Article

The Impact of COVID-19 on Erectile Dysfunction Recovery after Nerve-sparing Robot-assisted Radical Prostatectomy Procedures Performed by a Single Surgeon : A Retrospective Study

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Abstract: Purpose: The COVID-19 pandemic, triggered by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in over 160 million infections and 3.5 million fatalities worldwide. Evidence of SARS-CoV-2 presence in the highly vascularized penile tissue and the established correlation between COVID-19 and subsequent erectile dysfunction (ED) has emerged. Robot-assisted radical prostatectomy (RARP) is a popular procedure for prostate cancer because of its reliability and swift recovery rate. However, the ED prevalence post-surgery is believed to be comparable to open surgery, and postoperative ED significantly affects the patient's quality of life. Our study aimed to explore the effect of COVID-19 on ED recovery in patients undergoing bilateral nerve preservation during RARP. **Materials and Methods:** We conducted a retrospective study on 85 patients who underwent bilateral nerve-sparing RARP (nsRARP) at our institution between December 2017 and May 2021. Chart reviews and the International Index of Erectile Function-5 (IIEF-5) questionnaire facilitated the analysis. Our objective was to contrast ED recovery after surgery between SARS-CoV-2–infected and non-infected patients using preoperative IIEF-5 scores and scores at 6, 12, and 24 months post-surgery. We defined successful ED recovery as an IIEF-5 score of 17 or higher and successful sexual intercourse. We also compared ED recovery rates between the two groups, regardless of the timing of COVID-19 diagnosis. IBM's SPSS version 18.0 assisted in the statistical analysis, with Fisher's exact test and chi-square test used for comparing categorical variables. Independent t-tests determined mean differences between baseline and postoperative IIEF-5 scores. A p-value less than 0.05 was considered statistically significant. **Results:** From December 2017 to May 2021, our institution executed 213 RARP cases, with 185 of these involving nerve preservation. Among these patients, 133 had an IIEF-5 score of 17 or higher during preoperative EF assessment. We included 85 patients with consistent IIEF-5 records before surgery and at 6, 12, and 24 months post-surgery in this study. Of these, 44 and 41 patients comprised the COVID-19–positive and COVID-19–negative groups, respectively. The COVID-19–positive group had a higher proportion of diabetes mellitus (DM) patients (24 (54.55%) vs. 7 (17.07%), $p<0.001$). There was no significant difference in preoperative IIEF-5 scores or scores up to 6 months after surgery between the two groups. However, the IIEF-5 scores of the COVID-19–positive group were statistically lower after 12 and 24 months post-surgery. Additionally, the COVID-19–negative group showed a more considerable score increase between 6 and 12 months post-surgery, and the EF recovery rate was lower in the COVID-19–positive group starting from the 12th month after surgery. Within the COVID-19–positive group, no statistically significant difference in IIEF-5 scores was found between single infection and multiple reinfection groups. **Conclusions:** Principal component analysis revealed the impact of COVID-19 on ED recovery in patients who underwent nsRARP. The most substantial changes in IIEF-5 scores occurred between 6 and 12 months. From 12 months onwards, the COVID-19–positive group had significantly lower scores, and fewer patients had IIEF-5 scores above 17. However, the number of COVID-19 diagnoses did not significantly affect the IIEF-5 scores.

 doi:10.20944/preprints202306.1225.v1

Keywords: Erectile Dysfunction; COVID-19; Nerve-Sparing Robot-Assisted Radical Prostatectomy; IIEF-5

INTRODUCTION

COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in China in December 2019 and has since become a global pandemic [1,2]. Research indicates that SARS-CoV-2 targets cells and tissues expressing both angiotensin-converting enzyme 2 (ACE-2) and transmembrane protease serine 2 (TMPRESS-2)[3,4]. Notably, these receptors and genes are present in the endothelial cells of several organs, including the lungs, heart, and kidneys, where COVID-19 has been identified through electron microscopy. It has also been suggested that the vascular-rich erectile tissue in the penis could be a potential target for SARS-CoV-2 infection [5], a hypothesis supported by a study that confirmed a link between COVID-19 and subsequent erectile dysfunction (ED) [6].

ED following radical prostatectomy (RP) for prostate cancer (PCA) is considered an inevitable consequence of the surgery. Prevalence varies, with some studies reporting rates as high as 85% [7]. Nelson et al. found that only 16% of men maintained preoperative erectile function 2 years post-surgery, declining to 4% in men aged 60 and older [8]. Studies on ED rates post-RP have reported ranges from 14% to 90% [9] and from 12% to 96% [10], likely reflecting variability across different centers and surgeons.

Currently, RP with or without lymph node dissection is a common treatment for localized PCA [11-13]. Among the available treatments, robot-assisted radical prostatectomy (RARP) is favored due to its reliability and quicker recovery time [14]. However, despite advances in robotic technology allowing more precise surgeries, ED rates after RARP remain similar to those after open surgery [15,16], and recovery of erectile function post-RP has not significantly improved [17].

Nerve-sparing (NS) was introduced in the 1980s for RP [18], and the technique has been widely implemented in nerve-sparing RARP (nsRARP). While successful nerve preservation has been achieved, ED remains a major postoperative complication affecting quality of life [19].

Research has proposed a connection between SARS-CoV-2 infection and ED, though the exact mechanism remains unclear. Even with the widespread use of RARP, the prevalence of ED remains persistently high, typically around 80%. This study was designed to assess postoperative erectile function recovery in patients with normal preoperative erectile function who underwent nsRARP, and to examine the impact of COVID-19 on such recovery. We conducted a retrospective and indirect review of the International Index of Erectile Function-5 (IIEF-5) scores of patients diagnosed with PCA who underwent nsRARP. This study received approval from the Sungkyunkwan University School of Medicine Samsung Medical Center Research Ethics Committee (SCMC 2023-04-006).

MATERIALS AND METHODS

From December 2017 to May 2021, we conducted a retrospective analysis of patient charts and International Index of Erectile Function-5 (IIEF-5) questionnaires at our institution. We only included patients who underwent bilateral nerve-sparing RARP (nsRARP) performed by a single surgeon. Patients with a higher disease stage—such as those who did not undergo bilateral nerve-sparing due to suspected extracapsular extension on magnetic resonance imaging (MRI)—were excluded from the study.

Our focus was on patients who achieved preoperative IIEF-5 scores of 17 or above. We evaluated the changes in these patients' IIEF-5 scores following surgery, considering the presence of postoperative ED and the patient's COVID-19 status. We determined clinical staging based on preoperative MRI findings. Through a review of electronic medical records (EMR), we assessed baseline comorbidities, body mass index (BMI), and COVID-19 status, subsequently comparing differences between groups.

Nerve-sparing was not performed for patients with suspected extracapsular extension on MRI unless a strong patient request was made; in such cases, bilateral nerve-sparing was executed. Our

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study included 16 patients with clinical stage 3 disease. We excluded patients who underwent androgen deprivation therapy (ADT) or radiation therapy due to biochemical recurrence (BCR).

Since nerve-sparing techniques and extent can vary among surgeons, this study minimized confounding variables by focusing on patients who underwent nsRARP performed by a single surgeon, who is also the study's author. Patients who underwent bilateral nerve-sparing procedures received routine phosphodiesterase-5 inhibitor (PDE5i) therapy for at least 1 month postoperatively. However, a separate analysis regarding PDE5i usage was not conducted due to the small number of patients (only 10) who continued taking PDE5i for economic reasons.

The IIEF-5 questionnaire—a tool for assessing erectile function—categorizes scores as follows: 22-25: no ED, 17-21: mild ED, 12-16: mild to moderate ED, 8-11: moderate ED, 5-7: severe ED. Our study aimed to compare the recovery of postoperative ED between SARS-CoV-2–infected patients and those not infected based on preoperative and postoperative IIEF-5 scores. Erectile function recovery was defined as achieving a score of 17 or above and having successful sexual intercourse. We compared recovery rates between the two groups.

We did not categorize the timing of SARS-CoV-2 infection as either preoperative or postoperative. For statistical analysis, we utilized SPSS software version 18.0 (IBM Co., Armonk, NY, USA). Fisher's exact test and chi-square test were employed to compare categorical variables between the two groups. To compare the mean differences between baseline and postoperative IIEF-5 scores, we performed an independent t-test. We deemed $p<0.05$ to indicate statistical significance.

RESULTS

Between December 2017 and May 2021, our institution carried out 213 RARP procedures, all performed by one surgeon. Of these, 185 procedures incorporated nerve-sparing techniques. We conducted preoperative erectile function evaluations using the International Index of Erectile Function-5 (IIEF-5) questionnaire and found that 133 patients scored 17 or above. From this pool, we included 85 patients in this study, all of whom maintained IIEF-5 records before surgery, as well as at 6 months, 1 year, and 2 years postoperatively. These participants were divided into two groups: 44 in the COVID-19–positive group and 41 in the COVID-19–negative group.

In the overall patient sample, 69 (81.18%) were diagnosed with clinical stage 2, and 16 (18.82%) with stage 3. Comparing the COVID-19–positive and COVID-19–negative groups, a significantly higher proportion of patients in the COVID-19–positive group had diabetes mellitus (DM) (54.55% vs. 17.07%, $p<0.001$) (Table 1). Preoperative IIEF-5 scores did not significantly differ between the COVID-19–positive and COVID-19–negative groups (19.75 ± 1.97 vs. 19.15 ± 1.70, $p=0.135$), nor did the scores at 6 months post-operation (13.05 ± 2.45 vs. 13.27 ± 3.46, $p=0.732$). However, by 12 months post-surgery, the COVID-19–positive group demonstrated lower IIEF-5 scores compared to the negative group (13.68 ± 2.36 vs. 15.71 ± 2.90, $p<0.001$), a trend that continued at the 24-month mark (15.48 ± 2.60 vs.17.22 ± 2.93, $p=0.005$).

Table 1. Characteristics of the COVID-19–positive and COVID-19–negative groups.

	COVID-19 diagnosis		
	No (n=41)	**Yes (n=44)**	**P-value**
Age	69.07 ± 7.86	66.14 ± 7.70	0.086
Diabetes mellitus			<0.001
No	34 (82.93)	20 (45.45)	
Yes	7 (17.07)	24 (54.55)	
Hypertension			0.483
No	24 (58.54)	29 (65.91)	
Yes	17 (41.46)	15 (34.09)	
Smoking			0.838
No	29 (70.73)	32 (72.73)	
Yes	12 (29.27)	12 (27.27)	
Body mass index	27.69 ± 2.55	27.09 ± 2.44	0.268
Heart disease			0.929
No	38 (92.68)	41 (93.18)	

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Yes	3 (7.32)	3 (6.82)	
Clinical T stage (MRI)			0.205
2	31 (75.61)	38 (86.36)	
3	10 (24.39)	6 (13.64)	
IIEF score			
Pre	19.15 ± 1.70	19.75 ± 1.97	0.135
Post (6 months)	13.27 ± 3.46	13.05 ± 2.45	0.732
Post (12 months)	15.71 ± 2.90	13.68 ± 2.36	<0.001
Post (24 months)	17.22 ± 2.93	15.48 ± 2.60	0.005
Difference from 0 to 6 months	-5.88 ± 3.59	-6.70 ± 1.69	0.174
Difference from 6 to 12 months	2.44 ± 2.12	0.64 ± 2.07	<0.001
Difference from 12 to 24 months	1.80 ± 1.61	1.51 ± 1.63	0.422

Values are n (%) or mean ± standard deviation.

Regarding changes in IIEF-5 scores up to 6 months postoperatively, both groups saw a decrease without significant differences (-6.70 ± 1.69 vs. -5.88 ± 3.59, p=0.174). However, between 6 to 12 months postoperatively, the COVID-19–negative group exhibited a more significant score increase (0.64 ± 2.07 vs. 2.44 ± 2.12, p<0.001). Though scores continued to rise between 12 and 24 months, no significant difference was found (1.51 ± 1.63 vs. 1.80 ± 1.61, p=0.422) (Table 1).

Erectile function recovery, defined as an IIEF-5 score of 17 or higher, showed no significant difference between groups up to 6 months postoperatively (18.18% vs. 34.15%, p=0.137). However, from 12 months onwards, a significant divergence appeared in the erectile function recovery rate (9.09% vs. 48.78%, p<0.001), persisting between 12 and 24 months (38.64% vs. 70.73%, p=0.004) (Table 2).

Table 2. International Index of Erectile Function-5 (IIEF-5) questionnaire scores.

Time point IIEF-5 category	COVID-19 diagnosis group No (n=41)	 Yes (n=44)	P-value
Pre			0.120
<17	0 (0.00)	0 (0.00)	
17-21	38 (92.68)	35 (79.55)	
22-25	3 (7.32)	9 (20.45)	
Post 6 months			0.137
<17	27 (65.85)	36 (81.82)	
17-21	14 (34.15)	8 (18.18)	
22-25	0 (0.00)	0 (0.00)	
Post 12 months			<0.001
<17	21 (51.22)	40 (90.91)	
17-21	20 (48.78)	4 (9.09)	
22-25	0 (0.00)	0 (0.00)	
Post 24 months			0.004
<17	12 (29.27)	27 (61.36)	
17-21	28 (68.29)	17 (38.64)	
22-25	1 (2.44)	0 (0.00)	

Values are n (%)

In comparing patients with a single COVID-19 diagnosis to those with multiple reinfections, no statistically significant differences emerged in IIEF-5 scores or other variables (Table 3).

Table 3. The COVID-19 reinfection and erectile dysfunction.

Variable	Categories (no. of COVID-19 diagnoses) One (n=26)	 Multiple (n=18)	P-value
Age	67.27 ± 8.29	64.50 ± 6.64	0.245
Diabetes mellitus			0.019
No	8 (30.77)	12 (66.667)	
Yes	18 (69.23)	6 (33.33)	
Hypertension			0.576

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No	18 (69.23)	11 (61.11)	
Yes	8 (30.77)	7 (38.89)	
Smoking			0.506
No	20 (76.92)	12 (66.67)	
Yes	6 (23.08)	6 (33.33)	
Body mass index	26.95 ± 2.22	27.29 ± 2.78	0.656
Heart disease			>0.999
No	24 (92.31)	17 (94.44)	
Yes	2 (7.69)	1 (5.56)	
Clinical T stage (MRI)			0.208
2	24 (92.31)	14 (77.78)	
3	2 (7.69)	4 (22.22)	
IIEF score			
Pre	20.12 ± 1.93	19.22 ± 1.96	0.140
Post (6 months)	13.04 ± 2.52	13.06 ± 2.41	0.982
Post (12 months)	13.73 ± 2.54	13.61 ± 2.57	0.871
Post (24 months)	15.81 ± 2.06	15.00 ± 3.24	0.317
Difference from 0 to 6 months	-7.08 ± 1.65	-6.17 ± 1.65	0.079
Difference from 6 to 12 months	0.69 ± 2.46	0.56 ± 1.38	0.832
Difference from 12 to 24 months	2.08 ± 1.65	1.39 ± 1.50	0.165
Recovery time			
Within 6 months	5 (19.23)	3 (16.67)	>0.999
Within 12 months	1 (3.85)	3 (16.67)	0.289
Within 24 months	11 (42.31)	6 (33.33)	0.548

Values are n (%) or mean ± standard deviation.

DISCUSSION

RARP is a primary treatment for localized prostate cancer [20]. Yet, postoperative ED remains a prevalent issue, affecting 70.4% of patients [21]. Studies have indicated that RARP advantages, such as enhanced surgical vision and precision, do not necessarily improve functional outcomes like ED [15,16]. ED following RARP is commonly attributed to direct or indirect injury to neurovascular bundles controlling erection mechanisms, caused by surgery-induced stretching, heating, and ischemia [22]. As COVID-19 is an endothelial disease with systemic manifestations resulting from an imbalance in endothelial thrombotic/fibrinolytic dynamics [23], and since ED is considered a signature of endothelial dysfunction [24,25], this further complicates the issue.

Several recent studies report a higher prevalence of ED among COVID-19–positive patients [1]. Sansone et al. and other researchers have noted sexual dysfunction and life quality impairments after COVID-19 diagnosis (and recovery) [26,27,28]. A study by Kresch et al. found COVID-19 RNA in all penile biopsy samples from patients with a COVID-19 history, suggesting that related endothelial damage could impede penile vascular flow, leading to ED [5]. Likewise, other research has detected viral particles in the endothelial cells of COVID-19–affected organs, including the penis [29]. Chu et al. linked new-onset ED with COVID-19, proposing it could arise from COVID-19-induced endothelial cell dysfunction [6].

Previous research examining rehabilitation programs for post-RP ED recovery identifies age, preoperative erectile function and sexual desire, confidence, and intercourse satisfaction as recovery predictors [30,31]. Nearly 39 penile rehabilitation methods have been reported, with phosphodiesterase type 5 inhibitors (PDE5i) like tadalafil widely recognized as facilitating ED recovery [32]. Moncada et al. found that daily tadalafil (5 mg) significantly improved International Index of Erectile Function (IIEF) scores and penile length [33, 34], and several studies have shown rehabilitation treatments like PDE5i, vacuum erection devices, and intracorporeal injection treatments improving IIEF-5 scores and erectile function [35]. In their research, Seo et al. observed that 1 year after surgery, the tadalafil group presented notably higher IIEF-5 scores compared to the control group (13.2±5.6 vs. 7.7±4.8, $p<0.0001$). Within the tadalafil group, it was seen that both bilateral and unilateral nerve-sparing (NS) groups reported higher scores across all five domains of the IIEF-5 at the 1-year mark, compared to the unilateral non-NS group [36]. As it pertains to the timeline for erectile function recovery following surgery, several investigations have indicated that less than 50% of patients recover erectile function within 3 months of undergoing non-nerve-sparing radical

 doi:10.20944/preprints202306.1225.v1

prostatectomy. It has been further suggested that patients experiencing neurapraxia may require over 24 months for recovery [37,38]. However, alternative research posits that the recovery period typically spans approximately 18 to 24 months [39,40]. Interestingly, diverging from these patterns, Kim and Sung found in their study that tadalafil facilitated comparable levels of erectile function recovery after 1 or 2 years of use [41].

This study was conducted from December 2017 through May 2021, focusing on patients who underwent nsRARP. To minimize variations in factors such as surgical methods, this study only included operations performed by a single surgeon. The period was set considering the surgeon's change from transperitoneal to retroperitoneal approaches post-May 2021 and the necessary erectile function recovery time post-surgery. We included 213 prostate cancer-diagnosed patients undergoing RARP in the study, with 185 (86.85%) undergoing nerve-sparing and meeting the criteria of pre-surgery IIEF-5 score of 17 or above, along with continuous 2-year survey assessments. Of these, we focused on 85 patients not undergoing anti-deprivation therapy (ADT) or radiation therapy and experiencing biochemical recurrence (BCR).

A study by Chu et al. [6] found males contracting COVID-19 to be older than their uninfected counterparts, with a higher prevalence of diabetes mellitus (DM) and hypertension. Our study likewise found a higher proportion of DM in the COVID-19–positive group (24 [54.55%] vs. 7 [17.07%], $p<0.001$). Due to the limited sample size, we could not perform propensity score matching. Comparing our COVID-19–negative group scores (preoperative, 6-month, and 12-month IIEF-5 scores: 19.15 ± 1.70, 13.27 ± 3.46, and 15.71 ± 2.90, respectively) with findings reported by Noh et al. [42] (tadalafil group scores: 19.7, 14.2, and 15.6), we find a similarity. The proportion of patients achieving erectile function recovery was lower in our study (14 [34.15%] at 6 months and 20 [48.78%] at 12 months) than the preoperative and postoperative tadalafil groups (60.0% vs. 52.4% and 80.0% vs. 71.4%, respectively), possibly due to the lower continuous PDE5i administration in our study.

Our research revealed no substantial discrepancies in the IIEF-5 questionnaire scores between the COVID-19–positive and COVID-19–negative groups up to 6 months post-surgery. Nevertheless, starting from the 1-year mark, significant differences were discernible in the IIEF-5 scores, with the COVID-19–positive group consistently scoring lower than the negative group at both the 12- and 24-month mark. The decline in IIEF-5 scores from pre-operation to 6 months post-operation was more pronounced in the COVID-19–positive group, but this difference did not reach statistical significance. However, the increase in IIEF-5 scores between 6 and 12 months post-operation was significantly less for the COVID-19–positive group compared to the negative group. From 12 to 24 months, the score increase was not significantly different between the two groups.

Published studies, including those by Montorsi et al. [43] and Noh et al. [42], highlighted periods of robust erectile function recovery between 6 and 12 months after nerve-sparing radical prostatectomy (NSRP). Furthermore, Harirugsakul et al. [44] investigated the impact of COVID-19 on male patients who did not undergo prostate surgery and found the highest prevalence of ED at the 3-month mark post-infection. Interestingly, these males were, on average, in their forties.

Rabbani F et al. [45] posited that oral medications might not show immediate effects in the early post-surgery period, as it might take up to two years for the cavernous nerves to heal. As the healing process progresses and nerves start secreting Nitric Oxide (NO), oral medications might become increasingly effective. Chu et al. [6] found that males with a history of COVID-19 had an increased risk of ED diagnosis over time compared to those without COVID-19.

Despite a slower IIEF-5 score increase in the COVID-19–positive group between 6 and 12 months, there were no statistically significant differences in score increases over time. Moreover, when comparing the proportion of participants with a sufficient IIEF-5 score for erectile function (EF) recovery, a similar trend was noticed. After 12 months, the COVID-19–positive group demonstrated a statistically lower rate of EF recovery compared to the negative group. This suggests that COVID-19 might impact EF recovery, not immediately post-nsRARP, but rather in the period around 12 months pre-and-post-surgery.

The lack of significant difference in IIEF-5 scores up to 6 months post-surgery might be due to incomplete nerve recovery in both groups, making the diagnosis of COVID-19 less impactful. The fact that the IIEF-5 scores did not progressively increase in our study could be attributed to the 2-year

 doi:10.20944/preprints202306.1225.v1

period representing the typical timeframe for EF recovery. Alternatively, this period might represent further aging, which can increase the likelihood of factors contributing to ED, such as decreased male hormones.

In our research, we found that patients in both the COVID-19–positive and COVID-19–negative groups were in their late sixties. Regrettably, most patients did not undergo testosterone testing. We were unable to identify differences in ED recovery based on a single SARS-CoV-2 infection vs. reinfection, underscoring the need for further research.

This study concentrated on patients undergoing nsRARP performed by a single surgeon, which likely reduced variability. However, even with a single surgeon, nerve preservation levels might differ among patients, and we could not verify the extent of nerve-sparing through pathological examination by a urologist.

After a patient recovers from COVID-19, the severity of the previous COVID-19 episode and the patient's overall health can affect COVID-19-related ED. However, we did not properly assess these factors. Similarly, we did not consider psychological or mental factors that could influence ED recovery. Despite suggesting a potential association between COVID-19 and ED, our study had limitations in confirming specific causality and mechanisms.

In our research, we employed the IIEF-5 questionnaire at 6, 12, and 24-month intervals for comparison. Nonetheless, given the retrospective nature of the study, instances abounded where the questionnaire could not be administered within the precise time frames, inevitably impacting the accuracy of our findings. Kim et al. [46] determined a correlation between preoperative serum testosterone levels and erectile function post-RP. However, we were unable to verify this relationship due to the absence of serum testosterone level measurements in our data.

Contemporary studies [47] have reported that surgical treatment for urinary incontinence did not substantially improve erectile function. Della Camera et al. proposed that urinary incontinence following RP affects the quality of life [48], with their study suggesting that the presence of urinary incontinence significantly influenced their reported outcomes. Mitchell et al. further disclosed that 44.4% of patients encountered incontinence during sexual activity at 3 months post-surgery, as well as 36.1% at 24 months post-surgery [49], indicating potential contributors to increased ED. Tsikis et al. [50] revealed that 45% of ED patients had concurrent urinary incontinence, while only 27% of non-ED patients had incontinence, thereby suggesting that ED is an independent predictor of urinary incontinence. However, our research could not provide a comprehensive evaluation of the effect of incontinence on ED, and we acknowledge this as a limitation.

While existing research largely reports on the correlation between ED and COVID-19, the precise pathophysiology remains unclear. Further, well-designed, long-term studies are needed to explicate the role of COVID-19 in ED.

CONCLUSIONS

We observed the impact of COVID-19 on erectile function recovery in patients who underwent nsRARP using PCA. We discerned no significant influence of infection within the first 6 months post-surgery. However, the most considerable shift in IIEF-5 score was between 6 and 12 months. Subsequently, the infected group displayed significantly lower scores and a lower percentage of patients achieving an IIEF-5 score of 17 or higher. Despite this, we found no statistically significant differences in the number of COVID-19 episodes and IIEF-5 scores between the two groups, nor were differences observed in other variables.

Acknowledgments: None.

Conflicts of Interest: The author declare no competing interests for the present study.

Funding: The author received no specific funding for this work.

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