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Calculus-induced obstructive hydronephrosis and herpes zoster risk: a retrospective analysis of the TriNetX global database

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Abstract

Background This study investigates the association between urolithiasis-induced hydronephrosis and the reactivation of herpes zoster (HZ).

Methods This retrospective cohort study utilized data from the TriNetX database. Participants aged ≥ 20 years with a newly diagnosis of "calculus of kidney with calculus of ureter" between 2011 and 2022 were included. The cohort was divided into two groups: those with (case) and without (control) "hydronephrosis with renal and ureter calculus obstruction." The primary endpoint was the diagnosis of HZ within 1- and 2-year post-index date, comparing outcomes between the case and control groups. Propensity score matching was applied to create a 1:1 matched cohort. Risk ratios and odds ratios were calculated to evaluate the association between exposure and outcome.

Results Before matching, there were 40,615 participants in the case group and 68,085 in the control group. After propensity score matching, the cohorts were balanced, with 38,100 participants in each group. Compared to patients without hydronephrosis, those with hydronephrosis had a higher risk of HZ, with risk ratios and odds ratios of 1.585 and 1.588 within 1 year, and 1.305 and 1.308 within 2 years, respectively.

Conclusions A significant association between calculus-induced obstructive hydronephrosis and increased HZ incidence, with particularly elevated risk observed during the first year following diagnosis. These findings suggest the importance of monitoring for HZ in patients with obstructive uropathy.

Keywords TriNetX, Urolithiasis, Hydronephrosis, Herpes zoster

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Background

Urolithiasis is characterized by the formation and presence of calculi within the urinary system, affecting approximately 2–20% of the global population [1–4]. In their comprehensive analysis of the Global Burden of Disease study data spanning from 1990 to 2019, Borumandnia and colleagues documented distinct regional variations in urolithiasis incidence trends. While the majority of global regions exhibited an upward trajectory, Eastern Europe, Central Europe, and Southeast Asia demonstrated notable declining patterns, with decremental rates of − 71.4, − 56.2, and − 9.2 per 100,000 population, respectively. Conversely, the Caribbean region emerged as the area with the most pronounced increase in urolithiasis incidence, followed by Central Asia, recording incremental rates of 48.3 and 34.3 per 100,000 population, respectively [5]. However, from a global perspective, Lang and colleagues' analysis revealed that the age-standardized incidence of urolithiasis demonstrated a significant downward trend, declining from 1696.2 per 100,000 population in 1990 to 1394.0 per 100,000 population in 2019, corresponding to an average annual percentage change of − 0.7% throughout this observational period [6].

Urolithiasis represents a significant etiological factor in the development of hydronephrosis. Hydronephrosis is characterized by the dilatation of the renal collecting system, encompassing either unilateral or bilateral kidney involvement, resulting from mechanical or functional obstruction of urinary outflow at any point distal to the renal pelvis. In the adult population, acute urinary outflow obstruction characteristically manifests with a persistent, obtuse discomfort attributed to distension of the renal capsule, interspersed with paroxysmal episodes of severe pain precipitated by genitourinary peristaltic activity that transiently elevates intraluminal pressure [7].

Hsiao et al. reported that among urinary tract infection patients with urolithiasis, those with ureteral stones complicated by hydronephrosis exhibit a significantly higher risk of developing acute kidney injury. A further analysis identified ureteral stones with concomitant hydronephrosis as an independent risk factor for acute kidney injury, with an odds ratio (OR) of 2.299 [8]. Therapeutic intervention for hydronephrosis necessitates urinary tract decompression, which can be achieved through two primary modalities: percutaneous nephrostomy or retrograde ureteral stenting. Percutaneous nephrostomy demonstrates superior patient tolerability compared to retrograde ureteral stenting, as evidenced by diminished post-procedural urinary symptoms and enhanced quality-of-life metrics [9]. The decreased symptomatic burden associated with percutaneous nephrostomy may be attributed to the circumvention of lower urinary tract irritation, which is commonly observed in patients with indwelling ureteral stents.

Herpes zoster (HZ), caused by the varicella–zoster virus, is a viral infection marked by a painful rash or blistering skin eruption. Typically, the rash presents as a localized band or cluster of lesions in a specific region of the body. HZ demonstrates significant associations with various systemic conditions, including diabetes mellitus (DM) [10, 11], obesity [12], malignancies [13, 14], and psychiatric disorders, particularly depression [15, 16]. Notably, there is a documented correlation between HZ and pain-associated musculoskeletal conditions, specifically frozen shoulder [17], lateral epicondylitis [18], and de Quervain tenosynovitis [19]. Given that hydronephrosis frequently manifests with pain, a potential relationship between hydronephrosis and HZ reactivation warrants investigation. This investigation aims to clarify the potential association between HZ reactivation and urolithiasis-induced hydronephrosis, focusing on the relationship between these clinical entities.

Materials and methods

Data source

This retrospective cohort study leveraged data from TriNetX, a global health research network that aggregates real-world data from electronic health records of approximately 155 million patients across 144 healthcare organizations worldwide at the time of analysis. The TriNetX platform provides access to comprehensive clinical data elements, including patient demographics, diagnostic codes (utilizing International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]), procedural interventions, and pharmaceutical prescriptions. The network's database undergoes systematic de-identification and anonymization processes in accordance with privacy regulations, thereby exempting this research from formal ethical review requirements. This federated database architecture ensures compliance with data protection standards while facilitating large-scale observational research.

Study population

This investigation identified eligible participants aged ≥ 20 years who received a newly diagnosis of "calculus of kidney with calculus of ureter" (ICD-10-CM: N20.2) between January 1, 2011, and December 31, 2022. The study cohort was stratified into two distinct groups based on the presence (case) or absence (control) of "hydronephrosis with renal and ureter calculus obstruction" (ICD-10-CM: N13.2). The index date was established as the initial documentation of "calculus of kidney with calculus of ureter" diagnosis. Exclusion criteria encompassed pre-existing diagnoses of chronic kidney disease

(ICD-10-CM: N18) or HZ (ICD-10-CM: B02) prior to the index date. Baseline demographic and clinical characteristics were extracted, including age, sex, and pertinent comorbidities: DM (ICD-10-CM: E08–E13), overweight and obesity (ICD-10-CM: E66), neoplasms (ICD-10-CM: C00–D49), osteoarthritis (ICD-10-CM: M15–M19), depressive episodes (ICD-10-CM: F32), systemic lupus erythematosus (SLE) (M32) and inflammatory bowel disease (IBS) (K50–52). To minimize potential confounding factors and selection bias, propensity score matching was implemented using the TriNetX platform's proprietary matching algorithm to generate a 1:1 matched cohort. The propensity score model incorporated the following variables: age, sex, and all aforementioned comorbidities. This matching procedure facilitated the creation of comparable case and control groups with balanced baseline characteristics.

Primary outcome and statistical analysis

The primary endpoint was defined as the incident diagnosis of HZ (ICD-10-CM: B02) within 1- and 2-year post-index date, comparing outcomes between the case and control cohorts. The analysis was conducted utilizing the TriNetX analytics platform. Statistical analyses encompassed both descriptive and inferential methodologies. The quality of propensity score matching was evaluated using standardized differences (SD), with an SD threshold of <0.1 indicating adequate balance between groups for baseline characteristics. Effect sizes were quantified through both risk ratios (RR) and OR, accompanied by their respective 95% confidence intervals (95% CI). The threshold for statistical significance was established at a two-sided p value <0.05. The dual approach of reporting both RR and OR provides complementary perspectives on the association between exposure and outcome, enhancing the robustness of our findings. This analytical framework allows for comprehensive assessment of the temporal relationship between nydronephrosis due to obstructive urolithiasis and subsequent HZ development.

Results

The participant selection algorithm is illustrated in Fig. 1. The flowchart provides a detailed overview of the cohort refinement process, starting with patients

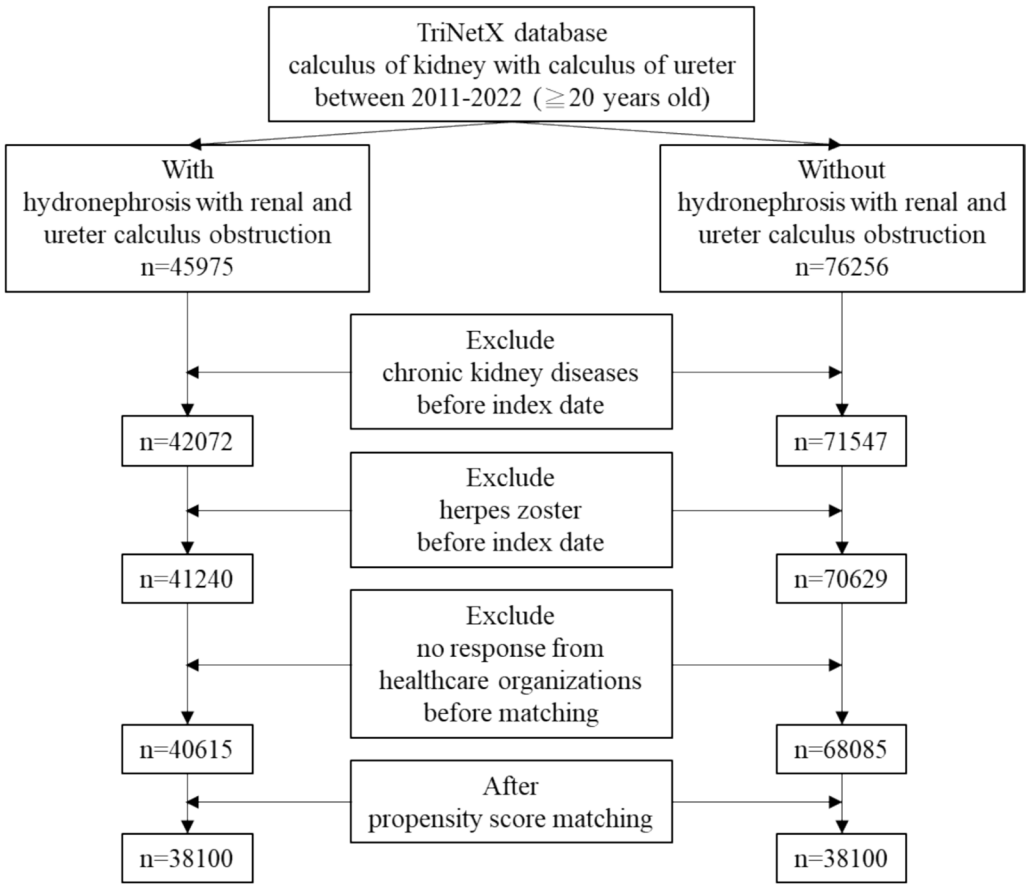

Fig. 1 Flowchart of patients' selection

identified in the TriNetX database diagnosed with kidney and ureteral calculi between 2011 and 2022, specifically those aged over 20 years. Initially, 45,975 patients with hydronephrosis and obstruction due to renal and ureteral calculi were identified, while a comparison group of 76,256 patients without such conditions was established. The first exclusion step removed patients with chronic kidney diseases prior to the index date, reducing the groups to 42,072 and 71,547, respectively. Subsequently, patients with a history of HZ before the index date were excluded, further refining the cohorts to 41,240 and 70,629. Patients for whom healthcare organizations did not provide responses were excluded in the next step, narrowing the groups to 40,615 and 68,085 participants. Finally, propensity score matching was applied to balance the demographic and clinical characteristics of the groups, resulting in two well-matched cohorts of 38,100 patients each.

Table 1 presents the characteristics of the case and control cohorts before matching. The cases group comprises 40,615 individuals, while the controls include 68,085 individuals. Demographically, the mean age at index was higher in the cases group (54.3 ± 16.5 years) compared to controls (51.6 ± 16.9 years). Gender proportions also differ, with females comprising 42.6% of cases and 40.3% of controls, and males 51.5% in cases vs. 56.6% in controls. Clinically, conditions such as DM, overweight and obesity, osteoarthritis, neoplasms, depressive episodes, SLE and IBS are more prevalent in the cases group than in controls, with significant *p* values (< 0.001). These results demonstrate notable disparities in baseline characteristics between cases and controls, underlining the need for propensity score matching to minimize confounding in subsequent analyses.

Table 2 summarizes the characteristics of the case and control cohorts after propensity score matching. Both

Table 1 Characteristics of case and control cohorts before propensity score matching

	Cases (*n*, %) (*n* = 40,615)	**Controls (*n*, %) (*n* = 68,085)**	***p* value**	**Std diff**
Age at index (mean ± SD)	54.3 ± 16.5	51.6 ± 16.9	< 0.001	0.165
Female	17,295 (42.6%)	27,453 (40.3%)	< 0.001	0.046
Male	20,916 (51.5%)	38,532 (56.6%)	< 0.001	0.102
Comorbidities				
Diabetes mellitus	8355 (20.6%)	7454 (10.9%)	< 0.001	0.266
Overweight and obesity	10,752 (26.5%)	8727 (12.8%)	< 0.001	0.349
Osteoarthritis	9232 (22.7%)	8141 (12.0%)	< 0.001	0.288
Neoplasms	12,498 (30.8%)	12,615 (18.5%)	< 0.001	0.287
Depressive episode	6740 (16.6%)	5893 (8.7%)	< 0.001	0.241
Systemic lupus erythematosus	213 (0.5%)	204 (0.3%)	< 0.001	0.035
Inflammatory bowel disease	4371 (10.8%)	4037 (5.9%)	< 0.001	0.175

SD: standard deviation

Table 2 Characteristics of case and control cohorts after propensity score matching

	Cases (n, %) (*n* = 38,100)	**Controls (n, %) (*n* = 38,100)**	***p* value**	**Std diff**
Age at index (mean ± SD)	53.9 ± 16.6	53.9 ± 16.6	0.825	0.002
Female	16,040 (42.1%)	15,971 (41.9%)	0.613	0.004
Male	20,102 (52.8%)	20,132 (52.8%)	0.828	0.002
Comorbidities				
Diabetes mellitus	6977 (18.3%)	7030 (18.5%)	0.620	0.004
Overweight and obesity	8752 (23.0%)	8654 (22.7%)	0.398	0.006
Osteoarthritis	7682 (20.2%)	7636 (20.0%)	0.678	0.003
Neoplasms	10,770 (28.3%)	10,865 (28.5%)	0.445	0.006
Depressive episode	5604 (14.7%)	5621 (14.8%)	0.862	0.001
Systemic lupus erythematosus	170 (0.4%)	159 (0.4%)	0.543	0.004
Inflammatory bowel disease	3688 (9.7%)	3627 (9.5%)	0.453	0.005

SD: standard deviation

groups consist of 38,100 individuals, and the matching process successfully balanced the baseline characteristics. Demographically, the mean age at index is nearly identical between cases and controls (53.9 ± 16.6 years), with no statistically significant difference. Similarly, the proportions of females (42.1% in cases vs. 41.9% in controls) and males (52.8% in cases vs. 52.8% in controls) are well-balanced. For clinical conditions, all variables show negligible differences between the two groups. For example, the prevalence of DM is 18.3% in cases vs. 18.5% in controls, and overweight and obesity is 23.0% in cases vs. 22.7% in controls. Similar results are observed for osteoarthritis, neoplasms, depressive episodes, SLE and IBS. The propensity score matching effectively balanced the case and control cohorts, as demonstrated by the minimal standardized differences and non-significant *p* values across all variables, ensuring comparability for subsequent analyses.

Table 3 presents an analysis of the risk of specific outcomes within 1 and 2 years, comparing the case and control groups prior to propensity score matching. Table 4 provides an analysis of risk for patients experiencing specific outcomes within 1 and 2 years, comparing case and control groups after propensity score matching. For outcomes within 1 year, 206 patients in the case group and 130 in the control group experienced the outcome. The RR is 1.585 (95% CI 1.273–1.973), indicating that patients in the case group are 58.5% more likely to encounter the outcome compared to those in the control group. The OR similarly shows a significant increase, at 1.588 (95% CI 1.274–1.979), reflecting a consistent result in terms of the odds of experiencing the outcome. Within 2 years, 338 patients in the case group and 259 in the control group experienced the outcome. The RR decreases slightly to 1.305 (95% CI 1.111–1.533), signifying a 30.5% higher risk for cases. The OR, at 1.308 (95% CI 1.112–1.538), aligns closely, showing a modest increase in risk over this longer timeframe. This result demonstrates that patients in the case group have consistently higher risks and odds of experiencing outcomes compared to controls, with stronger effects observed in the first year.

Discussion

To the best of our knowledge, this represents the inaugural investigation elucidating the association between hydronephrosis and HZ occurrence among individuals with urolithiasis. Our findings demonstrate that patients with concurrent urolithiasis and hydronephrosis exhibited a 1.6-fold increased risk of HZ development within a 1-year follow-up period, compared to those presenting with urolithiasis alone. This novel observation suggests a potential mechanistic relationship between upper urinary tract obstruction and varicella–zoster virus reactivation, contributing to our understanding of the complex interplay between hydronephrosis and HZ development.

Two meta-analysis studies have identified potential risk factors for HZ, including DM, endocrine and metabolic disorders, cancer, and depression [20, 21]. Poirrier and colleagues conducted an epidemiological analysis examining the incidence of HZ infection among individuals with DM utilizing U.S. commercial claims data. Their findings demonstrated significantly elevated rates of HZ among diabetic patients compared to non-diabetic controls, with incidence rates of 9.8 and 2.6 per 1,000 person-years, respectively. After adjusting for potential confounding variables, the investigators determined that patients with diabetes exhibited an 84% higher risk of developing HZ, suggesting DM may

Table 3 Risk analysis for patients with outcomes within 1- and 2-year periods before propensity score matching

	Patients with outcomes		Risk ratio (95% CI)	Odds ratio (95% CI)
	Cases (risk) (*n* = 41,567)	Controls (risk) (*n* = 71,089)		
Within 1 year	233 (0.561%)	192 (0.270%)	2.075 (1.715, 2.511)	2.081 (1.719, 2.521)
Within 2 years	384 (0.924%)	355 (0.499%)	1.850 (1.602, 2.136)	1.858 (1.607, 2.147)

Table 4 Risk analysis for patients with outcomes within 1- and 2-year periods after propensity score matching

	Patients with outcomes		Risk ratio (95% CI)	Odds ratio (95% CI)
	Cases (risk) (*n* = 38,100)	Controls (risk) (*n* = 38,100)		
Within 1 year	206 (0.541%)	130 (0.341%)	1.585 (1.273, 1.973)	1.588 (1.274, 1.979)
Within 2 years	338 (0.887%)	259 (0.680%)	1.305 (1.111, 1.533)	1.308 (1.112, 1.538)

be an important risk factor for HZ infection [22]. In a meta-analysis encompassing five cohort studies, Lai and colleagues corroborated previous findings regarding the association between DM and HZ risk. The investigators reported HZ incidence rates of 7.22 and 4.12 per 1000 person-years among diabetic and non-diabetic populations, respectively. Through statistical synthesis of these cohort studies, the researchers demonstrated that DM was associated with a 60% increased risk of HZ development, providing robust epidemiological evidence for DM as a significant risk factor for HZ infection [23].

Chen and colleagues conducted a population-based cohort study utilizing the National Health Insurance Research Database of Taiwan to examine the relationship between obesity and HZ occurrence. The investigation encompassed a total study population of 37,710 subjects, equally distributed between obesity and control cohorts (n= 18,855 per cohort). The researchers demonstrated that individuals with obesity exhibited a modestly elevated risk of HZ compared to non-obese controls (adjusted hazard ratio [aHR] =1.09). Notably, stratified analysis revealed that subjects with morbid obesity demonstrated a substantially increased risk of HZ development compared to those with non-morbid obesity (aHR =1.47) [12]. These findings suggest a graded association between adiposity and HZ risk, with morbid obesity conferring a particularly pronounced elevation in susceptibility to HZ infection.

In an epidemiological investigations, researchers examined the association between malignancy and HZ risk. Habel and colleagues conducted a longitudinal study of 14,670 newly diagnosed cancer patients, identifying 424 incident HZ cases during a median follow-up period of 22 months. The observed incidence rates were markedly elevated, with 31 cases per 1,000 person-years among patients with hematologic malignancies and 12 cases per 1,000 person-years among those with solid tumors. When standardized by age and sex relative to the general U.S. population, the incidence rates were 4.8-fold and 1.9-fold higher in hematologic and solid malignancy cohorts, respectively [13]. These findings were subsequently corroborated by Qian and colleagues in a larger cohort study encompassing 20,286 patients with newly diagnosed malignancies, documenting 16,350 HZ events. Through analysis, the investigators demonstrated substantially elevated risks of HZ among patients with hematological malignancies (aHR =3.74) and solid tumors (aHR =1.30) compared to cancer-free controls [14]. Collectively, these investigations provide compelling evidence that malignancy represents a significant risk factor for HZ infection, with particularly pronounced risk elevation observed among patients with hematological malignancies [13, 14].

In investigations examining the relationship between psychological conditions and HZ risk, researchers have documented an association between depression and increased HZ occurrence. In a large-scale epidemiological study utilizing Taiwan's National Health Insurance database, Liao and colleagues analyzed 22,886 patients with depression and demonstrated a 30% higher incidence of HZ compared to non-depressed controls. After adjustment for potential confounders, depression remained independently associated with HZ risk (aHR =1.11) [15]. These findings were subsequently validated in an independent investigation utilizing the Korean National Health Insurance database. Choi and colleagues reported a higher prevalence of HZ infection among individuals with depression compared to those without (6.8% vs. 6.3%). A further analysis identified a modest yet statistically significant increase in the risk of HZ among patients with depression (aHR =1.09) [16]. These concordant findings from two large Asian populations suggest that psychological conditions, particularly depression, may represent an underappreciated risk factor for HZ infection. The observed association may be mediated through depression-induced alterations in immune function, highlighting the potential importance of psychological health in viral reactivation.

Metabolic syndrome components, including DM and obesity, along with IBS [24], have been identified as risk factors for HZ development. Furthermore, these factors have demonstrated associations with urinary calculi formation. Epidemiological data from Taiwan presented by Chang et al. [25] revealed an elevated prevalence of nephrolithiasis among individuals with metabolic syndrome compared to those without this condition (OR =1.32). A recent meta-analysis by Dassanayake et al., [26] encompassing 11 studies, established a statistically significant association between metabolic syndrome and nephrolithiasis, with a pooled adjusted OR of 1.22. These findings substantiate the correlation between metabolic syndrome and renal calculi. Gaspar et al. [27] documented that urolithiasis manifested in 95 individuals (10.5%) from 901 patients diagnosed with Crohn's disease, with a gender distribution revealing male predominance (61.81%) compared to female representation (38.19%). Miyajima et al. [28] elucidated that male sex, previous glucocorticoid therapeutic intervention, and diminished residual small intestinal length constitute risk factors for urolithiasis in patients with Crohn's disease. Their multivariate analysis confirmed that these variables represent statistically significant predictors for the development of urinary calculi in this patient population. The relationship between IBS and nephrolithiasis has been established.

Based on the comprehensive review of established risk factors for HZ, including metabolic disorders (DM,

obesity), malignancies (particularly hematological cancers), and psychological conditions (depression), our investigation revealed a novel association between hydronephrosis and HZ occurrence in patients with urolithiasis. Notably, this relationship persisted after rigorous propensity score matching that accounted for known risk factors including DM, obesity, malignancy, osteoarthritis, depression, SLE and IBS. The persistence of this association after controlling for established risk factors suggests that hydronephrosis may represent an independent physiological stressor capable of modulating immune function and facilitating viral reactivation.

Pain-associated diseases have been identified as being correlated with the development of HZ. Given that hydronephrosis is a condition that can induce significant pain, it is plausible that an association exists between hydronephrosis and the occurrence of HZ. Research by Generaal and colleagues demonstrated that chronic pain conditions are associated with immune dysregulation, characterized by elevated baseline inflammatory markers, including C-reactive protein, interleukin-6, and tumor necrosis factor-alpha, compared to healthy controls [29]. Further elucidating the immune mechanisms, Yang et al. [30] identified distinct roles for both innate and adaptive immune cells in pain progression. Specifically, they found that innate immune cells (neutrophils, macrophages, and mast cells) facilitate the transition from acute to chronic pain states, while adaptive immune cells (B and T lymphocytes) are primarily involved in pain initiation, with T cells additionally contributing to pain resolution. In the context of hydronephrosis, Huang et al. demonstrated elevated serum levels of intercellular adhesion molecule-1 (ICAM-1) in patients with unilateral hydronephrosis secondary to ureteral calculi. Their findings suggest ICAM-1's potential role in renal immune responses to ureteral obstruction [31]. Moreover, emerging evidence indicates that ICAM-1 may serve dual functions in cellular scavenging and pathogen entry mechanisms [32]. Given these interconnected immune pathways, it is reasonable to hypothesize that hydronephrosis-induced immune dysregulation may influence HZ reactivation risk.

This retrospective study has several notable limitations that warrant consideration. Primarily, as the data was sourced from the TriNetX database, patient follow-up may have been incomplete if individuals sought subsequent care at healthcare organizations outside the TriNetX network, potentially affecting the comprehensiveness of our findings. However, this study focuses only on year 1 and year 2, which may reduce the likelihood of loss to follow-up. While we cannot provide precise follow-up completion rates, we have conducted analyses based on the available data within these 2 years. Second, the reliance on ICD-10 coding for diagnosis introduces misclassification bias. We attempted to mitigate this limitation by employing more specific diagnostic codes—"calculus of kidney with calculus of ureter" rather than the broader "urolithiasis," or "ureteral stones" and "hydronephrosis with renal and ureteral calculous obstruction" instead of general "hydronephrosis." These more stringent diagnostic criteria were implemented to minimize potential classification bias. Third, the unavailability of raw data within the TriNetX platform precluded additional analyses beyond those permitted by the system's inherent capabilities. Fourth, the TriNetX database does not provide certain granular clinical details, such as the severity grade of hydronephrosis, which could have offered valuable insights into disease progression and outcomes. Finally, this study relies on diagnostic codes, which may not accurately reflect the true exposure or outcome status of all individuals. Such misclassification is a well-recognized limitation in studies utilizing administrative or electronic health record data. When the likelihood of misclassification is similar across comparison groups—a condition known as non-differential misclassification—the resulting bias generally attenuates the observed associations, shifting effect estimates toward the null. Consequently, this may lead to more conservative estimates of the true relationship. Despite these limitations, the study's considerable strengths lie in its large sample size and the global nature of the TriNetX database, which enhances the generalizability of our findings and provides clinicians with robust evidence to inform clinical decision-making. Future prospective studies are warranted to elucidate the causal relationship between hydronephrosis and HZ onset.

Conclusion

This study demonstrates a significant association between calculus-induced obstructive hydronephrosis and increased HZ incidence, with particularly elevated risk observed during the first year following diagnosis. These findings suggest the importance of monitoring for HZ in patients with obstructive uropathy.

Abbreviations

aHR	Adjusted hazard ratio
CI	Confidence interval
DM	Diabetes mellitus
HZ	Herpes zoster
IBS	Inflammatory bowel disease
ICAM-1	Intercellular adhesion molecule-1
ICD-10-CM	International classification of diseases, tenth revision, clinical modification
OR	Odds ratio
RR	Risk ratio
SLE	Systemic lupus erythematosus

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Author contributions
W.-C. Hsieh conceived and developed the study concept and drafted the initial manuscript. S.-Y. Su, C. Lee, and C.-Y. Hsu conducted the statistical analyses, created the figures and tables, and contributed to the interpretation of the results. C-Y Hsu supervised the study, provided ongoing guidance throughout its progression, and approved the final manuscript for submission. All authors reviewed and approved the final version of the manuscript.

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Data availability
The data analyzed in this investigation are accessible through the TriNetX platform (https://trinetx.com/), a publicly available healthcare research database that facilitates real-world evidence generation.

Declarations

Ethics approval and consent to participate
The patient data in the TriNetX database are de-identified and anonymized; therefore, ethical consent was not required for its use. All procedures were conducted in strict compliance with applicable guidelines and regulations. Research involving human participants or human data adhered to the ethical principles outlined in the "Declaration of Helsinki".

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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