.

The quality of life of the patients was assessed by the IPSS score. Logistic regression had identified the determinants of poor quality of life with the calculation of the Odds ratio. The performance of the IPSS score was evaluated by the ROC curve with the determination of the area under the curve (efficient test if the air under the curve is greater than 50%). For all the tests carried out, the value of p <0.05 was the threshold of statistical significance.
Ethical considerations
The collection of data and their transcription had respected the principle of confidentiality. The use of the results of this study is limited to the strict exploitation linked to its objectives.

Results
Sociodemographic data of patients who have benefited from a TURP
The socio-demographic data of the patients are illustrated in Table 1. The average age of the patients was 70.1 ± 6.3 years with a predominance of patients in the age group over 70 years (53.8%). The majority of these patients were unemployed (46.2%). They had a university education (81.5%) with secure funding in the majority of cases (86.2%).

Clinical data of patients having benefited from a TURP
As shown in Table 2, dysuria was the main complaint which motivated in the majority of cases the patients to consult, i.e. 72.3%. Hypertension was the most common medical history with 46.2%. The surgical history of RTUP and hernia repair was the most encountered in patients with each 15.4%.

Paraclinical data of patients having benefited from a TURP
ECBU was performed in 46 patients or 70.8%. Half of the results (50.0%) were pathological. The most common germ was Klebsiella pneumoniae in 19.6% followed by E. Coli in 15.2%. The prostate volume was ≥60 g in 50.8%, with a post-voiding residue ≥66 ml in 50.8%. Pre and post operative D biblemtry was performed in 6.2%.

The table shows that 76.9% of patients had had an anapath. Grade 4 / HT prostate carcinoma was more frequently encountered.

Table 3: Distribution of patients operated on from TURP to CPAP according to the paraclinical examinations carried out and their results.

| Variables                  | Effectif (n=65) | %  |
|----------------------------|-----------------|----|
| **ECBU**                   |                 |    |
| Realized                   | 46              | 70.8|
| No                         | 19              | 29.2|
| **ECBU Results**           |                 |    |
| Sterile                    | 23              | 50.0|
| Pathological               | 23              | 50.0|
| **Germes**                 |                 |    |
| E. Coli                    | 7               | 15.2|
| Klebsiella Pneumoniae      | 9               | 19.6|
| Staphylococcus             | 3               | 6.5 |
| Candida trachomatis        | 1               | 2.2 |
| Enterobacter cloacal       | 5               | 10.9|
| **Ultrasound**             |                 |    |
| Test performed             |                 |    |
| <60 g                      | 32              | 49.2|
| ≥60 g                      | 33              | 50.8|
| **Post voiding residual**  |                 |    |
| <66 ml                     | 32              | 49.2|
| ≥66 ml                     | 33              | 50.8|
| **Pre and post operative flow measurement** | | |
| No                         | 61              | 93.8|
| Yes                        | 4               | 6.2 |
| **Anapath**                |                 |    |
| No                         | 15              | 23.1|
| Yes                        | 50              | 76.9|
| **Anapath results**        |                 |    |
| Prostate carcinoma grade 4 / HT | 23            | 46.0|
| HFLA / chronic aspecific prostatitis | 13        | 26.0|
| HFLA PIN 1-2 / chronic aspecific prostatitis | 14        | 28.0|

Terms of the intervention
All procedures were performed by an Urologist. The majority of interventions lasted more than 120 minutes. AR was the most widely used anesthesia (93.8%). Ten point eight percent of patients were transfused during the procedure (see Table 4).

Table 4: Procedures for the surgical intervention of patients operated from TURP to CPAP

| Variables                  | Effectif (n=65) | %  |
|----------------------------|-----------------|----|
| **Operator**               |                 |    |
| Urologist                  | 65              | 100.0|
| **Follow up time intervention** |             |    |
| < 60 minutes               | 3               | 4.6 |
| ≥60-120 minutes            | 28              | 43.1|
| ≥120 minutes               | 34              | 52.3|
| **Type of anesthesia**     |                 |    |
| RA                         | 61              | 93.8|
| AG+RA                      | 4               | 6.2 |
| Intraoperative transfusion | 7               | 10.8|

Table 1: Socio-demographic data of patients operated from TURP to CPAP

| Variables          | Effectif (n=65) | %  |
|--------------------|-----------------|----|
| **Age**            |                 |    |
| Mean ±SD           | 70.1±6.3        |    |
| <60 years          | 5               | 7.7 |
| 60-69 years        | 25              | 38.5|
| ≥70 years          | 35              | 53.8|
| **Marital status** |                 |    |
| Married            | 59              | 90.8|
| Unmarried          | 6               | 9.2 |
| **Profession**     |                 |    |
| Official           | 17              | 26.2|
| Unemployed         | 30              | 46.2|
| Independent        | 18              | 27.7|
| **Level of study** |                 |    |
| Secondary          | 12              | 18.5|
| University         | 53              | 81.5|
| **Funding**        |                 |    |
| Secured            | 56              | 86.2|
| Insecured          | 9               | 13.8|

Table 2: Distribution of patients operated on from TURP to CPAP according to admission complaints and medical and surgical history

| Plaintes            | Effectif (n=65) | %  |
|---------------------|-----------------|----|
| Dysuria             | 47              | 72.3|
| Nysturia            | 17              | 26.2|
| Pollakiuria         | 15              | 23.1|
| RUA                 | 14              | 21.5|
| Polyuria            | 7               | 10.8|
| Gross Hematuria     | 3               | 4.6 |
| Mictalgia           | 3               | 4.6 |
| Hypogastralgia      | 3               | 4.6 |
| **Antécédents**     |                 |    |
| HBP                 | 30              | 46.2|
| Alcohol             | 16              | 24.6|
| Diabete miliitus    | 11              | 16.9|
| TURP                | 10              | 15.4|
| Hernial cure        | 10              | 15.4|
| Allergy             | 9               | 13.8|
| Appendectomy        | 5               | 7.7 |
| Urinary tract infection | 3            | 4.6 |
| craniotomy          | 2               | 3.1 |
Post-operative evolution of patients after RTUP

Table 5 shows that 13 patients (20.0%) presented postoperative complications, including 3 deaths (4.6%). Acute urinary retention was the most observed complication in 30.8%.

| Table 5: Post-operative evolution of patients having benefited a TURP in CPAP |
|---------------------------------|---------------------|---------------------|
| **Evolution**                   | **Effectif (n=65)** | **Pourcentage (%)** |
| Operating suites                |                     |                     |
| Simple                          | 52                  | 80.0                |
| Complicated                     | 13                  | 20.0                |
| **Types of complications**      |                     |                     |
| RUA                             | 4                   | 30.8                |
| Urinary incontinence            | 3                   | 23.1                |
| Hémorraghe                      | 2                   | 15.4                |
| Urinary tract infection         | 2                   | 15.4                |
| Erectile dysfunction            | 2                   | 15.4                |

Symptom assessment using the International Prostate Symptom Score (IPSS)

Figure 1 highlights that after evaluation 46.2% of patients had mild symptoms after the operation.

Patient quality of life

Figure 2 shows that twenty percent of the patients who underwent PTRT had a poor quality of life.

Determinants of the poor quality of life of patients after a TURP

Patients with complications were 8 times more likely to have a poor quality of life (OR 8.2). A severe IPSS score exposed the same risk (OR 7.5).

| Table 6: Determinants of poor quality of life in patients operated on from RTUP to CPAP |
|---------------------------------|---------------------|---------------------|
| Variables                       | Quality of life     | OR (95% CI)         | p-value |
| Operating suites                |                     |                     |
| Simple                          | 50(96.2)            | 2(3.8)              | 1       |
| Complicated                     | 2(15.4)             | 11(84.6)            | 8.2(4.54-12.64) | <0.001 |
| Score IPSS                      |                     |                     |
| Light                           | 29(96.7)            | 1(3.3)              | 1       |
| Moderate                        | 19(90.5)            | 2(9.5)              | 3.57(1.30-5.99) | 0.002 |
| Severe                          | 4(28.6)             | 10(71.4)            | 7.50(4.19-9.66) | 0.001 |

Performance of the IPSS score on the quality of life of patients

Figure 3 shows an area under the curve of 0.857 [95% CI (0.709-1.00)], the value of the IPSS score in our study shows good performance predicting poor quality of life for patients with a score optimal of 18, corresponding to a sensitivity of 88.0% and a specificity of 90.7% (Youden’s index 0.607).
Discussion
Poor prostate health begins, among other things, with benign prostatic hyperplasia, which causes voiding disorders in 50% of men over the age of 50. Among this population, twenty to forty percent of men over the age of 60 will undergo surgery. This study involved 65 patients who underwent RTUP as an alternative to AVH or failed medical treatment. Regarding the socio-demographic data of patients, the present study found an average age of 70.1 ± 6.3 years with a predominance of patients in the age group over 70 years (53.8%). These results are similar to those of other authors [14,20]. These various findings confirm that benign prostatic hyperplasia and prostate cancer occur at a high frequency after the age of 50 [13,14].

The majority of patients were unemployed (46.2%). This differs from the observation made by BANO P, who reports a predominance of cultivators at 33.3% in his study on transurethral resection of the prostate (RTUP) in a saline environment [15]. This difference is related to the fact that in our environment cultivators generally classify themselves as unemployed because of the lack of organization in this sector of work. This study further noted that eighty-one point five percent of patients were university educated. Indeed, the high level of education is an opportunity because it allows a better understanding of the factors of vulnerability and a better perception of the existing therapeutic modalities. Academics understand the different types of treatment, they wanted an alternative to the proposed AVH or they had heard of RTUP. Funding for care was secure for the majority of patients (86.2%). This is justified by the cost of RTUP which is not accessible to the average Congolese.

In relation to the clinical data of the patients, the present series has shown that dysuria was the main complaint which motivated the consultation in the majority of cases. Our results differ from those of MINUCK M [16], who finds in his study the UK in 90% and BANO P [15], in his study on transurethral resection of the prostate (RTUP) in saline environment only finds pollakiuria as the main reason for consultation in 23 patients, or 33.3%. This difference is related to the fact that the patients consulted late in the first but earlier in the second. This series has shown that hypertension is the most common medical history. On the other hand, RTUP and hernia repair were the most encountered surgical history in patients. Our observations are along the same lines as those of BANO P., who reports the prevalence of hypertension at 23.1% and inguinal or inguinoscrotal hernia repair in 24.6% of cases [15]. As well as BAI F et al [17], who note hypertension and diabetes mellitus. Some RTUPs when they are sparse expose to early prostate regrowth in case of BPH. And if it is an unstabilized CaP, in its natural evolution again obstructs the prostatic urethra. As for the presence of the hernia, it is justified by the fact of the sentinel hernia following an intra-abdominal hyperpressure exerted to urinate in case of TUBA.

Most of our patients are in their 60s, hypertension is present, linked to social stress. It can also be indicative of kidney or heart disease.

The paraclinical data of our patients revealed that, the EBCU was carried out in 46 patients or 70.8% among which 50% had returned pathological. The most common germ was Klebsiella pneumoniae (19.6%) followed by E. Coli (15.2%). These findings are close to those of BANO P [15] and CISSE D [18], which found Escherichia coli in 8.7% and 45.0% respectively. As for the prostate volume, this study showed that it was in 50.8% greater than 60g. These observations differ from those of BANO P, which found in its study a prostate weight between 30.1-60 g (59.42%) with an average of 57.92 g [15]. As well as CISSE D [18] which reports between 30-60 g in 57.4%, with an average weight of 57.7 ml. They are also similar to those of HOUDA H [19] which finds an average of 65 g as well as SEREY-EIFFEL S, which notes an average prostatic volume of 71.4 g [20] and BAI et al. [17]. 84, 85g.

This high weight which was found in our study is justified by the fact that the limit weight of 60 to 70g reported required for monopolar resection is only theoretical and does not apply to bipolar resection as performed at CPAP. For our series, we have removed prostates of all sizes.

During this study, all procedures were performed by an Urologist. The majority of interventions lasted more than 120 minutes. Our duration is higher than that of FOURNIER et al., In their study on the complications of transurethral resection of the prostate in relation to the 100 cases found that the duration of the intervention varies between 20 and 105 minutes [21]. This high duration in our series is linked to didactic and coaching reasons for assistants (learning curve). It is linked to the fact that certain RTUPs have been associated with castration or treatment of inguinal or inguino-scrotal hernias and Cystorrarphy.

This series revealed that the postoperative stay was on average 4.52 days ZANGO B reports a duration of 68-70 minutes [13]. Our results remain within the standards because the duration mentioned in the literature is 2 to 5 days. We also note that it often depends on the operator's assessment of the degree of hemostasis.

We noted that AR was the most common type of anesthesia (93.8%). Similar results are reported by BANO P (20), who made the same observation in 100% of patients and ZANGO B [22] in 75% of cases. In fact, since RTUP is pelvic surgery, RA is the most suitable. General anesthesia is often done during conversion or depending on the patient’s comorbidities.

In relation to the post-operative evolution of patients, this study noted that out of the 65 RTUPs performed, 20% of the complications were observed within a median time of 5 (EQ: 3-7) days among which 3 deaths or 4, 6% mortality rate. The success rate was 80%. BANO P [20], reaches the same conclusions with the simple operative suites within 48 hours in 87% of the patients and one case of death on the 2nd postoperative day (4%). As well as CISSE D (25), which found 92.5% of simple operating suites, ZANGO B [22], 88.2%, MINUCK M [16], 86%, Jonathan S [23], 84% of suites simple operating procedures.

This series also showed that acute urinary retention, urinary incontinence, hemorrhage, urinary tract infection and erectile dysfunction were the complications seen after TURP. Our results differ from those of MISRAI et al. who finds complications related to the equipment, including the excessive temperature of the irrigation serum which caused burns of the urethra and / or the bladder, and the intraoperative complications linked to the gesture, essentially rectal wounds [24]. They are also similar to those of FOURNIER et al., Who in their study on the complications of transurethral resection of the prostate in relation to the 100 report hemorrhage, acute retention of urine when the bladder catheter is removed, orchiepithymitis and urinary tract infection [21]. RUA dominates our complications because of postoperative prostate edema, incarceration of shavings and blood clots in the urinary catheter eyelets and subsequently urethral stenosis.

Regarding the assessment of symptoms according to the IPSS score, this study showed that after assessment, 21.5% of patients
had severe prostatic symptoms, 32.3% of moderate symptoms and 46.2% of mild symptoms. Or an improvement of 78.5%. Our results are in the same direction as those of authors like: MOUHTADI M, in his study on the fate of long-term patients after transurethral resection of the prostate which found an improvement in the IPSS score which went from 22.8167% before the intervention at 5.3833 at 1 year with an improvement of 76.4% [23]. Deliveliotis et al., On the other hand, in a Greek study evaluating the effect of prostate surgery on quality of life, note that resection does not induce a significant increase 2 years after treatment [26]. This difference is linked to the fact that the appreciation of the quality of life is also cultural and multidimensional. Some elderly patients have associated deficits that they wish to be resolved after an RTUP.

In relation to the quality of life of the patients, the study showed that 20% of the patients who underwent a TURP had a poor quality of life. Patients with complications had 8 times the risk of poor quality of life (OR 8.2), as well as those with moderate and severe symptoms (OR 3.57 and 7.5). These results are similar to those of the Iranian team of Hadi et al [27]. This team worked on elderly people with other comorbidities due to their poor quality of life as in the MOUHTADI M study [23].

The performance of the IPSS score on the quality of life of the patients was assessed by the ROC curve, which showed an area under the curve of 0.857 [95% CI (0.709-1.00)], the value of the IPSS score in our study presents a good predictive performance of the poor quality of life of patients with an optimal score of 18, corresponding to a sensitivity of 88.0% and a specificity of 90.7% (Youden's index 0.607). Our results are similar to those of: MOUHTADI M [23], SALINAS et al [28], TUBARO and Vecchia [29] who also found that the high value of the IPSS score was directly linked to poor quality of life.

**Conclusion**

TURP currently occupies an important place in urological surgical activities in Kinshasa due to its efficiency and advantages compared to AVH. The findings made through this study revealed a considerable improvement in patients' urinary function and their general quality of life. However, it has detected certain complications (acute urinary retention, urinary incontinence, hemorrhage, urinary tract infection and erectile dysfunction) with an impact on quality of life. Hence the interest of informed consent.

**Conflict of interest**

No conflict of interest has been declared by the authors.

**Author’s contribution**

AMT, MLN and DMM designed, collected, interpreted, written and corrected the manuscript. ANN and GMM analyzed the data, read and corrected the article. JKK, APM, LL and PDK supervised, interpreted and corrected the article. All authors have read and approved the final version of the article.

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