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Positive Association of Male Overactive Bladder Symptoms and Androgen Deprivation: A Nationwide Population-based Cohort Study

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Abstract. *Background/Aim: The role of androgen in the modulation of voiding function is still uncertain. The aim of this study was to evaluate the association of androgen deprivation therapy (ADT) and overactive bladder (OAB) in men in a population-based cohort. Materials and Methods: This study examined the records of newly-diagnosed prostate cancer subjects receiving ADT only in the Taiwan National Health Insurance Research Database in the years between 2001 and 2007. As controls men without cancer were selected and divided into three groups, 1) benign prostate hyperplasia treated with an alpha-blocker (BPH-alpha blocker), 2) BPH treated with a 5-alpha reductase inhibitor (BPH-5ARI) and 3) healthy controls. OAB events were censored by definition of drug prescriptions for more than one month and risk analysis among each group was performed. Results: The healthy control group had decreased risk of OAB compared to the prostate cancer group and the BPH-5ARI group showed a higher risk of OAB than the prostate cancer group. Subgroup analysis showed that independently of age or comorbidities, the prevalence of OAB was significantly lower in the healthy control group. Moreover, the cumulative incidence of OAB showed a time-dependent pattern with a significant increase after ADT for 5 years. Conclusion: Androgen deprivation in prostate cancer patients was associated with an increased risk of OAB that was treatment duration-dependent. This result is consistent with an inhibitory role of androgen in the modulation of male voiding function.*

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Sex hormones including androgen and estrogen bind to steroid receptors that are widely distributed in human tissues (1, 2). In genitourinary tract, sex hormones not only control the appearance and function of sex organs, but may also influence lower urinary tract function (3). Our previous human population cohort studies as well as experimental studies on female rats suggested that estrogen may influence the voiding function in females (4, 5). However, the role of androgen in the modulation of male voiding functions is less certain. Epidemiological studies showed that aging which is accompanied by decreased serum testosterone levels (6, 7) is also associated with increased prevalence of overactive bladder (OAB). We also showed that orchiectomy decreased the volume threshold for inducing micturition in a rat model (8). Based on current evidence, serum testosterone seems to play a role in the modulation of voiding function in men (9). However, a relationship between serum testosterone level and OAB has not been established.

In this study, a nationwide population-based insurance database was used to examine a possible link between androgen deprivation therapy (ADT) and OAB in prostate cancer patients. The data were compared with data obtained from healthy controls and from patients with benign prostate hyperplasia (BPH).

Materials and Methods

Data sources. All data in this study were obtained from the Taiwan National Health Insurance Research Database (NHIRD), which is managed by the Taiwan National Health Research Institute (NHRI).

The Taiwan National Health Insurance (NHI) program covers at least 99% of the population of the island since 1995. In this study, a systemic sampling from the Taiwan NHIRD between 2001 and 2007 with a total of 1,000,000 individuals was used. These random subjects have been approved by the NHRI to be representative of the general population in Taiwan. The study protocols were approved by the institutional review board (IRB) of Taichung Veterans General Hospital (CE13151-1) and were in accordance with the guidelines of the IRB. There were no statistically significant differences in age and general healthcare between the sample group and all enrollees (data not shown). The database contains medical information regarding ambulatory care, inpatient care, and prescription drugs. Diagnoses were coded according to the International Classification of Disease, 9th revision (ICD-9) which was incorporated into the database since 2000. The database used in this study can be interlinked by the scrambled unique individual's personal identification number (PIN). The NHRI safeguards the privacy and confidentiality of all beneficiaries and transfers the health insurance data to health researchers after ethical approval has been obtained. In this analysis, access to the NHIRD has been approved by the NHRI Ethics Review Committee.

Study population and end-point. Four groups of patients were included in our analysis: prostate cancer with ADT only, BPH with alpha-blockers only, BPH with 5-alpha reductase inhibitors (5ARIs), and healthy controls. The patient selection, sampling and exclusion criteria are shown in Figure 1. Inclusion criteria in the prostate cancer study group met two conditions: (i) newly diagnosed prostate cancer between 2001 and 2007; and (ii) ADT treatment. The exclusion criteria in the study group were: (i) any interventional prostate surgeries or radiation therapy prior to inclusion or after inclusion; (ii) chemotherapy or targeted therapy; (iii) medications for OAB for more than 1 month or OAB diagnosis before prostate cancer diagnosis; (iv) existence of neurological diseases requiring 3 or more visits to outpatient clinics or 1 or more inpatient visits and (v) other types of cancer. The diagnosis of prostate cancer was defined as code ICD-9-CM 185.0. Neurologic diseases were coded ICD-9-CM from 320 to 359 including the majority of central or peripheral neurological diseases. ADT was defined as luteinizing hormone release hormone (LH-RH) agonists or antagonists and other types of anti-androgens. Chemotherapy or targeted therapies were identified by drug scientific names. Medications for OAB were trospium, imipramine, flavoxate, propiverine, oxybutynin, tolterodine and solifenacin. In the BPH group, subjects who met the following criteria were also excluded: (i) receiving interventional prostate surgeries; (ii) previous OAB history; (iii) any kinds of neurologic diseases coded ICD-9-CM from 320 to 359; Incident cases of lower urinary tract symptoms were identified from the NHIRD after the upstream patient selection. The ratio of the number of subjects in the healthy control group to the number of prostate cancer patients was 2:1.

In all four groups, comorbidities, including myocardial infarction (MI, ICD-9-CM 410), heart failure (ICD-9-CM 428), peripheral vascular disease (PVD, ICD-9-CM 443), cerebrovascular accident (CVA, ICD-9-CM 434), dementia (ICD-9-CM 290-294), chronic obstructive pulmonary disease (COPD, ICD-9-CM 490-496), mild chronic liver disease except cirrhosis (CLD, ICD-9-CM 571, except 571.2, 571.5, 571.6), chronic kidney disease (CKD; ICD-9-CM 582–583), diabetes mellitus (DM, ICD-9-CM 250), hyperthyroidism (ICD-9-CM 410–414) were recorded.

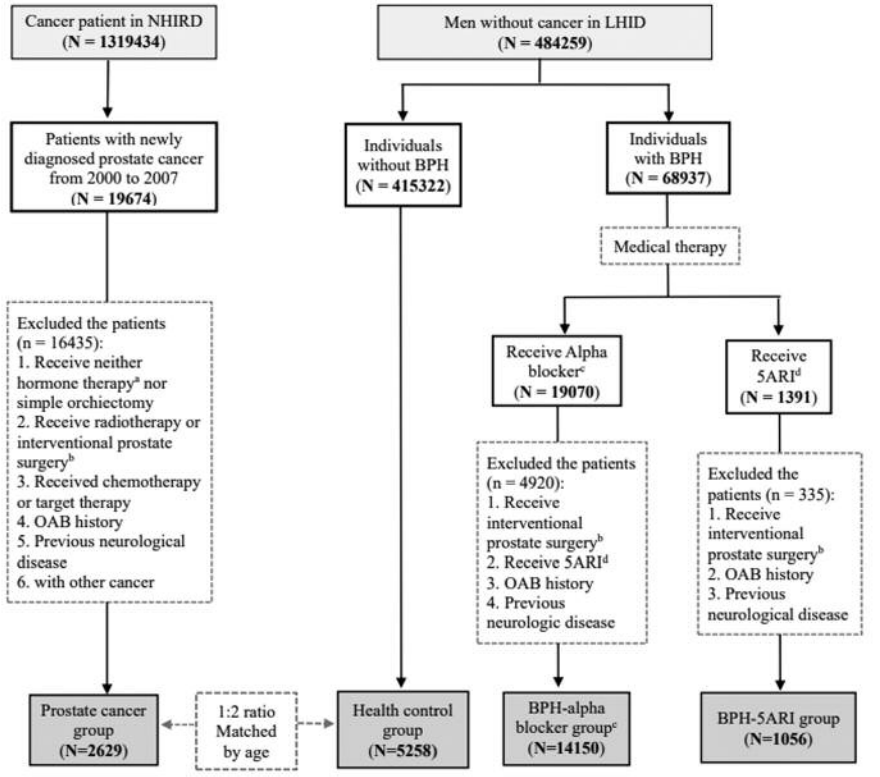
Statistical analysis. The data are presented as the mean values and standard deviations (SD) for continuous variables, and proportions for categorical variables. The differences between continuous values were analyzed by using t test for continuous variables, and chi-square test for categorical variables. Multivariate Cox proportional hazard regression was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the association between the prevalence of OAB and the four divided groups. Propensity analysis was used for further confirming this association. The cumulative incidence curves were plotted *via* the Kaplan–Meier method with statistical significance examined by the log-rank test. All statistical analyses were carried out by SAS software version 9.2 (SAS Institute, Inc., Cary, NC, USA). A p-value of <0.05 indicated statistically significant differences.

Results

There were 19,674 subjects who met the primary inclusion criteria in the study group. After elimination of subjects based on exclusion criteria. 2,629 cases were selected as study subjects. The control group included 484,259 subjects selected randomly from a 1 million non-cancer population. Among them, 415,322 subjects were selected as healthy controls without BPH. After 1:2 match with study subjects, 5258 subjects were selected as healthy controls. The BPH-alpha blocker included 14,151 individuals who received alpha-blockers as principal treatment without any 5ARI. The BPH-5ARI group included 1,056 subjects who received medications of 5ARI as principal treatment with or without any alpha-blockers.

Table I which compares the ages and comorbidities of the four groups shows that the prostate cancer group had an older age ($p<0.001$) than the other 2 BPH groups, but not the healthy controls. The mean age of the prostate cancer cohort was 73.8 years at the time of the survey. A comparison of comorbidities shows a variation among groups. The prostate cancer group had a higher proportion of MI ($p<0.001$), heart failure ($p<0.001$), CVA ($p<0.001$), COPD ($p<0.001$), CLD ($p<0.001$), CKD ($p<0.001$) and DM ($p<0.001$) than the healthy control group. The healthy controls had a higher proportion of hyperthyroidism ($p<0.001$) than the prostate cancer group. In regard to PVD and dementia, there was no statistically significant difference between the two groups ($p=0.11$ and $p=0.41$ respectively). The prostate cancer group also had higher proportion of all the chronic disease variables except hyperthyroidism than the BPH-alpha blocker group. However, the prostate cancer group and the BPH-5ARI group were similar in MI, PVD, CVA, dementia, CKD, and DM. The prostate cancer group had a higher proportion of heart failure and COPD ($p=0.002$ and $p=0.04$ respectively), while the BPH-5ARI group had a higher proportion of CLD and hyperthyroidism ($p=0.003$ and $p<0.0001$ respectively).

In the prostate cancer group 109 OAB cases were identified with the rate of 56.6 per 10,000 person-years compared to only 3 cases in the healthy control group (0.85 per 10,000



[a]: Hormone therapy (ATC code): L02AE01-05, L02BX01-02;

[b]: Prostate surgery: including radical protatectomy, salvage prostatectomy, simple prostatectomy and transurethral resection of prostate with any energy sources;

[c]: Alpha blockers (ATC code): C02CA04, G04CA01-04;

[d]: 5-alpha reductase inhibitor (ATC code): G04CB01-02, G04CA52.

5ARI: 5 alpha reductase inhibitor; BPH: benign prostate hyperplasia; LHID: Longitudinal Health Insurance Database; NHIRD: National Health Insurance Research Database; OAB: overactive bladder.

Figure 1. *Flow diagram showing the process of overactive bladder (OAB) patient sampling and participation.*

person-years, Table II). The crude model showed a significant decreased risk of OAB in the BPH-alpha-blocker (HR=0.57, 95%CI=0.46-0.7) and in the healthy control group (HR=0.01, 95%CI=0.005-0.05) compared to the prostate cancer group. After adjustment for comorbidities, the OAB risk was still lower in both groups (HR=0.7, 95%CI=0.56-0.87, HR=0.02, 95%CI=0.01-0.05 respectively) compared to the prostate cancer group. However, the BPH-5ARI group showed a significantly higher risk of OAB (adjusted HR=1.49, 95%CI=1.08-2.06) compared with the prostate cancer group.

In a subgroup analysis, the healthy control group exhibited a low OAB risk in both age groups (0 in the age <65 years and HR=0.02, 95%CI=0.56-0.87, in the age ≥65 years). OAB risk was also lower in the healthy control group with (HR=0.01, 95%CI=0.001-0.07) and without comorbidities (HR=0.02, 95%CI=0.01-0.09) (Table III). Compared to the prostate cancer group, the BPH-alpha blocker group showed no difference in OAB risks below age 65 (HR=0.64, 95%CI=0.35-1.18) or without comorbidities (HR=0.69, 95%CI=0.46-1.03) (Table III). The risk decreased in the BPH-alpha blocker group at ages above 65 (HR=0.68, 95%CI=0.54-0.87) and in the subgroup with comorbidities (HR=0.7, 95%CI=0.54-0.91) (Table III). However, the BPH-5ARI group exhibited a higher risk of OAB at ages above 65 (HR=1.5, 95%CI=1.02-2.2) or with comorbidities (HR=1.58, 95%CI=1.08-2.3) compared with the prostate cancer group.

Table I. *Baseline variables among the four groups.*

Variable	Prostate cancer N=2,629	BPH-alpha blocker N=14,150	BPH-5ARI N=1,056	Health control N=5,258	*p*-Value		
					Prostate cancer *vs.* healthy control	Prostate cancer *vs.* BPH-alpha blocker	Prostate cancer *vs.* BPH-5ARI
Age group (years)*	73.8 (7.77)	62.3 (11.3)	66.3 (9.91)	73.5 (7.96)	0.26	<0.0001	<0.0001
<45	2 (0.08)	720 (5.09)	9 (0.85)	4 (0.08)			
45-64	309 (11.8)	7,270 (51.4)	450 (42.6)	618 (11.8)			
≥65	2,318 (88.2)	6,160 (43.5)	597 (56.5)	4636 (88.2)			
Comorbidity							
MI	96 (3.65)	304 (2.15)	32 (3.03)	147 (2.80)	0.04	<0.0001	0.35
Heart failure	248 (9.43)	716 (5.06)	67 (6.34)	384 (7.30)	0.001	<0.0001	0.002
PVD	73 (2.78)	260 (1.84)	30 (2.84)	115 (2.19)	0.11	0.002	0.91
CVA	581 (22.1)	2,198 (15.5)	222 (21.0)	970 (18.5)	0.0001	<0.0001	0.47
Dementia	77 (2.93)	224 (1.58)	24 (2.27)	172 (3.27)	0.41	<0.0001	0.27
COPD	1,172 (44.6)	4,817 (34.0)	432 (40.9)	1,621 (30.8)	<0.0001	<0.0001	0.04
CLD	431 (16.4)	2,724 (19.3)	217 (20.6)	464 (8.82)	<0.0001	0.0006	0.003
CKD	63 (2.40)	197 (1.39)	17 (1.61)	60 (1.14)	<0.0001	0.0001	0.14
DM	547 (20.8)	2611 (18.5)	234 (22.2)	829 (15.8)	<0.0001	0.005	0.36
Hyperthyroidism	0	87 (0.61)	11 (1.04)	20 (0.38)	0.001	<0.0001	<0.0001

MI: Myocardial infarct; PVD: peripheral vascular disease; CVA: cerebrovascular accident; COPD: chronic obstructive pulmonary disease; CLD: chronic liver disease; CKD: chronic kidney disease; DM: diabetes mellitus.

Figure 2 shows a time-dependent increase in the cumulative incidence of OAB among the prostate cancer, BPH-alpha blocker and the BPH-5ARI groups (Log-Rank test, $p<0.0001$).

Discussion

Our study indicated that androgen ablation treatment is associated with an increased risk of OAB and that an increase in treatment duration increases cumulative risk of OAB. We also found some interesting points from this cohort study. First, androgen ablation therapy in prostate cancer patients eventually generated OAB incidence that equaled the incidence of OAB in BPH. Second, the rate of OAB in the prostate cancer group seemed to increase with age similarly to the increase observed in both BPH groups. Below the age of 65, the risk of OAB did not differ between prostate cancer group and both BPH groups, suggesting that the younger age may tolerate more structural changes. Third, the prominent delay in the development of OAB after the start of ADT possibly also indicates slowly developing structural changes in the lower urinary tract, rather than rapid physiological changes that have been demonstrated after castration in animals (8).

Since ADT is still the pivotal treatment in advanced prostate cancer, OAB which might occur after ADT should be taken into consideration during patient care. ADT alone has been shown to increase osteoporosis and possibility of fracture while OAB may also increase the risk of fracture in the elderly (10, 11).

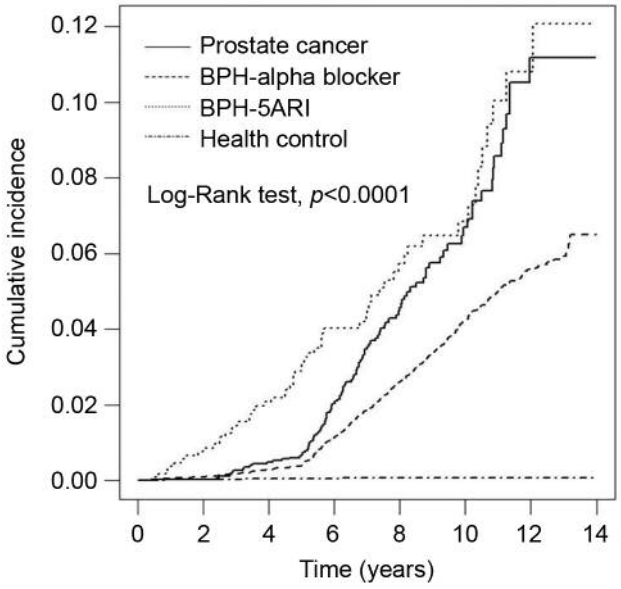


Figure 2. *Kaplan–Meier cumulative incidence of developing OAB among four groups (p<0.0001, log-rank test) (n=23,093).*

Our findings also corresponded to previous epidemiological studies. Kopp *et al.* performed a cross-sectional study of 5990 fracture patients and found that ADT was associated with increased risk of urinary incontinence which also rose with increasing treatment duration (12). Carlsson *et al.* used a nationwide population-based study in the evaluation of long-

Table II. *Multi-variant analysis of OAB risk*.

Variables	Event	Patient-Years	Rate	Model 1 (95%CI)	Model 2 (95%CI)
Treatment					
Prostate cancer	109	19,260	56.6	ref	ref
BPH-alpha-blocker	501	128,644	38.9	0.57 (0.46-0.70)	0.70 (0.56-0.87)
BPH-5ARI	58	7,714	75.2	1.29 (0.94-1.77)	1.49 (1.08-2.06)
Health control	3	35,226	0.85	0.01 (0.005-0.05)	0.02 (0.01-0.05)
Age, years	-	-	-	1.01 (1.01-1.02)	1.02 (1.01-1.02)
MI					
No	655	186,710	35.1	ref	ref
Yes	16	4,133	38.7	1.22 (0.74-2.00)	0.92 (0.55-1.52)
Heart failure					
No	628	181,264	34.7	ref	ref
Yes	43	9,579	44.9	1.49 (1.09-2.03)	1.14 (0.83-1.57)
PVD					
No	656	187,443	35.0	ref	ref
Yes	15	3,400	44.1	1.39 (0.83-2.32)	1.09 (0.65-1.82)
CVA					
No	532	161,900	32.9	ref	ref
Yes	139	28,944	48.0	1.63 (1.35-1.96)	1.31 (1.08-1.59)
Dementia					
No	655	187,805	34.9	ref	ref
Yes	16	3,038	52.7	1.83 (1.12-3.01)	1.30 (0.78-2.15)
COPD					
No	400	128,337	31.2	ref	ref
Yes	271	62,506	43.4	1.49 (1.28-1.74)	1.19 (1.02-1.40)
CLD					
No	534	159,623	33.5	ref	ref
Yes	137	31,221	43.9	1.36 (1.13-1.64)	1.24 (1.02-1.50)
CKD					
No	658	188,297	34.9	ref	ref
Yes	13	2,546	51.1	1.58 (0.91-2.74)	1.29 (0.74-2.24)
DM					
No	540	158,415	34.1	ref	ref
Yes	131	32,429	40.4	1.28 (1.05-1.55)	1.08 (0.89-1.31)
Hyperthyroidism					
No	668	189,877	35.2	ref	ref
Yes	3	967	31.0	0.87 (0.28-2.72)	0.85 (0.27-2.65)

Model 1: Crude model. Model 2: Adjusted for age, MI, heart failure, PVD, CVA, dementia, COPD, CLD, CKD, DM and hyperthyroidism. MI: Myocardial infarct; PVD: peripheral vascular disease; CVA: cerebrovascular accident; COPD: chronic obstructive pulmonary disease; CLD: chronic liver disease; CKD: chronic kidney disease; DM: diabetes mellitus.

Table III. *Subgroup analysis of four groups per 10,000 person-years*.

	Prostate cancer		BPH-alpha blocker		BPH-5ARI		Health control	
Variables	Rate	HR (95%CI)	Rate	HR (95%CI)	Rate	HR (95%CI)	Rate	HR (95%CI)
Age groups*								
<65	44.7	ref	33.3	0.64 (0.35-1.18)	61.5	1.35 (0.65-2.78)	0	-
≥65	58.3	ref	46.9	0.68 (0.54-0.87)	87.0	1.50 (1.02-2.20)	1.01	0.02 (0.01-0.06)
Comorbidity**								
No	53.8	ref	32.7	0.69 (0.46-1.03)	55.9	1.21 (0.64-2.29)	0.53	0.01 (0.001-0.07)
Yes	57.9	ref	43.2	0.70 (0.54-0.91)	84.5	1.58 (1.08-2.30)	1.21	0.02 (0.01-0.09)

* Model adjusted for age, myocardial infarct, heart failure, peripheral vascular disease, stroke, dementia, chronic obstructive pulmonary disease, chronic liver disease, chronic kidney disease, diabetes mellitus and hyperthyroidism. **Model adjusted for age.

term functional outcomes among prostate cancer patients regardless of treatment duration association. ADT treatment alone also was associated with increased risk of urinary incontinence compared with active surveillance (13).

However, because of the different methods used in the present study, there are some differences from those previous studies. For example, two other Asian prospective studies showed an improvement of lower urinary tract symptoms (LUTS) in prostate cancer patients who received ADT (14, 15). Their finding focused on prostate volume decrease, urodynamic parameters and improvement of voiding scores while the storage symptom scores were not different. The mean follow-up periods were 2 years or less and the sample sizes were less than 200 subjects.

In order to clarify the impact of male LUTS in the general population in our study, BPH patients were included for comparison with the prostate cancer group. The BPH-alpha blocker group still showed a decreased risk in OAB (HR=0.7, 95%CI=0.56-0.87) after modification for age and chronic comorbidities. Interestingly, BPH-5ARI seemed to be associated with a higher risk of OAB than prostate cancer. This was quite reasonable in this database setting since the prostate size must be larger than 30 ml or the maximal voiding flow must be smaller than 15 ml/min according to the reimbursement regulation. With this regulation, these patients should have more severe LUTS than the other 3 groups. This is an important point, since previous studies found the 50% coexistence rate of bladder outlet obstruction and OAB (7, 16, 17). In Figure 2, both the BPH groups showed a parallel time-dependent increase of OAB incidence which implies a similar potential of the two groups. The prostate cancer study group showed a significant rise of the cumulative incidence speed after 5 years of ADT treatments. This phenomenon suggests ADT accelerates the rate of OAB formation after treatment for 5 years.

This study has several limitations. First, the definition of OAB was based on consecutive drug prescriptions for treatment of OAB for a period more than one month instead on the diagnosis of OAB. Although this method was more relevant in clinical situations in terms of physicians' habits and insurance regulations, it included patients who had only storage symptoms such as frequency and nocturia, not OAB. Second, in order to eliminate the impact of neurologic diseases and anatomic influence to the lower urinary tract after local therapies, all subjects who were diagnosed with neurological disorders or had been submitted to procedures mentioned in the database were excluded. This resulted in censored OAB subject reduction to only 3 in the healthy control group decreasing the power of this study. Third, our study group included prostate cancer patients who were easier to seek medical service than healthy subjects. Previous epidemiological studies all showed that a quite low percentage of OAB patients seek medical services. This may have influenced the result of this study.

Conclusion

Our study disclosed that ADT was associated with an increased risk of OAB in prostate cancer patients. This result explained the role of androgen in maintenance of male voiding threshold and highlighted *de novo* development of OAB after ADT which may influence quality of life in the elderly prostate cancer patients.

Conflicts of Interest

The Authors declare no competing financial interests.

Acknowledgements

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