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Could HoLEP change the further management of incidental prostate cancer?

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Introduction: Holmium Laser Enucleation of the Prostate (HoLEP) represents an effective and well-established technique in the treatment of lower urinary tract symptoms (LUTS) related to benign prostatic hypertrophy (BPH). We evaluated patients with BPH and concomitant or incidentally detected prostate cancer (PCa) treated with HoLEP and the subsequent clinical management.

Materials and Methods: We performed a retrospective review of patients treated with HoLEP at a single institution. We analyzed total pre- and postoperative prostate-specific antigen (tPSA), multi-parametric magnetic resonance (mpMRI) imaging, and pathology results in patients with a PCa diagnosis performed before HoLEP (group 1) and incidentally at HoLEP (group 2).

Results: We analyzed a total of 147 consecutive patients: 16 (10.9%) patients already had a PCa diagnosis before HoLEP, and in 18 (12.2%) patients PCa was incidentally detected at HoLEP. The tPSA level at 3 months after HoLEP dropped by 85.8% (from 14.34 ng/ml to 2.04 ng/ml) in patients of group 1 and by 86.5% (from 3.94 ng/ml to 0.53 ng/ml) in patients of group 2; the values remained stable up to 12 months after HoLEP. By including even those patients who underwent cancer treatment post-HoLEP, all patients in both groups survived without cancer progression (based on their initial PCa status).

Conclusions: Patients undergoing HoLEP might receive a PCa diagnosis in more than 10% of cases. The HoLEP technique can be performed even in patients with PCa, at any stage of the disease, to treat LUTS. The procedure does not negatively impact oncological outcomes even when PCa is diagnosed before or at HoLEP. Surely, the durability of the success of this approach to management needs further investigation.

KEYWORDS

benign prostatic hypertrophy, Holmium laser enucleation, prostate cancer, incidental prostate cancer, PSA

Introduction

The significance of iPCa in clinical terms and the necessity for adjuvant treatment remain controversial. Currently, HoLEP is considered a recommended BPH technique for patients complaining of lower urinary tract symptoms (LUTS). Several studies reported favorable overall long-term outcomes (1, 2), but only a few studies focused on the postoperative functional outcomes in the event of iPCa.

Clinical management of T1a/T1b iPCa detected after BPH surgery is well established and rarely requires subsequent active treatment; conversely, the surgical treatment of enlarged symptomatic glands with known low-risk PCa on active surveillance (AS) is not well established, and radical prostatectomy is often advised with the aim of treating An old paradigm is being challenged: in the past, patients with prostate cancer (PCa) were considered "untouchable" until they developed severe obstructive symptoms; now, PCa represents a comorbidity rather than a strict inclusion/exclusion criterion for surgical relief of bladder outlet obstruction (BOO) caused by benign prostatic hyperplasia (BPH).

Holmium laser enucleation of the prostate (HoLEP) represents an effective and durable transurethral surgery for the treatment of BOO due to BPH (3, 4), regardless of prostate size (5, 6). Furthermore, HoLEP has also demonstrated excellent perioperative outcomes in elderly patients (7).

Even though "classic" trans-urethral resection of the prostate (TURP) has been extensively studied, data regarding an increased risk of localized disease spread, progression, metastasis, and cancer-specific mortality due to the endoscopic technique are conflicting: some studies suggest no correlation between the procedure and PCa (8, 9), while others report a procedure-related disease progression (10, 11).

T1a-T1b PCa detected in the histopathological specimens of men treated with surgery for BPH represents incidental prostate cancer (iPCa) (12, 13). Preoperative prostate-specific antigen (PSA) screening and prostate biopsy lead to a decrease in iPCa incidence during surgery for BPH (14, 15), with rates of iPCa at TURP and HoLEP of 5.2%-6.4% and 5.6%-8.1%, respectively (12–16). Moreover, matched pair analysis between HoLEP and open prostatectomy established no difference in the detection rate of PCa in patients with large prostates (17). Some reports indicate PSA density and age as iPCa risk factors (13–17). Elkoushy et al. reported overall survival (OS) rates for iPCa of 72.8% and 63.5% at 5 and 10 years, respectively (18).

both pathologies simultaneously (19).

To date, there is no extensive knowledge about the role of HoLEP in patients with PCa detected preoperatively, during the procedure, or postoperatively, and only a few studies have focused on the oncological outcomes of low-, intermediate-, and high-risk PCa after HoLEP.

Hence, we evaluated all patients treated with HoLEP at our institution with a PCa diagnosis (before or at the time of HoLEP), and their oncological outcomes.

Materials and methods

Patients

From a prospectively maintained institutional database, we reviewed, after the Institutional Review Board's approval, a total of 147 consecutive patients treated with HoLEP from December 2020 to August 2021, with completely available data on clinicopathological and tPSA (preoperative and 1-year postoperative), and with a minimum follow-up of 12 months.

Preoperatively, all patients underwent tPSA dosage, a digital rectal exam (DRE), a trans-rectal ultrasound, or a multiparametric MRI (mpMRI) of the prostate; in the event of PIRADS v2.1 ≥3 at MRI report, patients underwent a standard 12-core + target prostate biopsy.

Baseline and clinicopathologic variables were analyzed.

Based on when they were diagnosed with PCa, patients were categorized into two groups: before HoLEP (group 1), or at the postoperative stage (group 2). These two groups were compared to each other and a cohort of patients without a PCa diagnosis who were treated with HoLEP.

Patients were stratified based on Grade Group (GG) according to the 2014 ISUP-endorsed grading system.

All HoLEP procedures were performed by three experienced surgeons (≥50 procedures).

The minimum follow-up was 12 months (median 16 months [IQR 14-18]).

Inclusion/exclusion criteria

Inclusion criteria:

- Patients with BOO due to BPH;
- Patients treated with HoLEP;
- Patients with mpMRI PI-RADS v2.1 <3;
- Old or comorbid patients with suspicious mpMRI (PI-RADS v2.1 ≥3) informed about the risk of PCa detection at the final histological report and opted first for BOO relief and for subsequent cancer treatment, who gave informed consent.

Exclusion criteria:

- incomplete follow-up.

Endpoints

Primary endpoint: to assess the oncological outcomes of patients treated with HoLEP and with PCa (detected preoperatively, in the postoperative pathology specimen, or during follow-up).

Secondary endpoints: to assess oncological outcomes according to different therapeutic approaches (active surveillance, radiotherapy, hormone therapy, radical prostatectomy) (PSA trend, prostate-cancer-specific survival).

HoLEP procedure

HoLEPs have been performed at our institution with the following equipment: a Lumenis Versa Pulse™ Holmium laser with settings of 2.0 J and 60 Hz (maximum power of 120 W), a 26Fr continuous-flow Storz laser resectoscope, and a 550-µm laser fiber. The procedure followed the technique described by Gilling et al. (20). The Lumenis VersaCut™ Morcellator was employed for the removal of the enucleated prostatic lobes.

Initially, the T-L technique consisted of a series of incisions performed by laser to determine landmarks: two T-shape incisions performed at the 5 and 7 o'clock positions at the level of the bladder neck, two bilateral L-shape incisions performed at the level of the verumontanum to mark the apex and to limit the sphincter, and a T-shape incision at the 12 o'clock position of the bladder neck and posterior to the level of verumontanum (21).

At the end of the surgery, a 22F three-way catheter was inserted and continuous flow irrigation was maintained until the following morning. In the absence of hematuria or other complications, the catheter was removed on the second postoperative day.

Statistics

Median values with interquartile ranges (IQR) and mean with standard deviations (SD) were reported for non-normally and normally distributed continuous variables, respectively; frequencies with proportions (%) were used for categorical variables.

The student t-test and Mann-Whitney U test were used for continuous data, and the chi-square test for categorical values was used to evaluate differences between the groups.

Results

The baseline and clinicopathological characteristics were summarized in Table 1.

Out of 147 patients treated with HoLEP, 34 patients received a PCa diagnosis, either before HoLEP (16 patients) (Table 2) or after HoLEP in the final histopathological report (18 patients) (Table 3).

Out of 16 patients (10,9%) with PCa diagnosed prior to HoLEP, 12 patients had ≤GG2 PCa on AS, one had GG3 PCa on AS and one was receiving LHRH therapy; one patient had GG4 PCa on AS and one patient had GG5 PCa receiving LHRH therapy.

After HoLEP, PCa was confirmed in 5/16 patients (31,2%), without no upgrade or downgrade from the baseline PCa. Eleven patients underwent AS, one patient underwent androgen deprivation therapy (ADT); three patients underwent radiotherapy (RT) + ADT, and one patient underwent systemic chemotherapy. All patients underwent curative treatment after three months.

Out of 18 patients with incidental PCa at HoLEP, 16 patients (88.9%) were detected with ≤GG2 PCa and started AS or watchful waiting (WW) protocols based on the clinical characteristics of each patient; one patient underwent robot-assisted radical prostatectomy (RARP) (surgery proceeded without complications, and the PSA was undetectable at the last follow-up), and one patient underwent RT+ADT after three months. Considering low- or intermediate-risk groups according to the D'Amico classification, any patient enrolled in the AS protocol received disease staging. The patient selected for treatment with curative intent underwent a total body CT scan and bone scan before treatment. A confirmation biopsy was performed.

For intermediate-risk patients (GG2), the AS protocol was designed as an alternative to treatment with curative intent based on patient choice.

In group 1, the median tPSA was 14.34 ng/ml and 2.04 ng/ml at the initial evaluation and three months after HoLEP, respectively, with a decrease of 85.8%; the value remained stable for 12 months.

In group 2, the median tPSA was 3.94 ng/ml and 0.35 ng/ml at initial evaluation and three months after HoLEP, respectively, with a decrease of 86.5%; the value remained stable for 12 months.

Figure 1 shows the PSA trend after HoLEP considering only patients treated with AS in the iPCa group. 5alpha-reductase inhibitors (5ARIs) were suspended in all patients after surgery, and they did not affect PSA levels.

Patients of both groups survived without cancer progression.,

Discussion

For patients who are candidates for HoLEP, a comprehensive preoperative assessment is needed so that the eventual iPCa diagnosis can be considered. In spite of a complete preoperative PCa-risk assessment with a prostate mpMRI and/or biopsy, the incidence of iPCa at HoLEP can reach up to 15% (22).

PCa is routinely detected through prostate biopsies, but the rate of false-negative results should be fully considered (23, 24). When preoperative prostate mpMRI was investigated to exclude cancer before HoLEP in patients with a suspicion of PCa, a negative mpMRI was considered necessary to lower iPCa rates in a new approach to the

TABLE 1 Baseline and clinicopathologic characteristics.

	TOTAL	BPH	PCa			*P value (BPH vs iPCa)*	*P value (PCa Pre-HoLEP vs iPCa)*
			Total	Pre-HoLEP	incidental		
N° of pts (%)	147 (100%)	113 (76.9%)	34 (23.1%)	16/34 (47.1%)	18/34 (52.9%)	–	-
Median age, yrs (range) ***	69 (47-87)	69 (47-87)	69.5 (53-84)	68.5 (53-84)	72 (58-82)	0,87	*0,56*
Median total PSA, ng/ml (range) ***	3.60 (0.13-280)	3.10 (0.13-32.25)	9.14 (0.13-100)	14.34 (0.13-100)	3.94 (1.10-8.45)	0,26	*0,06*
Median prostate volume, cc (range) ***	71 (20-263)	70 (20-263)	75 (21-250)	74.5 (21-194)	80 (40-250)	0,63	*0,07*
Median PSA density, value (range) ***	0.050 (0.003-4.667)	0.048 (0.003-0.205)	0.055 (0.006-4.667)	0.111 (0.006-4.667)	0.098 (0.009-1.670)	0,95	*0,30*
Pre-HoLEP mpRM performed, n° of pts (%) **	43 (29.3%)	23/113 (20.4%)	20/34 (58.8%)	12/16 (75%)	8/18 (44.4%)	<0.01	*0,32*
Positive mpRM, n° of pts (%) *	30 (20.4%)	13/113 (11.5%)	17/34 (50%)	11/16 (68.7%)	6/18 (33.3%)	<0.01	*0,17*
Median mpRM PI-RADS score, value (range) ***	3 (1-5)	3 (1-5)	3.5 (1-5)	4 (1-5)	3 (3-5)	0,98	*0,31*
Lesions from positive mpRM, n° (range) ***	1 (1-3)	1 (1-2)	1 (1-3)	1 (1-3)	1 (1-2)	0,94	*0,92*
Pre-HoLEP biopsy, n° (%) **	26 (17.7%)	7/113 (6.2%)	18/34 (52.9%)	16/16 (100%)	2/18 (11.1%)	<0.01	*<0.01*
negative, n° (%)	11 (7.5%)	7/113 (6.2%)	2/34 (5.9%)	0	2/18 (11.1%)	0,95	*<0.01*
positive, n° (%)	15 (10.2%)	0/113 (0%)	16/34 (47.1%)	16/16 (100%)	0/18 (0%)	<0.01	*0,12*
≤ GG1, n° (%)	11 (7.5%)	–	9/34 (26.5%)	9/16 (56.2%)	–	–	-
≥ GG2, n° (%)	4 (2.7%)	–	7/34 (20.6%)	7/16 (43.8%)	–	–	-
HoLEP positive histopathology report **							
total	23 (15.6%)	–	25/34 (73.5%)	7/16 (43.8%)	18/18 (100%)	–	*<0.01*
≤ GG1 (included ASAP, HGPIN, STUMP), n° (%)	19 (12.9%)	–	19/34 (55.9%)	4/16 (25%)	15/18 (87.5%)	–	*<0.01*
≥ GG2, n° (%)	4 (2.7%)	–	6/34 (17.6%)	3/16 (18.8%)	3/18 (12.5%)	–	*0,46*
3-months post-HoLEP median tPSA ng/ml (range) ***	0.50 (0.03-7)	0.50 (0.03-7)	1.29 (0.16-6.47)	2.04 (0.33-6.47)	0.53 (0.16-2.25)	0,99	*0,01*
12-months post-HoLEP median tPSA ng/ml (range) ***	0.50 (0.00-3.30)	0.50 (0.10-3)	0.71 (0.00-3.30)	1.07 (0.00-3.30)	0.35 (0.16-1.30)	0,38	*0,01*

**PIRADS ≥3, **Chi-square test, ***T-student test.*

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TABLE 2 Patients with PCa prior-HoLEP (group 1).

Patients	Age	Clinical history	Histopathology at HoLEP	Total PSA at T0	Total PSA at 3-months	Total PSA at 6-months	Total PSA at 12-months	Treatment
1	67	GG1	Negative	9,70	0,68	0,75	0,81	AS
2	62	GG1 in AS	Negative	8,30	2,40	2,30	2,40	AS
3	68	GG1 in AS	ASAP	7,73	1,41	1,10	1,00	AS
4	78	GG3 in LHRH	Negative	0,13	0,33	0,10	0,10	LHRH
5	61	GG1 in AS	HG-PIN	8,27	0,80	0,70	0,70	AS
6	84	GG2	Negative	4,10	6,47	0,90	0,90	RT
7	72	GG2	Negative	17,60	0,40	0,50	0,50	AS
8	81	GG2	Negative	7,95	1,00	1,10	1,00	AS
9	66	GG1 in AS	GG1 pT1b	9,40	1,50	1,50	1,50	AS
10	70	GG1 in AS	Negative	7,70	1,00	0,60	0,60	AS
11	62	GG1 in AS	Negative	3,99	1,00	0,60	0,60	AS
12	82	GG1	GG1 pT1b	29,00	5,10	4,10	3,30	AS
13	53	GG5 in LHRH	GG5	100,00	6,47	6,10	1,00	Docetaxel
14	54	GG1 in AS	Negative	7,70	1,50	1,80	1,80	AS
15	81	GG4	GG4	1,90	0,50	0,30	0,30	RT
16	76	GG3	GG3	6,00	2,10	0,60	0,60	RT

AS, active surveillance; RT, radiotherapy.

management of obstructed patients with an abnormal tPSA and/or a suspect digital rectal exam (25).

Preoperative tPSA, PSA density, small prostate volume, age, and several other clinical factors have been suggested as predictors of iPCa; however, PSA density and increased age are considered independent predictors of iPCa (26, 27).

The reported wide range of iPCa rates after HoLEP (8.1 to 40%) may be influenced by the different baseline characteristics of evaluated patients (28). Moreover, by including only patients with raised PSA and/or abnormal DRE, the different populations may have been affected by selection bias (29, 30). PSA-guided approaches to predict iPCa in LUTS patients with very large prostates are not accurate. In a recent study, Magistro et al. demonstrated that the overall detection rate of iPCa showed no difference between patients with high (>10 ng/ml) and low (<10 ng/ml) PSA before surgery (31).

The HoLEP is a modern, non-invasive, effective technique to manage BOO due to BPH; it guarantees safe, long-term functional results, as shown by many reports, including a randomized trial (32). Unlike other BPH laser surgeries with vaporization effects, the HoLEP allows for endoscopic enucleation of the prostate to obtain a histological specimen, which may sometimes reveal iPCa. Moreover, HoLEP is associated with more favorable long-term functional outcomes than monopolar and bipolar TURP (33–36).

An accurate preoperative diagnostic investigation is required when PCa is suspected and BPH surgery is being considered.

Herlemann et al. (28) reported a rate of 40% of iPCa in patients treated with HoLEP, despite a negative preoperative prostate biopsy: the authors highlighted the need for a different path in selected patients in terms of pre-surgical diagnosis.

Elkoushy et al. (18) reported the AS as the usual oncological management of iPCa (31, 32); however, active treatment (radical prostatectomy, or RT) is sometimes required, despite a negative impact on the patient's quality of life (37).

Radical prostatectomy, RT, HT, and AS/WW are options for the clinical management of iPCa after HoLEP. Despite the fact that AA is appropriate for most patients, an optimal protocol has not yet been established. Moreover, radical prostatectomy is another feasible choice, but it is hampered by the risks of urinary incontinence and erectile dysfunction related to surgery. Furthermore, the results of RT after HoLEP require additional research to be validated (22).

Gellhaus et al. reported a rate of urinary incontinence of about 27% in patients treated with RARP after HoLEP; moreover, the authors reported similar positive margins and biochemical recurrence rates in patients without a previous history of BPH surgery. The authors highlighted that mpMRI should be considered to rule out PCa in selected cases, especially in young patients with high PSA density and a negative standard prostate

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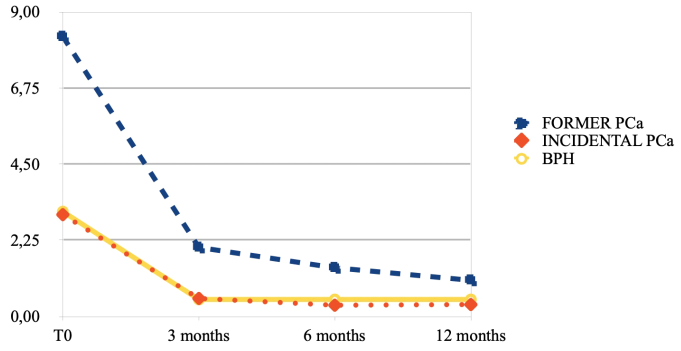
TABLE 3 Patients with iPCa post-HoLEP (group 2).

Patients	Age	Clinical history	Histopathology at HoLEP	Total PSA at T0	Total PSA at 3-months	Total PSA at 6-months	Total PSA at 12-months	Treatment
1	72	–	GG1 pT1a	1,10	0,22	0,20	0,20	AS
2	74	–	ASAP	2,91	0,16	0,17	0,30	AS
3	66	–	GG2 Gle4 (5%)	1,49	0,20	0,20	0,20	AS
4	73	–	STUMP	5,49	0,16	0,20	0,20	AS
5	79	–	ASAP	5,71	0,20	0,20	0,20	AS
6	63	–	HG-PIN	4,29	1,00	1,00	0,90	AS
7	67	–	GG1 pT1a	1,10	0,60	0,17	0,20	AS
8	82	–	GG1 pT1a	2,40	0,57	0,50	0,60	AS
9	76	–	GG1 pT1a	1,49	0,48	0,50	0,50	AS
10	77	–	GG1 pT1a	2,53	0,27	0,30	0,30	AS
11	58	–	HG-PIN + ASAP	8,45	0,60	0,22	0,40	AS
12	72	–	HG-PIN	1,80	0,30	0,20	0,17	AS
13	67	–	GG1 pT1a	1,10	0,27	0,20	0,20	AS
14	67	–	GG1 pT1a	3,20	0,27	0,30	0,30	AS
15	66	–	GG1 pT1a	2,00	0,20	0,16	0,16	AS
16	76	–	GG5	3,10	0,29	0,17	0,17	AS
17	69	ASAP + PIN3	GG1 pT1a + PIN3	14,50	1,50	1,20	1,30	AS
18	61	ASAP +HGPIN	GG3	8,27	2,25	0,05	0,00	RARP GG1 pT2 pN0 R0 LV0

AS, active surveillance.

biopsy who are candidates for HoLEP. The authors concluded that this (novel) approach might lead to low iPCa rates (38).

Age, preoperative tPSA, small prostate volume, PSA density, and preoperative biopsy are among the most significant evaluated and established iPCa predictors. In univariate and multivariate analysis, Bhojani et al. reported only age as an independent iPCa predictive factor (17), whereas in their regression analyses Herlemann et al. (28) and Elkoushy et al.



FORMER PCa	8,27	2,04	1,44	1,07
INCIDENTAL PCa	3,01	0,53	0,33	0,35
BPH	3,10	0,50	0,50	0,50

FIGURE 1
The trend of total PSA among BPH and PCa patients.

(18) highlighted only PSA density (cut-off values of 0.15 ng/mL/cc and 0.092 ng/mL/cc, respectively).

In our study, by comparing the baseline characteristics (age, median tPSA, median prostate volume, and median PSA density) of the two groups, we reported no statistically significant differences due to the homogeneity of the two groups.

In particular, by comparing the tPSA of the two groups, we did not observe statistically significant differences by comparing their pre- and post-HoLEP values. Even though the tPSA alone should not be considered exhaustive in terms of oncological follow-up, it surely represents the first parameter to be considered for further PCa assessment.

Tominaga et al. described how postoperative tPSA gradually increased in a cohort of 25 patients who underwent HoLEP for BPH and with iPCa (13). Differently, Elmansy et al. showed how the PSA velocity was statistically higher in iPCa patients when compared to BPH patients (1.28 *vs.* 0.13 at 1-year with a p-value <0.022, and 2.4 *vs.* 0.09 at three-years follow-up with a p-value of <0.001) (39). In our experience, tPSA values were stable over time in both groups, and we did not observe any statistically significant differences between groups or sub-groups, even with a one-year follow-up.

The performance of HoLEP did not preclude subsequent treatments in the case of iPCa; moreover, in our experience, even patients with a previous clinically significant PCa diagnosis underwent HoLEP. As reported by Becker et al. (40), the HoLEP alleviated BOO symptoms without affecting oncological outcomes, suggesting that this endoscopic approach is effective, feasible, and safe for patients with LUTS due to BPH and concurrent PCa who are unfit for radical prostatectomy or have no indication for the procedure. Moreover, in a trend toward increasingly personalized treatment, the AS or WW approaches have been considered based on the clinical characteristics of each patient: the key to the decision-making process should always consist of a shared process between the physician and the patient.

The main limitations of this study were the retrospective analysis, the non-randomized study, the small sample size, the small iPCa group, the lack of sample size calculation, the lack of matching of the two analyzed groups, and the short follow-up.

Conclusions

Men with low-risk PCa on AS can be safely treated with HoLEP to relieve LUTS due to BPH without compromising oncological outcomes. The postoperative follow-up with tPSA and mpMRI is necessary to identify PCa progression that might require further active treatment. Further research is necessary in order to define the optimal AS protocol and to assess the long-term cancer-specific outcomes.

In patients with a suspicion of PCa who are candidates for HoLEP, PCa screening with tPSA and prostate mpMRI is recommended to reduce iPCa as much as possible (37), given that more than 10% of patients might receive an iPCa diagnosis. After HoLEP for BPH, patients with iPCa might only be monitored with tPSA and/or prostate mpMRI; moreover, no further active treatment for PCa is precluded.

Surely, further investigations with longer follow-ups are needed to assess the durability and success of these approaches.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Veneto Institute of Oncology (IOV) IRCCS. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: LD, AP and AC. Methodology: LD, PC and AC. Validation: AC, AA, AP, GB and MM. Formal analysis: LD. Investigation: AC, AM, PC, EM and DD. Data curation: LD. Writing—original draft preparation: LD, PC, EE and DD. Writing—review and editing: AC. Visualization: AC, GB and MM. Supervision: AP. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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