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ORIGINAL ARTICLE

Outcomes of an enhanced recovery after radical cystectomy program in a prospective multicenter study: compliance and key components for success

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Abstract

Objective To investigate the effect of an Enhanced Recovery After Surgery (ERAS) program on complications and length of stay (LOS) after radical cystectomy (RC) and to assess if the number and type of components of ERAS play a key role on the decrease of surgical morbidity.

Materials and methods We analyzed the data of 277 patients prospectively recruited in 11 hospitals undergoing RC initially managed according to local practice (Group I) and later within an ERAS program (Group II). Two main outcomes were defined: 90-day complications rate and LOS. As secondary variables we studied 90-day mortality, 30-day readmission and transfusion rate.

Results Patients in Group II had a higher use of ERAS measures (98.6%) than those in Group I (78.2%) ($p < 0.05$). Patients in Groups I and II experienced similar complications (70.5% vs. 66%, $p = 0.42$). LOS was not different between Groups I and II (12.5 and 14 days, respectively, $p = 0.59$). The risk of having any complication decreases for patients having more than 15 ERAS measures adopted [RR = 0.815; 95% confidence interval (CI) 0.667–0.996; $p = 0.045$]. Avoidance of transfusion and nasogastric tube, prevention of ileus, early ambulation and a fast uptake of a regular diet are independently associated with the absence of complications.

Conclusions Complications and LOS after RC were not modified by the introduction of an ERAS program. We hypothesize that at least 15 measures should be applied to maximize the benefit of ERAS

Keywords Urothelial cancer · Bladder cancer · ERAS · Radical cystectomy

Abbreviations

RC	Radical cystectomy
ERAS	Enhanced recovery after surgery
PRORAC	Programa de Recuperacion Acelerada en Cistectomia
SLP	Site's local practice
LOS	Length of stay
Hb	Hemoglobin
CCI	Charlson Comorbidity Index
TURB	Transurethral resection of the bladder
QOL	Quality of life
RCT	Randomized clinical trial
RR	Relative risk
IQR	Interquartile range
CI	Confidence interval
IRB	Institutional review board
MIS	Minimally invasive surgery

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Introduction

Radical cystectomy (RC) remains a surgical procedure with a major impact on the morbidity and mortality of patients with complications rate ranging from 20 to 57% [1]. Several initiatives have been undertaken in recent years to minimize the adverse effects of RC such as centralization policies [2] and improved intraoperative anesthetic care [3].

Enhanced recovery after surgery (ERAS) protocols have been used in colorectal surgery since 2012 and have been applied in urology, particularly to RC [4, 5]. One problem with ERAS regimens is their complexity since they comprise in excess of 20 components during the preoperative, intraoperative and postoperative courses of RC, in which health- and non-health-related personnel are involved.

In addition, the evidence behind the use of ERAS for RC is still limited. The only randomized clinical trial by Karl et al. [6] showed improved quality of life and a reduced incidence of wound healing disorders, fever and deep vein thrombosis for patients in whom a partial ERAS approach was applied. This trial did not implement the full protocol of ERAS with its 20 + components as we understand it today and does not provide details of the surgical procedure such as the number of nodes retrieved, operative time or the use of minimally invasive surgery (MIS).

A recent meta-analysis concludes that ERAS after RC reduces complications and length of stay (LOS). However, the authors acknowledge that these conclusions are only supported on observational studies mostly using historical controls [7].

The main objectives of the study were the incidence of complications and LOS. In addition, we report the assessment of number and type of components of the ERAS program based on the only prospective multicenter study to date.

Materials and methods

During November 2014 to February 2017, we launched the *Programa de Recuperación Acelerada en Cistectomía* (PRORAC) study which was registered by the Spanish Agency on Drugs and Medical Devices (AEMPS), and also in https://www.clinicaltrials.gov (NCT02328417) and monitorized by Effice (Contract Research Organization, Madrid, Spain).

This research was performed in 11 public hospitals in Madrid (Table 1S) after approval by each Institutional Review Board (IRB). All patients included in the present study gave written informed consent.

For each participating hospital, the acceptance of the study was signed by the Urology and Anesthesiology chairperson and data were entered into a web-based database. The content of the ERAS program to be applied was discussed and accepted after consensus was reached among representatives of both specialties with special instructions to have the nutrition, transfusion and nursing professionals involved (Table 2S).

Study design

Due to the complexity of the ERAS approach and the fact that some hospitals had already incorporated into their practice one or several of the ERAS components, we defined two different groups of patients consecutively operated during the recruitment time. From November 2014, RC submitted patients were assigned to Group I and managed according to the site's local practice (SLP) at the time of entry into the study. Subsequently, from December 2015 to February 2017, all patients at all sites were entered into Group II (ERAS) and a local ERAS coordinator enforced the implementation of every ERAS component to each patient recruited.

Study inclusion criteria were consecutively applied to all patients who underwent RC for bladder cancer. No exclusion criteria were applied.

Sample size calculation

A previous analysis of the administrative discharge database of the 350 RCs performed in the entire region of Madrid in 2011 showed a complication rate of 75% and a mean LOS of 21.6 (SD 16.5 days). We considered as clinical relevant a 20% and a 30% reduction in the complications rate and LOS, respectively. With a two-sided type I error of 0.05 and a power of 80%, the overall sample size needed was 188 subjects.

Because of the multicenter nature of the study accounting the recruitment of Group I allowed some sites to enter more patients than initially needed into this Group. This was communicated to the central IRB and we were given written consent to recruit a similar number of cases for Group II. The IRB considered that we were not adding any risk to patients in Group II.

Statistical analysis

Univariate analysis was carried out and differences in qualitative variables were studied with chi-squared or Fisher's exact test. Quantitative variables were analyzed with two-sample t test or two-sample Wilcoxon test, depending on the data distribution.

Our primary analysis focused on the linear effect of number of ERAS components on complication incidence, LOS and 90-day mortality. In addition, the number of ERAS components was grouped into quartiles with the last two

combined due to the low number of cases: < 10, 10–14 and ≥ 15 ERAS components. We estimated the effects as risk ratios using Poisson regression models [8]. Risk ratios were unadjusted and also adjusted by age, gender, Charlson Comorbidity Index (CCI), T stage and minimally invasive surgery (MIS).

All analyses were performed using SPSS 17® and STATA 13®. All tests were two sided and *p* values less than 0.05 were considered statistically significant.

Results

In all, 277 patients were recruited during the study period in the 11 participating hospitals: 130 patients in Group I (SLP) and 147 in Group II (ERAS). Patient characteristics for Groups I and II are shown in Table 1. Mean age was 68.4 and 70.3 years ($p = 0.065$) for Groups I and II, respectively. No differences were found for ASA and CCI, neoadjuvant chemotherapy, clinical stage or grade, preoperative hemoglobin or body mass index. Pathological stage after cystectomy was equivalent in both groups with an overall rate of pT0 = 12.6%, $pT_{a\text{-}1} = 15.5$ and $pT_{2–4} = 70.1$.

From the surgical perspective (Table 2), both groups were equally managed, 58.8% of the RCs having a MIS approach with no difference ($p = 0.58$) for Groups I and II. Likewise, no difference was detected in the type of urinary diversion or total operative time. Cystoprostatectomy was performed faster in Group II (mean 100 min) than in Group I (mean 120 min, $p < 0.001$). Length of the incision was the same in both groups (median 12 cm).

The median number of nodes retrieved was larger in Group II (14) than in Group I (12, $p = 0.031$) and N status

Table 1 Clinical demographics

	Overall *n* = 277 (%)	Group I *n* = 130 (%)	Group II *n* = 147 (%)	*p* value
Age (mean, SD)	69.45 ± 8.87	68.4 ± 9.41	70.39 ± 8.29	0.065
BMI (mean, SD)	27.57 ± 4.21	28.04 ± 4.4	27.15 ± 4	0.087
Sex				
Male	235 (84.8)	108 (83.1)	127 (86.4)	0.442
Female	42 (15.2)	22 (16.9)	20 (13.6)	
CCI				
0	66 (24.4)	34 (26.8)	32 (22.4)	0.225
1–2	120 (44.4)	60 (47.2)	60 (42)	
≥ 3	84 (31.1)	33 (26)	51 (35.7)	
ASA status				
1	8 (2.9)	7 (5.4)	1 (0.7)	0.069
2	139 (50.4)	64 (49.2)	75 (51.4)	
3	120 (43.5)	53 (40.8)	67 (45.9)	
4	9 (3.3)	6 (4.6)	3 (2.1)	
Neoadjuvant chemotherapy	61 (22.2)	26 (20.3)	35 (23.8)	0.486
Previous treatment				
Insulin	74 (26.8)	36 (27.9)	38 (25.9)	0.7
Statins	119 (43)	49 (37.7)	70 (47.6)	0.096
Antithrombotics	85 (30.8)	35 (27.1)	50 (34)	0.217
Hypertension	155 (56)	68 (52.3)	87 (59.2)	0.219
TURB T stage				
T1	48 (17.6)	23 (18.3)	25 (17.1)	0.807
T2	205 (75.4)	93 (73.8)	112 (76.7)	
T3–T4	19 (7)	10 (7.9)	9 (6.2)	
TURB grade (WHO 2004)				
Low grade	4 (1.5)	0	4 (2.8)	0.129
High grade	256 (98.5)	118 (100)	138 (97.2)	
Preoperative Hb g/dl (mean, SD)	12.62 ± 2	12.6 ± 1.99	12.64 ± 2.02	0.873
Preoperative albumin g/dl (mean, SD)	4.03 ± 0.78	3.91 ± 0.61	4.13 ± 0.89	0.082

SD standard deviation, *TURB* transurethral resection of the bladder, *Hb* hemoglobin, *IQR* interquartile range, *CCI* Charlson Comorbidity Index, *ASA* American Society of Anesthesiology

Table 2 Surgical features

	Overall $n = 277$ (%)	Group I $n = 130$ (%)	Group II $n = 147$ (%)	p value
RC approach				
Open	114 (41.2)	54 (41.5)	60 (40.8)	0.904
Laparoscopic	153 (55.2)	72 (55.4)	81 (55.1)	
Robotic	10 (3.6)	4 (3.1)	6 (4.1)	
Diversion approach				
Open	267 (96.4)	127 (97.7)	140 (95.2)	0.508
Laparoscopic	9 (3.2)	3 (2.3)	6 (4.1)	
Robotic	1 (0.4)		1 (0.7)	
Type of diversion				
Ureteroileostomy	207 (75)	95 (73.1)	112 (76.7)	0.591
Orthotopic neobladder	36 (13)	17 (13.1)	19 (13)	
Heterotopic continent diversion	1 (0.4)	0	1 (0.7)	
Other	32 (11.6)	18 (13.8)	14 (9.6)	
Incision				
Supra–subumbilical	67 (24.5)	37 (28.9)	30 (20.7)	0.289
Subumbilical	165 (60.4)	73 (57)	92 (63.4)	
Umbilical–subumbilical	41 (15)	18 (14.1)	23 (15.9)	
RC time (median, IQR)	118.5 (80–150)	120 (97.5–160)	100 (70–142.5)	**< 0.001**
Lymphadenectomy time (median, IQR)	60 (40–90)	60 (40–87)	60 (40–90)	0,372
Diversion time (median, IQR)	100 (78–135)	95 (80–130)	100 (77.25–143.75)	0.504
Surgery time (median, IQR)	275 (220.75–350)	290 (230.5–345)	275 (215–350)	0.552
Length of incision (median, IQR)	12 (9–17)	13 (9–18)	12 (9–16)	0.488
Total fluids (L) (median, IQR)	2.5 (1.8–3.5)	3 (2–4)	2.2 (1.5–3)	**< 0.001**
Blood loss (mL) (median, IQR)	500 (300–800)	600 (368.75–1000)	500 (300–700)	**< 0.001**

RC radical cystectomy, *IQR* interquartile range

was also different between groups (Nx = 13.2% in Group I and 4.1% in Group II, $p = 0.047$).

Table 3 depicts the use of each ERAS component in Groups I (SLP) and II (ERAS). As anticipated, in this contemporary study, all measures were used to some extent (13.8–77.9%) in Group I. In contrast, because of the complexity of the program, any measure was fully implemented in every patient of Group II. The adoption of each of the ERAS components was significantly higher in Group II with a mean range of use of 78.2–98.6%. The median number of ERAS components was 10 (IQR: 9–12) in group I and 19 (IQR: 17–21) in group II ($p < 0.001$).

Patients in Groups I and II experienced similar complication rates after RC (70.5% vs. 66%, RR = 0.935, CI 95% 0.796–1.099, $p = 0.417$).

Also, no difference was found when breaking down the complications by Clavien grade (45.4% and 46.3% for Clavien 1–2, and 24.6% and 19.7% for Clavien 3–5 for Groups I and II, respectively).

Even though the patients in Group II experienced shorter time of recovery of bowel sounds and passing flatus, this did not translate into an earlier time of passing feces or tolerance of regular diet. This could explain that median LOS was not different between Groups I and II (12.5 and 14 days, respectively, $p = 0.592$).

The 90-day death rate was lower for Group II compared to Group I (2.04% and 5.38%, respectively), although this difference was not statistically different ($p = 0.198$). The rate of re-intervention and visits to the emergency ward at 30 days were also similar in both groups (I and II): 15.4% and 12.9% ($p = 0.557$) and 36.7% and 34.6% ($p = 0.725$), respectively.

There was a lower rate of transfusions 37.7% and 26.5% ($p = 0.046$) but a higher incidence rate of wound infection in Group II (10% compared to 26.5% in Group I, $p < 0.001$).

For the overall study population, the number and type of measures applied for each individual are related to risk of complications, 90-day mortality and LOS using regression model with the number of measures as continuous variable (Table 4). Postoperative measures were associated with a lower risk of complications (RR = 0.954, $p = 0.019$), 90-day mortality rate (RR = 0.733, $p = 0.015$) and LOS (RR = 0.961, $p < 0.001$).

Similarly, we assessed in all patients the impact of the number of ERAS measures (< 10, 10–14, ≤ 15) on

Table 3 Measures applied in each group

	Group I, *n* (%)	Group II, *n* (%)
Preoperative		
1. Training on urostomy care/self-catheterization	85 (65.4)	135 (92.5)
2. Preoperative exercise and change habits	28 (21.5)	131 (89.7)
3. Anemia correction	86 (68.3)	124 (88.6)
4. Nutritional support	74 (77.9)	124 (96.1)
5. No oral bowel preparation	86 (66.2)	144 (98.6)
6. Carbohydrate load	21 (16.2)	116 (79.5)
7. Preoperative fasting (clear fluids to 2 h, solids to 6 h)	33 (25.4)	128 (87.7)
8. Preanesthesia drugs (No benzodiazepines)	71 (54.6)	128 (87.7)
9. Single-dose antibiotic prophylaxis	84 (64.6)	144 (98)
Intraoperative		
10. Skin preparation	95 (73.1)	133 (90.5)
11. Reduction of transfusion	66 (50.8)	119 (81)
12. Restriction of i.o. fluids	35 (26.9)	121 (82.3)
13. Preventing i.o. hypothermia	119 (91.5)	144 (99.3)
14. Incision closure with running monofilament (4:1)	75 (57.7)	141 (95.9)
Postoperative		
15. Long-term DVT prophylaxis	83 (64.3)	137 (93.2)
16. No NGT	50 (38.5)	128 (87.1)
17. Prevention of postop ileus (no morphics, gum chewing)	43 (33.1)	115 (78.2)
18. Prevention of nausea–vomiting (dexametasone/droperidol)	71 (54.6)	136 (92.5)
19. Postoperative analgesia	67 (51.5)	129 (87.8)
20. Early deambulation	46 (35.4)	127 (86.4)
21. Early oral fluids	18 (13.8)	117 (80.1)

There were statistically significant differences ($p < 0.05$) with higher adherence to the application of all the measures in Group II

DVT deep vein thrombosis, *NGT* nasogastric tube

Table 4 Risk ratio estimated with regression models using a number of measures applied as continuous variable, according to the stage of application

Outcome	Stage of application	RR unadjusted	95% CI		*p* value	RR adjusted	95% CI		*p* value
Complication	All	0.989	0.973	1.006	0.204	0.987	0.970	1.004	0.13
	Preoperative measures	0.993	0.956	1.031	0.707	0.991	0.953	1.030	0.635
	Intraoperative measures	0.974	0.922	1.030	0.364	0.970	0.915	1.029	0.315
	Postoperative measures	0.963	0.927	1.000	**0.048**	0.954	0.918	0.992	**0.019**
90-Day mortality	All	0.862	0.747	0.994	**0.041**	0.867	0.748	1.005	**0.058**
	Preoperative measures	0.791	0.622	1.007	0.057	0.824	0.637	1.064	0.137
	Intraoperative measures	0.663	0.44	0.999	**0.05**	0.636	0.353	1.146	0.132
	Postoperative measures	0.782	0.638	0.959	**0.018**	0.733	0.571	0.941	**0.015**
LOS	All	0.995	0.989	1.001	0.1	0.995	0.989	1.001	0.094
	Preoperative measures	1.011	0.997	1.024	0.129	1.010	0.996	1.025	0.163
	Intraoperative measures	1.007	0.987	1.027	0.507	1.012	0.990	1.034	0.295
	Postoperative measures	0.963	0.950	0.975	**< 0.001**	0.961	0.948	0.974	**< 0.001**

Adjusted by age, gender, Charlson, T stage and minimally invasive surgery

RR relative risk, *CI* confidence interval, *LOS* length of stay

Table 5 Risk ratio of number of ERAS component grouped in outcome variables

	Number of measures	*n*	RR unadjusted	95% CI		*p* value	RR adjusted	95% CI		*p* value
Complications	< 10	41	1 (ref.)	–	–	–				
	10–14	103	0.816	0.666	0.998	**0.048**	0.887	0.724	1.087	0.248
	≥ 15	132	0.805	0.664	0.976	**0.027**	0.815	0.667	0.996	**0.045**
90-Day mortality	< 10	42	1 (ref.)	–	–	–				
	10–14	103	0.163	0.033	0.81	**0.027**	0.225	0.053	0.962	**0.044**
	≥ 15	132	0.191	0.047	0.767	**0.02**	0.224	0.037	1.343	0.102
LOS	< 10	37	1 (ref.)	–	–	–				
	10–14	102	1.109	1.015	1.213	**0.023**	1.236	1.125	1.358	**0.000**
	≥ 15	131	1.006	0.922	1.098	0.891	1.054	0.961	1.157	0.263

Adjusted by age, gender, Charlson, T stage and minimally invasive surgery

RR relative risk, *CI* confidence interval, *LOS* length of stay

complications, 90-day death and LOS. In the adjusted analysis (Table 5), we show that the risk of having any complication decreases for patients having more than 15 measures adopted (RR = 0.815, $p = 0.045$).

Multivariate analysis (Table 6) reveals that the avoidance of transfusion and nasogastric tube, preventive measures of ileus, early ambulation and fast uptake of regular diet are associated with the absence of complications after adjusting for age, sex, CCI, T stage and MIS.

Time to bowel recovery and mobilization as well as the rate of complications sorted out by type are shown in Supplementary material (Tables 3S and 4S).

Discussion

RC stands out as the abdominal operation with a high rate of complications for which ERAS programs may be of value [1, 9–13]. ERAS programs were initially developed in colorectal surgery to reduce both risk of complications and LOS. A recent meta-analysis of ERAS in colorectal surgery including 13 RCTs concludes a RR of 0.66 (95% CI 0.54–0.80) for complications in favor of ERAS [14]. However, when using the GRADE methodology to assess the quality of each study included, the authors rated with moderate level of quality of evidence for the positive effect on LOS and perioperative morbidity. In addition, the authors point out two important limitations. First, the compliance and the degree of application of the different components of ERAS are seldom stated and second, there is no currently available evidence on

Table 6 Multivariate analysis for postoperative measures including all patients

	n	Complications incidence (%)	RR adjusted	95% CI		*p* value
Restriction of transfusion						
No	92	79	0.795	0.673	0.940	**0.007**
Yes	185	62				
Avoidance of NGT						
No	99	77	0.813	0.691	0.956	**0.012**
Yes	178	63				
Early mobilization						
No	104	77	0.831	0.707	0.975	**0.024**
Yes	173	62				
Early oral fluids						
No	141	76	0.791	0.666	0.940	**0.008**
Yes	135	60				

Adjusted by age, gender, Charlson, T stage and minimally invasive surgery

RR relative risk, *CI* confidence interval, *NGT* nasogastric tube

which of the different measures play an important role in the achievement of the clinical benefit. These observations may apply and deserve further investigation to the RC setting.

Our contemporary prospective multicenter study aims to add to current knowledge the value of ERAS in RC.

The benefit of ERAS for RC has been previously explored. In 2014, an RCT found an improved quality of life (primary end point) and reduction of morbidity for patients submitted to an early recovery program [6]. However, the components of their program differ markedly from the current understanding of ERAS especially due to a lack of intraoperative measures. Besides, compliance with the implementation of each component was not assessed.

More recently, a meta-analysis of ERAS after RC reports a RR of complications 0.85 (95% CI 0.74–0.97) in favor of ERAS [7]. However, no randomized clinical trials (RCT) were included in the analysis and the authors acknowledge the potential bias due to the observational nature of the studies, mostly using historical controls.

A single-center prospective study by Pang et al. [15] compares 393 patients on ERAS program with 60 non-ERAS patients, finding a reduction of 10 days in LOS (8 vs 18, $p = 0.001$) in favor of ERAS. Patients on ERAS had fewer readmissions than those without ERAS (15% vs. 25%, $p = 0.04$). However, no information on the impact of ERAS on the rate of complications is provided. Similarly, compliance with each ERAS component is not provided and no assessment of the individual impact of each measure is performed.

We believe that a contemporary RCT of zero-ERAS versus full-ERAS is not feasible because some of the measures have become widely adopted. In addition, it is not realistic to apply every measure to every individual patient. In our study, compliance with the implementation of ERAS was found to be reasonable for every one of the 21 measures. For the SLP stage of the study (Group I), the use of each component ranges between 13.8 and 91.5% and for the ERAS phase (Group II) these values increased to 78.2–99.3%.

Our study failed to show a benefit in the use of ERAS to reduce complications, LOS or mortality as opposed to others [6, 7, 15–17]. This may be partly due to the fact that we used as a comparator a contemporary series (Group I) with a LOS of 12.5 days.

Although the observed reduction in 90-day mortality of Group II (2.04%) compared to Group I (5.38%) did not reach statistical significance, such a reduction if true would be clinically important. A similar finding is reported by Pang [15] with 90-day mortality of 2.1% for the ERAS cohort and 5% for non-ERAS group ($p > 0.60$).

We have explored the relative value of each component to the surgical outcomes as well as the minimum number and category of measures that might provide a potential benefit by merging both groups. We believe that our study allows us to do so due to the close monitoring of the compliance throughout the entire study.

We hypothesize that the adoption of more than 15 components of ERAS achieves a reduction in complications and importantly, clinicians implementing this type of program should place special effort in the avoidance of both transfusion and nasogastric tube, prevention measures of ileus, early ambulation and a fast uptake of a regular diet among those 15 components.

An ERAS program encompasses measures along the entire operative procedure (pre-, intra- and postoperative); it is of value to ascertain which time period for implementing measures achieves a greater clinical benefit. Our study shows that the postoperative components of the ERAS program decrease the risk of complications, 90-day death rates and LOS (Table 4). Clearly, a specifically designed trial is required to confirm this finding.

Our study is not without limitations. The role of the professional team has not been taken into consideration. Admittedly, the role of the surgeon, anesthetist and nursing staff does make an impact that is difficult to quantify. A higher case frequency per surgeon or hospital also leads to better surgical outcomes and in our study, all hospitals performed less than 50 RC per year. Notwithstanding this, the mortality rate, operative time and number of nodes retrieved are comparable to current surgical standards [6, 15]. Besides, not being a randomized trial, the existence of potential bias cannot be ruled out.

Conclusions

Our study does not support the use of ERAS to reduce complications and LOS after RC. We hypothesize that at least 15 measures of the ERAS protocol should be applied. Postoperative measures are crucial and particularly avoidance of transfusion and nasogastric tube, prevention measures of ileus, early postoperative ambulation and fast uptake of a regular diet. These findings might need a specifically designed trial. Compliance with each individual component of an ERAS program should be described for a proper assessment of the protocol.

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Author contributions CL: project development, manuscript writing, and data collection. AG: data collection and manuscript editing. VH: manuscript editing and data collection. GFC: manuscript editing and data collection. JP: data collection. LA: data collection. AT: data collection. CH: data collection. MM: data collection. DS: data collection. CGE: data collection. AH: data collection. FO: data collection. MSC: data collection. JC: data collection. IC: data collection. EM: data collection. IR: data collection. JFA: data collection. LL: data collection.

CB: data collection. MSE: data collection. JB: data collection. MT: data collection. LD: data collection. VMC: data collection. EPF: data analysis. LFR: data collection. SGDV: data collection.

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the present study involving human participants were in accordance with the ethical standards of the Institutional Review Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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