

# The association between epididymo-orchitis and prostate cancer

## A nationwide population-based cohort study

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### Abstract

To determine whether epididymo-orchitis, a common infectious disease among men, is associated with subsequent prostate cancer (PCa) via a nationwide cohort study.

This nationwide population-based study of patients treated from 2001 to 2013 included a total of 4991 patients with epididymo-orchitis as the study group and 19,922 matched patients without epididymo-orchitis as a control group. We tracked the patients in both groups for a 5-year period to identify any new cases of PCa. Cox proportional hazards regressions were performed to calculate the hazard ratio (HR) of PCa during this 5-year follow-up period.

Of the 24,913 patients in the study, 235 (0.9%) were newly diagnosed with PCa during the 5-year follow-up period; 77 (1.5%) of those were from the epididymo-orchitis group and 158 (0.8%) were from the control group. Compared to the patients without epididymo-orchitis, the adjusted HR for PCa for the patients with epididymo-orchitis was 1.56 (95% confidence interval [CI]: 1.18–2.06) during the 5-year follow-up period. Ages of more than 70 years, higher incomes, hypertension, and hyperlipidemia were more strongly associated with

PCa in the study group than in the control group.

The results were associated with a 56% increased risk for PCa among patients with epididymo-orchitis. Epididymo-orchitis may play an etiological role in the development of PCa in Asian populations. Further studies are warranted, however, to investigate the relationship between epididymo-orchitis and PCa.

**Abbreviations:** aHR = adjusted hazard ratio, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, ICD-9-CM = The International Classification of Diseases, Ninth Revision, Clinical Modification, LHID2000 = Longitudinal Health Insurance Database 2000, NHIRD = National Health Insurance Research Database.

**Keywords:** epididymo-orchitis, national health insurance research database, prostate cancer

### 1. Introduction

Epididymo-orchitis is characterized by inflammation of the epididymis and testes. Nearly 600,000 cases of epididymo-orchitis occur per year in the United States, accounting for 1/144 (0.69%) outpatient visits among 18 to 50-year-old males.<sup>[1]</sup> The typical symptoms of acute epididymitis are swelling and tenderness of the

epididymis or scrotum. Orchitis is usually from inflammation of the epididymis.<sup>[2,3]</sup> The infection source of epididymo-orchitis is mostly direct extension from urethra or from the bladder. Sexually transmitted infections (STIs) and urinary tract infections (UTIs) are the major causes of epididymo-orchitis. In addition, prostatitis is a risk factor for epididymo-orchitis.<sup>[4]</sup> Moreover,

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J-ML, C-CY, H-CC, and W-LH contributed equally to this work.

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prostatitis has also been reported to be a risk factor for prostate cancer (PCa).<sup>[5]</sup>

PCa is the second most commonly occurring cancer among men worldwide, with more than 1.1 million patients having been diagnosed with and 330,000 have died from PCa in 2012.<sup>[6]</sup> In Taiwan, the incidence of PCa increases year by year, and PCa is the fifth most common form of cancer in men.<sup>[7]</sup> Several risk factors for PCa have been reported, including age, family history, and race.<sup>[8,9]</sup> Using the Surveillance, Epidemiology, and End Results (SEER) database Rosenblatt et al conducted a study of 753 PCa patients treated between 1993 and 1996 and found no association between epididymitis and PCa.<sup>[10]</sup> However, their study was conducted in the 1990s and enrolled a relatively small number of cases. Furthermore, the increasing incidence of PCa in Asia in recent years makes it important to clarify the predisposing risk factors for PCa. As such, the present 13-year nationwide population-based study was conducted in order to evaluate the relationship between epididymo-orchitis and PCa in an Asian population.

## 2. Methods

### 2.1. Data source

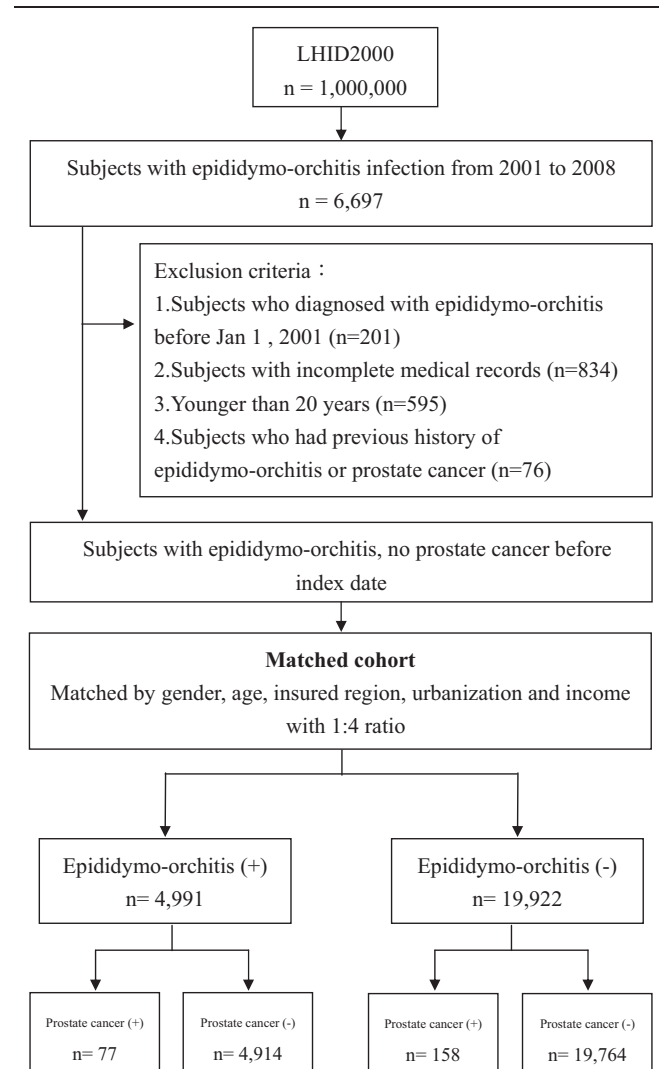
The National Health Insurance Research Database (NHIRD) of Taiwan is an administrative database derived from the National Health Insurance (NHI) program, a nationwide healthcare program established in 1995. The NHI program covers 99% of the 23 million residents of Taiwan.<sup>[11]</sup> We designed this retrospective cohort study utilizing the Longitudinal Health Insurance Database 2000 (LHID2000), which is a subdataset of the NHIRD.<sup>[12]</sup> The LHID2000 contains the health records for 1 million people randomly selected from among the 23 million residents included in the NHIRD in the year 2000. More specifically, the LHID2000 and NHIRD contain detailed inpatient and outpatient medical information for individual patients, including the dates of clinic visits and hospital admissions, disease diagnoses, medical procedures and surgical procedures, and medication prescriptions. All the diagnoses listed in the databases were made according to the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM), and all the data included in the data anonymized. Approval for this study was received from the Institutional Review Board of the Tri-Service General Hospital (approval number: TSGHIRB NO B-104-21.)

### 2.2. Study subjects

All the patients included in the study were included in the LHID2000 and were treated between January 2000 and December 2013. More specifically, we selected patients who were newly diagnosed with epididymo-orchitis (ICD-9-CM: 604) between 2001 and 2008 as the study group (Fig. 1). The exclusion criteria for the study group were as follows:

- (1) patients who were diagnosed with epididymo-orchitis before January 1, 2001 (n=34),
- (2) patients with incomplete medical records (n=402),
- (3) patients who were aged 0 to 19 years old (n=1397), and
- (4) patients with a history of epididymo-orchitis or PCa (n=26).

A control group of patients without epididymo-orchitis was also selected, with these patients matched to the patients with epididymo-orchitis at a 1:4 ratio. The control patients



**Figure 1.** Flowchart of recruitment of subjects from the 1-million random sample of the NHIRD from 2000 to 2008 in Taiwan. NHIRD = National Health Insurance Research Database.

without epididymo-orchitis were matched to the study group by age, monthly income, geographic area of residence, urbanization level of residence, and index date of epididymo-orchitis diagnosis (that is, for the epididymo-orchitis patients). A total of 19,922 subjects were enrolled in the control group.

A total of 4991 patients with epididymo-orchitis were enrolled as the study group. The diagnoses of epididymo-orchitis were based on clinical presentations, meaning they were based on the symptom of painful swelling of the scrotum, which may also have been combined with fever, frequency, and urgency. The diagnoses of epididymo-orchitis were made by urologists. Furthermore, we only included patients who had received antibiotic treatment and ultrasonography of the scrotum in this study. From January 1, 2001, to December 31, 2008, the index date for each patient was defined as the date that the diagnosis of epididymo-orchitis was made. We tracked each subject for a 5-year period following his index date in order to note any subsequent cases of PCa (ICD-9-CM:185).<sup>[13]</sup>

### 2.3. Outcome and covariates

The outcome of interest was the incidence of new cases of PCa in both the study group and control group during the 5-year follow-up period. In Taiwan, patients diagnosed with PCa are registered in the Registry for Catastrophic Illness Patient Database (RCIPD), with the medical records being fully evaluated in order to ensure that meeting of the diagnostic criteria is confirmed by experts assigned by the NHI administration. Following such confirmation, the patients with PCa receive waivers for further medical payments after receiving a catastrophic illness certification.

Covariates including age, monthly income, geographic area of residence, urbanization level of residence, and comorbidities were examined in both groups. Age was categorized into 6 groups: 20 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, and older than 70 years. Monthly income in New Taiwan Dollars (NTD) was divided into 4 categories: less than NTD 20,000, NTD 20,000 to NTD 39,999, NTD 40,000 to NTD 59,999, and more than NTD 60,000. The geographic area of residence in Taiwan was divided into northern region, central region, southern region, and other region. The urbanization level of residence was classified from 1 (highest) to 4 (lowest). Comorbidities including hypertension (ICD-9-CM: 401–405), hyperlipidemia (ICD-9-CM: 272), diabetes mellitus (ICD-9-CM: 250), coronary heart disease (ICD-9-CM: 410–414), chronic kidney disease (ICD-9-CM: 585, 586, 588), cerebral vascular accident (ICD-9-CM: 430–438), chronic obstructive pulmonary disease (COPD) (ICD-9-CM: 491, 492, 496), alcoholism (ICD-9-CM: 291, 303, 305.00, 571.1, 571.2, 571.3, 790.3, V11.3), obesity (ICD-9-CM: 278), tobacco use disorder (ICD-9-CM: 305.1, 491.0, 491.2, 492.8, 496, 523.6, 649.0, 989.84, V15.82.), sexually transmitted infections (STIs) (including syphilis, ICD-9-CM: 090–097), trichomoniasis (ICD-9-CM: 131), genital warts (ICD-9-CM: 054.1 078.11), chlamydia trachomatis (ICD-9-CM 078.8, 078.88), and gonorrhea (ICD-9-CM: 098) were also noted.

### 2.4. Statistical analysis

Descriptive statistics for the characteristics of the study subjects were analyzed and calculated using the Student *t* test and Chi-square test. We used a 1:4 propensity-score matched analysis with age, monthly income, geographic area of residence, and urbanization level of residence for both the epididymo-orchitis group and control group. The Cox proportional hazards regression model was used to calculate the risk of subsequent PCa and to obtain the effects of potential confounders. We calculated the hazard ratios (HRs) for the 2 groups at 95% confidence intervals (CIs). Adjustment for potential covariates (including age, income, geographic area of residence, level of urbanization of residence, and comorbidities) was performed in all models. We used the SPSS software version 19.0 (SPSS Inc., Chicago, IL) and Microsoft SQL Server 2008 software for data analysis. A 2-sided *P* value < .05 was viewed as the threshold for statistical significance.

## 3. Results

A total of 24,913 men were enrolled and analyzed in this 13-year nationwide population-based study. Among them, 4991 had epididymo-orchitis and served as the study group, while 19,922 had no epididymo-orchitis and served as the control group. The demographic characteristics of the patients are shown in Table 1.

**Table 1**

**Demographic characteristics associated with the epididymo-orchitis patients and control group.**

Characteristics	Epididymo-orchitis patients, n (%)	Control subjects, n (%)	<i>P</i> value
No. of cases	4991	19922	
Gender			
Male	4991 (100%)	19922 (100%)	
Age			1
20–29	1065 (21.3%)	4258 (21.4%)	
30–39	1034 (20.7%)	4129 (20.7%)	
40–49	944 (18.9%)	3773 (18.9%)	
50–59	685 (13.7%)	2739 (13.7%)	
60–69	494 (9.9%)	1962 (9.8%)	
≥ 70	769 (15.5%)	3061 (15.5%)	
Insured region			.999
Northern Taiwan	2706 (54.2%)	10817 (54.3%)	
Middle Taiwan	895 (17.9%)	3566 (17.9%)	
Southern Taiwan	1258 (25.3%)	5018 (25.2%)	
Other (Eastern Taiwan and outlying islands)	132 (2.6%)	521 (2.6%)	
Urbanization			1
1 (highest)	2410 (48.2%)	9633 (48.4%)	
2	1238 (24.8%)	4935 (24.8%)	
3	921 (18.5%)	3677 (18.5%)	
4 (lowest)	422 (8.5%)	1677 (8.3%)	
Insured amount NTD <sup>†</sup>			.996
<20000	3341 (66.9%)	13364 (67.1%)	
20000–39999	848 (17.0%)	3372 (16.9%)	
40000–59999	572 (11.5%)	2281 (11.4%)	
≥ 60000	230 (4.6%)	905 (4.5%)	
Comorbidity disease			
Diabetes Mellitus	916 (18.4%)	2425 (12.2%)	<.001*
Hypertension	1716 (34.4%)	4786 (24.0%)	<.001*
Hyperlipidemia	1137 (22.8%)	3351 (16.8%)	<.001*
Coronary heart disease	978 (19.6%)	2199 (11.0%)	<.001*
Cerebral vascular accident	692 (13.9%)	1546 (7.8%)	<.001*
COPD	977 (19.6%)	2179 (10.9%)	<.001*
Alcoholism	150 (3.0%)	370 (1.9%)	<.001*
Obesity	61 (1.2%)	112 (0.6%)	<.001*
Tobacco use disorder	934 (18.7%)	2083 (10.5%)	<.001*
STI	150 (3.0%)	207 (1.0%)	<.001*

COPD=chronic obstructive pulmonary disease, STI=sexually transmitted infection.

<sup>†</sup>NTD refers to New Taiwan dollars, of which 1 US dollar=30 TWD.

\* *P* < .05.

The mean age of the patients with epididymo-orchitis was 46.50 ± 18.20 years, while the mean age of the control group patients was 46.40 ± 18.10 years. The majority of the patients with epididymo-orchitis were aged 20 to 49 years old, and the majority of these patients lived in the northern part of Taiwan. Hypertension and hyperlipidemia were the most common comorbidities of the patients with epididymo-orchitis. Moreover, there were significantly higher prevalences of diabetes mellitus (DM), hypertension, stroke, coronary artery disease (CAD), COPD, obesity, alcoholism, tobacco use disorders, and sexually transmitted infections (STIs) among the patients with epididymo-orchitis than among the control group patients.

Table 2 shows the incidence of PCa and the results of the multivariable analysis of the 5-year follow-up for the patients with epididymo-orchitis and the control group. Among all 24,913 subjects, 235 (0.9%) were diagnosed with PCa during the

**Table 2**  
Individuals with and without epididymo-orchitis as predictors of prostate cancer identified by Cox regression.

	No. of cases	
	Epididymo-orchitis patients n = 4991	Without epididymo-orchitis subjects n = 19,922
With prostate cancer	77 (1.5%)	158 (0.8%)
Without prostate cancer	4914 (98.5%)	19764 (99.2%)
Average follow-up days	1807.7	1817.1
PY	24,718	99,179
IR	3.12	1.59
Crude HR	1.96 (1.49 to 2.57)**	

HR=hazard ratio, IR=incidence rate per 1000 person-years, PY=person-years.

\*\*  $P < .001$  for comparison between patients with 2 groups.

5-year follow-up period. There were 77 (1.5%) cases of PCa among the patients with epididymo-orchitis, and 158 (0.8%) cases of PCa in the control group. The incidence rates (IRs) of PCa were thus 3.12 per 1000 person-years in the epididymo-orchitis group and 1.59 per 1000 person-years in the control group. The patients with epididymo-orchitis had a crude HR of 1.96 (95% CI: 1.49–2.57) compared to the control group.

The cox regression analysis results regarding the independent risk factors of PCa are shown in Table 3. After adjusting for age, income, geography, urbanization, and comorbidities, the patients with epididymo-orchitis still had a significantly associated with an increased risk of subsequent PCa (adjusted hazard ratio [aHR]: 1.56, 95% CI: 1.18–2.06). Ages of more than 70 years, higher incomes, hypertension (aHR: 1.52; 95% CI: 1.09–2.13), and hyperlipidemia (aHR: 1.44; 95% CI: 1.07–1.93) were significant risk factors for PCa. The highest aHR in the different age groups was that for patients older than 70 years, which was 31.53 (95% CI: 11.32–87.80) compared to that for patients aged 20 to 29 years.

#### 4. Discussion

A review of the literature indicated that no large-scale study investigating the association between epididymo-orchitis and the incidence of PCa had previously been conducted. As such, we conducted this large nationwide cohort study with a 5-year follow-up period, the results of which demonstrated that epididymo-orchitis associated with an increased the risk of subsequent PCa. A Cox regression analysis indicated that, compared with the control group, the patients with epididymo-orchitis had a 56% increased risk of PCa.

There are several risk factors of PCa including chronic prostatic inflammation, urine reflux, and bladder outlet obstruction (BOO). Both urine reflux and BOO may lead subsequent inflammation of the prostate or damage the prostate epithelium.<sup>[14]</sup> It has been reported that chronic inflammation of the prostate may be a precursor of prostate carcinogenesis.<sup>[15]</sup> Proliferative inflammatory atrophy (PIA) consists of chronic inflammation of the prostate that has the possibility of further progressing to PCa.<sup>[16]</sup> PIA reduces the activity of glutathione S-transferase P1, thus decreasing the degree of protection from oxidative damage provided to the genome.<sup>[17]</sup> Epididymo-orchitis is an infection of the epididymis or testis. The pathogens that cause epididymo-orchitis most commonly originate in the urethra or the bladder. STIs and UTIs are major sources of

**Table 3**  
Independent risk factors of prostate cancer identity by Cox regression analysis in the 5 years follow-up period.

	Crude HR (95% CI)	Adjusted HR (95% CI)
Epididymo-orchitis	1.96 (1.49 to 2.57)**	1.56 (1.18 to 2.06)*
Age		
20–29	1	1
30–39	0.77 (0.17 to 3.46)	0.66 (0.15 to 2.97)
40–49	4.24 (1.41 to 12.76)*	3.05 (0.99 to 9.33)
50–59	10.93 (3.83 to 31.15)**	6.83 (2.34 to 19.89)**
60–69	25.15 (9.05 to 69.86)**	15.38 (5.41 to 43.78)**
≥70	49.24 (18.22 to 133.05)**	31.53 (11.32 to 87.8)**
Insured region		
Northern Taiwan	1	1
Middle Taiwan	0.66 (0.45 to 0.98)*	0.66 (0.44 to 0.99)*
Southern Taiwan	0.85 (0.62 to 1.16)	0.65 (0.47 to 0.91)*
Other (Eastern Taiwan and outlying islands)	0.87 (0.39 to 1.98)	0.65 (0.28 to 1.49)
Urbanization		
1 (highest)	1	1
2	0.64 (0.46 to 0.91)*	0.63 (0.45 to 0.89)*
3	0.87 (0.62 to 1.22)	0.83 (0.58 to 1.19)
4 (lowest)	0.60 (0.35 to 1.05)	0.54 (0.30 to 1.01)
Insured amount NTD <sup>†</sup>		
<20000	1	1
20000–39999	1.38 (0.23 to 1.91)	1.10 (0.65 to 1.87)
40000–59999	1.47 (0.28 to 2.19)	1.21 (0.68 to 2.14)
≥ 60000	2.10 (1.14 to 3.89)**	2.01 (1.11 to 3.61)*
Comorbidity disease		
Diabetes Mellitus	3.70 (2.83 to 4.82)**	1.25 (0.93 to 1.68)
Hypertension	5.76 (4.39 to 7.55)**	1.52 (1.09 to 2.13)*
Hyperlipidemia	2.84 (2.19 to 3.70)**	1.44 (1.07 to 1.93)*
Coronary heart disease	4.53 (3.49 to 5.89)**	1.12 (0.83 to 1.51)
Cerebral vascular accident	3.66 (2.74 to 4.89)**	0.79 (0.58 to 1.09)
COPD	5.17 (3.99 to 6.70)**	1.27 (0.81 to 2.01)
Alcoholism	0.40 (0.10 to 1.61)	0.58 (0.14 to 2.35)
Obesity	1.23 (0.31 to 4.94)	1.28 (0.32 to 5.18)
Tobacco use disorder	4.64 (3.57 to 6.03)**	1.43 (0.90 to 2.25)
STI	1.81 (0.81 to 4.08)	1.76 (0.78 to 3.97)

CI=confidence interval, COPD=chronic obstructive pulmonary disease, HR=hazard ratio, STI=sexually transmitted infection.

<sup>†</sup> NTD refers to New Taiwan dollars, of which 1 US dollar=30 TWD.

\*  $P < .05$ .

\*\*  $P < .001$ .

epididymo-orchitis.<sup>[4]</sup> The risk factors for epididymo-orchitis also include prostatitis, bladder obstruction, the insertion of a urinary catheter, and urethrocytoscopy.<sup>[4]</sup> One mechanism that could possibly explain the association between epididymo-orchitis and PCa is inflammation. Furthermore, prostatitis, STIs, and UTIs, which have been reported to increase the risk of PCa, also affect the risk of epididymo-orchitis.<sup>[18–21]</sup> Prostatitis, or chronic inflammation of the prostate, further results in carcinogenesis of the prostate. Wang et al conducted a study of 355 men with gonorrhea and 1420 controls and found that gonorrhea resulted in a 5-fold increased risk of PCa.<sup>[19]</sup> Meanwhile, gonorrhea infection is one of the major causes of epididymo-orchitis.<sup>[22]</sup> However, the possible mechanisms of PCa and the potential roles of asymptomatic prostatic inflammation and epididymo-orchitis require further investigation.

The high-income patients with epididymo-orchitis in this study were found to have associated with an increased risk of PCa, a finding which is compatible with those of previous studies.<sup>[23,24]</sup> Possible reasons for this increased risk include that these patients

have relatively high-fat diets or greater awareness of the need to seek out early screening for PCa. Age is a well-known risk factor for PCa, and this study also found an increased risk of PCa with age.<sup>[21]</sup> Hyperlipidemia was also associated with an increased risk of PCa in this study. Kitahara et al conducted a prospective study in Korea of 756,604 men, including 2490 cases of PCa. The results showed that 329 men in the highest quintile of total cholesterol ( $\geq 240$  mg/dL) had a 124% increased risk of PCa.<sup>[25]</sup> However, the association between hypertension and the risk of PCa is controversial. Liang et al conducted a meta-analysis of 21 published studies and found that hypertension resulted in a 108% increased risk of PCa.<sup>[26]</sup> Our study also revealed that hypertension increased the risk of PCa.

The main strength of this study is that it is a large cohort study utilizing a longitudinal nationwide database. However, it still had some limitations. First, the diagnosis of epididymo-orchitis was defined according to the ICD-9-CM code. The ICD-9-CM code 604.90 is used for both epididymitis and orchitis. As such, there may have misdiagnoses of other infections in our study. However, in order to minimize the possible impacts of misdiagnoses, we only enrolled patients who received antibiotic treatments and ultrasonography of the scrotum. Second, laboratory test results including those for urine cultures, C-reactive protein (CRP) levels, and PSA levels are not included in the NHIRD. Third, the stage and Gleason's scores of PCa, which may help to define the severity of PCa, are also not included in the NHIRD. Moreover, data regarding some risk factors of prostate cancer, such as those relating to family history and dietary habits, are likewise not included in the NHIRD. Finally, this study utilized a retrospective study design. Further prospective studies with a larger population and longer follow-up period are warranted to investigate the association between epididymo-orchitis and PCa.

## 5. Conclusion

In conclusion, our study is the first study to discover that patients with epididymo-orchitis have associated with an increased risk for subsequent PCa. Epididymo-orchitis infection may be a determining factor for PCa incidence due to the effects of chronic inflammation. Physicians may pay attention to this association when assessing patients with epididymo-orchitis. Further studies are warranted to investigate the association between epididymo-orchitis and PCa.

## Author contributions

All authors contributed to the creation of the manuscript. Wen-Lin Hsu, Jui-Ming Liu and Heng-Chang Chuang conceived, and designed the study. Ren-Jun Hsu and Heng-Chang Chuang provided administrative support. Chien-Yu Lin and Jui-Ming Liu analyzed and interpreted the data. All authors were involved in collection and assembly of data. All authors approved the final version of the manuscript.

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