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Comparative Risk of Developing Interstitial Cystitis With Childhood Gastrointestinal, Urological, Autoimmune, or Psychiatric Disorders

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ABSTRACT

Aims: Interstitial cystitis (IC) is a chronic urological condition associated with significant discomfort, posing diagnostic and therapeutic challenges. Although its etiology remains unclear, early-life conditions such as gastrointestinal (GI) disorders, urological anomalies (UA), psychiatric disorders (PD), and autoimmune diseases (AD) have been hypothesized as potential risk factors for developing IC in adulthood. This study aims to investigate these associations by conducting a retrospective cohort analysis utilizing data from the TriNetX US Collaborative Network, encompassing over 118 million patient records.

Methods: The study and control groups were established across four categories of childhood disorders, with IC incidence monitored over a 14-year period. Statistical methodologies, including propensity score matching and Kaplan-Meier survival analysis, were employed to compare outcomes between cohorts.

Results: Findings indicate that childhood GI and UA conditions significantly elevate the risk of IC in adulthood, with irritable bowel syndrome (IBS) and urinary tract infections (UTIs) exhibiting risk ratios of 2.9 and 3.2, respectively. Gender disparities were also noted, with females exhibiting higher incidences of diseases included, particularly UA and AD during adolescence. Additionally, individuals with these early-life conditions demonstrated a higher prevalence of comorbidities, underscoring the complex interplay of health factors contributing to IC pathogenesis.

Conclusions: These findings suggest that childhood GI and UA conditions may serve as predictive markers for IC, emphasizing the need for targeted early interventions and preventative care strategies. By identifying at-risk populations, this study provides valuable insights into early detection and management approaches, potentially mitigating the long-term burden of IC on affected individuals.

Trial Registration: This paper includes an observational retrospective study. No clinical trial has been conducted.

1 | Introduction

Interstitial cystitis (IC) a chronic condition characterized by bladder pain and frequent, urgent urination, poses significant challenges in both diagnosis and management [1]. Despite its debilitating nature, the etiology of IC remains poorly understood, and the identification of risk factors is crucial for developing preventive and therapeutic strategies [2, 3]. Emerging evidence suggests that early-life health conditions might play a pivotal role in the development of IC, yet the extent and nature of these associations remain largely unexplored [4–6].

Childhood disorders, including gastrointestinal (GI) conditions, urological anomalies (UA), and psychiatric disorders (PD), have been identified as potential precursors to various chronic diseases in adulthood [7–14]. For instance, childhood GI conditions like irritable bowel syndrome (IBS) and chronic constipation have been linked to later-life UA, suggesting a possible connection between early GI health and IC [15]. Similarly, congenital UA may predispose individuals to chronic bladder issues, including IC, due to structural and functional changes in the urinary tract [16, 17].

Autoimmune diseases (AD) in childhood such as juvenile idiopathic arthritis (JIA), Sjögren's syndrome (SS), and systemic lupus erythematosus (SLE) may also contribute to the development of IC through systemic inflammation and immune dysregulation [18–20]. These conditions often involve persistent inflammation and altered immune responses, potentially affecting bladder health over time [21]. Furthermore, PD in children, including anxiety, depression, and attention-deficit/hyperactivity disorder (ADHD), are known to have long-term impacts on overall health and may influence the susceptibility to chronic pain conditions, including IC, through neuroendocrine and psychological mechanisms [22].

To our knowledge, this study is the first to comprehensively explore the relationships among various childhood conditions and the risk of developing IC in adulthood. This approach is critical because understanding these early-life risk factors can provide unique insights into the pathways leading to chronic bladder conditions allowing for the identification of at-risk populations before IC symptoms manifest. By pinpointing early risk factors, our findings have the potential to inform targeted preventive interventions and improve long-term outcomes for individuals predisposed to IC, ultimately enhancing their quality of life.

2 | Methodology

2.1 | Data Source and Study Population

A retrospective cohort analysis was conducted utilizing data from the TriNetX US Collaborative Network [23]. This network provides access to anonymized electronic health records, encompassing a wide array of patient information, including diagnostic codes, procedural data, prescribed medications, laboratory results, and genomic profiles. The data set comprises records from approximately 118 million patients across 66 healthcare organizations in the United States, spanning various healthcare settings such as hospitals, primary care practices, and specialty clinics. The deidentification process adheres to the criteria outlined in Section 164.514(a) of the HIPAA Privacy Rule, with compliance validated by a formal determination from a qualified expert, as specified in Section 164.512(b)(1).

2.2 | Study Cohorts

To establish the study's cohorts, the TriNetX database was employed utilizing the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10) codes to identify patients who met specific diagnostic criteria [24]. Table SA1 details the ICD-10 codes used as the foundation for each diagnosis.

For each disease group (GI, UA, AD, PD), a distinct control group (CG) was established (4 CGs in total) comprised of patients who had no history of the corresponding disease or IC before the age of 16. This approach allows us to compare the incidence of IC across patients without pre-existing conditions specific to each disease group.

Additionally, several study group (SG) cohorts were formed to include patients with a history of diagnoses of specific childhood conditions before the age of 16, yet without a precedent IC diagnosis or other diseases in that disease group (21 SGs established in total). These cohorts are categorized as follows: Any GI, constipation, Inflammatory Bowel Diseases (IBD) which includes Crohn's diseases, ulcerative colitis, and other unspecified noninfective gastroenteritis and colitis, IBS, any UA, enuresis, urinary tract infections (UTI), vesicoureteral reflux (VR); any AD, SLE, rheumatoid arthritis (RA), JIA, SS, celiac disease (CD), type 1 diabetes (T1D); any PD, depression (which includes both major depressive disorder and unspecified depression), posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), bipolar disorder (BD), and ADHD. These cohort distinctions facilitate the exploration of the potential association between childhood conditions, either collectively or individually, and the prevalence of IC among patients.

2.3 | Outcome

The primary outcome measure was the incidence of IC within 14 years following the index event of visiting a TriNetX network center. IC was identified by (1) the presence of at least one documented diagnosis of IC in the TriNetX database, or (2) the presence of the prescription of pentosan polysulfate (a medication exclusively used to relieve symptoms associated with IC), during the follow-up period.

2.4 | Statistical Analysis

Propensity score matching was utilized to align patients within each of four major categories of childhood conditions—GI, UA, AD, and PD. For each category, CG patients were matched to SG patients, excluding the condition under investigation. For

instance, in studying GI conditions, patients were matched based on age, gender, and specific diagnoses from the other three categories (UA, AD, and PD). This approach ensures comprehensive control of confounding variables across similar conditions. A 1:1 matching ratio was maintained for robust comparison within each category. Propensity scores (ranging from 0 to 1) were calculated using logistic regression, incorporating covariates such as age, gender, and race. The greedy nearest neighbor algorithm was employed to optimize the matching process [25].

Risk assessments and Kaplan-Meier survival analyses were conducted to evaluate the outcomes. Risk assessments involved calculating the relative risk of IC incidence among different cohorts, considering factors such as age, sex, and history of diagnosis of any of the disease categories under study. Kaplan-Meier survival analysis was utilized to estimate the survival function from the observed data, providing insights into the time to event (IC diagnosis) for patients in both the baseline and study cohorts. This method enabled the comparison of survival curves and the identification of significant differences in IC incidence between the cohorts over time.

To ensure confidentiality, the TriNetX system automatically set the patient count to a minimum of 10 whenever the actual number of patients in any outcome within a cohort was fewer than 10. For statistical comparisons, continuous variables were analyzed using t-tests, while categorical variables were evaluated using chi-square tests with a predefined significance level of 0.05. All statistical analyses were performed utilizing the TriNetX analytics tool that is incorporated within the TriNetX platform.

3 | Results

3.1 | Demographics Characteristics and Comorbidities Patterns

The GI CG included 3 994 545 patients, and 535 824 patients were identified in the SG for any GI condition. The UA CG consisted of 4 448 497 individuals, complemented by 202 879 patients in the SG for any UA condition. For AD, the CG comprised 4 562 168 patients, with 89 117 patients in the SG having any of the considered ADs. Lastly, the PD category encompassed a CG of 3 968 816 patients, with 682 632 individuals in the SG diagnosed with any PD condition. Detailed demographic and disease-related distributions for the four major CGs and their corresponding SGs are presented in Table SA2–A5.

Gender distribution differed significantly between groups. Females accounted for 74.6% of individuals with any UA condition, compared to 51.2% in the control group without UA conditions. A similar pattern was observed across the other three primary disease categories—GI, AD, and PD—with females consistently representing a significantly larger proportion in the study group, though the differences were less pronounced than for UA. This trend persisted for specific conditions within these categories. For example, females made up 69.2% of patients diagnosed with depression in the psychiatric category. In the autoimmune category, the gender disparity was particularly striking in SLE, where 81.1% of the cohort were females.

The prevalence of comorbid conditions in the study groups was significantly higher than in the control groups, highlighting the complex medical profiles of these patients. The data revealed a high prevalence of ADs within both the GI and UA groups. For example, in patients without any GI conditions (No GI), the prevalence of SLE was merely 0.1%, whereas it surged to 1.0% among those with any GI condition (Any GI). A parallel trend was observed in the UA groups, where rheumatoid arthritis prevalence increased from 0.1% in the No UA group to 0.4% in the Any UA group. Additionally, psychiatric comorbidities were notably pronounced; the prevalence of major depressive disorder in the Any GI SG escalated to 17.8%, compared to 4.7% in the control group, highlighting a strong association between psychiatric and chronic physical conditions.

3.2 | Childhood Conditions as Moderators for Adulthood Interstitial Cystitis

Table 1 presents a comparative analysis of the risk of developing IC in adulthood among patients with various childhood conditions over a 14-year follow-up period. The results were adjusted for demographic factors and other comorbidities through propensity score matching. For detailed demographic and comorbidity information about the SGs and CGs after matching, please refer to Table SA6-26 in the supporting material. The findings indicate that individuals with any GI in childhood had a risk ratio of 1.18 (95% confidence interval [CI]: 1.01–1.37) for developing IC in adulthood. Specifically, childhood IBS exhibited the highest risk ratio of 2.90 (95% CI: 1.41–5.95) compared to the CG. IBD also showed an elevated risk ratio of 1.72 (95% CI: 1.29–2.30). On the other hand, childhood constipation had a risk ratio of 1.04 (95% CI: 0.85–1.27), which was not statistically significant.

For UA, patients with any childhood UA had a risk ratio of 2.89 (95% CI: 2.39–3.50) for developing autoimmune conditions in adulthood. Specifically, childhood UTI were associated with a higher risk ratio of 3.24 (95% CI: 2.62–3.99), while VR also showed an increased risk with a risk ratio of 2.20 (95% CI: 1.04–4.64). In contrast, childhood enuresis had a risk ratio of 1.091 (95% CI: 0.48–2.47), which was not statistically significant.

For AD, the analysis does not show a significant increased risk as indicated by the risk ratio of 1.104 (95% CI: 0.79–1.54). For specific conditions, the results are similarly insignificant. For instance, RA, JIA, and SS all show a risk ratio of 1, but given that the number of cases in both the study and control group is ≤ 10, these values offer little interpretative value, as the risk ratio of 1 is arbitrary under these conditions. For CD, the risk ratio was 1.80 (95% CI: 0.83–3.90), with the confidence interval crossing 1, likely due to the very small group size. Similarly, for SLE, the risk ratio was 1.10 (95% CI: 0.47–2.59), with the small sample size contributing to the wide confidence intervals and lack of statistical significance. Among PDs, any PD in childhood had a risk ratio of 1.40 (95% CI: 1.232–1.60) for developing IC in adulthood. Childhood depression was associated with a risk ratio of 1.34 (95% CI: 1.08–1.64), indicating a statistically

TABLE 1 | Adulthood IC differences between patients with different childhood conditions.

	Study Group		Control Group			
Childhood Conditions	**Incident Cases**	**Risk**	**Incident Cases**	**Risk**	**Risk Ratio**	**95% CI**
Any Gastrointestinal Condition	386	0.001	327	0.001	1.180	(1.019, 1.368)
Constipation	195	0.001	187	0.001	1.043	(0.853, 1.274)
Inflammatory Bowel Diseases	124	0.001	72	0.000	1.722	(1.288, 2.302)
Irritable Bowel Syndrome	29	0.003	10	0.001	2.900	(1.414, 5.947)
Any Urological Anomaly	414	0.002	143	0.001	2.895	(2.394, 3.501)
Enuresis	12	0.000	11	0.000	1.091	(0.481, 2.472)
Urinary Tract Infections	369	0.003	114	0.001	3.237	(2.624, 3.993)
Vesicoureteral Reflux	22	0.002	10	0.001	2.200	(1.042, 4.644)
Any Autoimmune Disease	74	0.001	67	0.001	1.104	(0.794, 1.537)
Systemic Lupus Erythematosus	11	0.002	≤ 10	0.002	1.100	(0.468, 2.588)
Rheumatoid Arthritis	≤ 10	0.004	≤ 10	0.004	1	(0.417, 2.398)
Juvenile Idiopathic Arthritis	≤ 10	0.001	≤ 10	0.001	1	(0.416, 2.402)
Sjogren's Syndrome	≤ 10	0.011	≤ 10	0.011	1	(0.418, 2.391)
Celiac Disease	18	0.001	≤ 10	0.001	1.800	(0.831, 3.898)
Type 1 Diabetes	23	0.000	30	0.001	0.767	(0.445, 1.320)
Any Psychiatric Disorder	543	0.001	387	0.001	1.403	(1.232, 1.598)
Depression	207	0.001	155	0.001	1.335	(1.085, 1.644)
PTSD	≤ 10	0.001	≤ 10	0.001	1	(0.416, 2.401)
GAD	35	0.001	28	0.001	1.·250	(0.761, 2.054)
Bipolar	≤ 10	0.001	≤ 10	0.001	1	(0.416, 2.401)
ADHD	76	0.000	72	0.000	1.056	(0.765, 1.457)

significant increased risk. For PTSD and BD, the risk ratio of 1 (95% CI: 0.42–2.40) does not provide meaningful information due to the small number of incidents (≤ 10) in both the study and control groups. Additionally, the risk ratios for ADHD at 1.06 (95% CI: 0.76–1.46) and GAD at 1.25 (95% CI: 0.76–2.05) were not statistically significant.

Kaplan-Meier survival analyses (Figure 1) demonstrate the survival probability of developing IC over a 14-year follow-up period among patients with and without different childhood conditions. This figure encompasses four subplots including the IC outcomes due to GI, UA, AD, and PD. The analyses reveal differences in survival curves between the CG and various SG cohorts.

GI, UA, and PD had a higher susceptibility to IC with a 14-year survival probability of 99.56%, 99.06%, and 99.49%, compared to 99.63%, 99.59%, 99.63% respectively in the related CG. This difference is statistically significant as evidenced by the log-rank test. (χ^2 = 21.48, 94.88, and 58.61, respectively; $p = 0{\cdot}000$). Proportional hazard analysis corroborates these findings, indicating a hazard ratio of 1.42 (95% CI: 1.22–1.64) for GI, 2.49 (95% CI: 2.06–3.01) for UA, and 1.66 (95% CI: 1.46–1.89) for PD.

However, the survival curve for the IC outcomes among AD patients demonstrates a lower susceptibility to IC with a 14-year survival probability of approximately 99.61%, compared to 99.54% in the related CG. This differences not statistically significant as indicated by the log-rank test ($\chi^2 = 0.351$, $p = 0.55$). The proportional hazard analysis further supports this finding, revealing a hazard ratio of 1.10 (95% CI: 0.79–1.54).

4 | Discussion

The goal of this population-level research was to explore the relationship between childhood medical conditions and the likelihood of developing IC in adulthood. Overall, results reveal that certain childhood conditions significantly increase the risk of developing IC. Among the four categories—GI, UA, PD, and AD—childhood GI disorders, UA, and PD were associated with increased IC risk, while AD did not show a significant effect. Notably, UA, such as UTI and VR, showed about three times the risk of developing IC compared to controls, suggesting an important connection between these disorders. This elevated risk is similar to that observed for childhood GI conditions like IBS, as both GI and UA involve inflammatory and infectious processes that could influence bladder health, possibly through changes in the local microbiome or immune responses [26–28].

Additionally, the findings indicate ADHD is not a risk factor for IC. While previous literature notes a relationship between anxiety and IC, current results demonstrate that the presence of GAD or PTSD in childhood does not predict IC [29, 30].

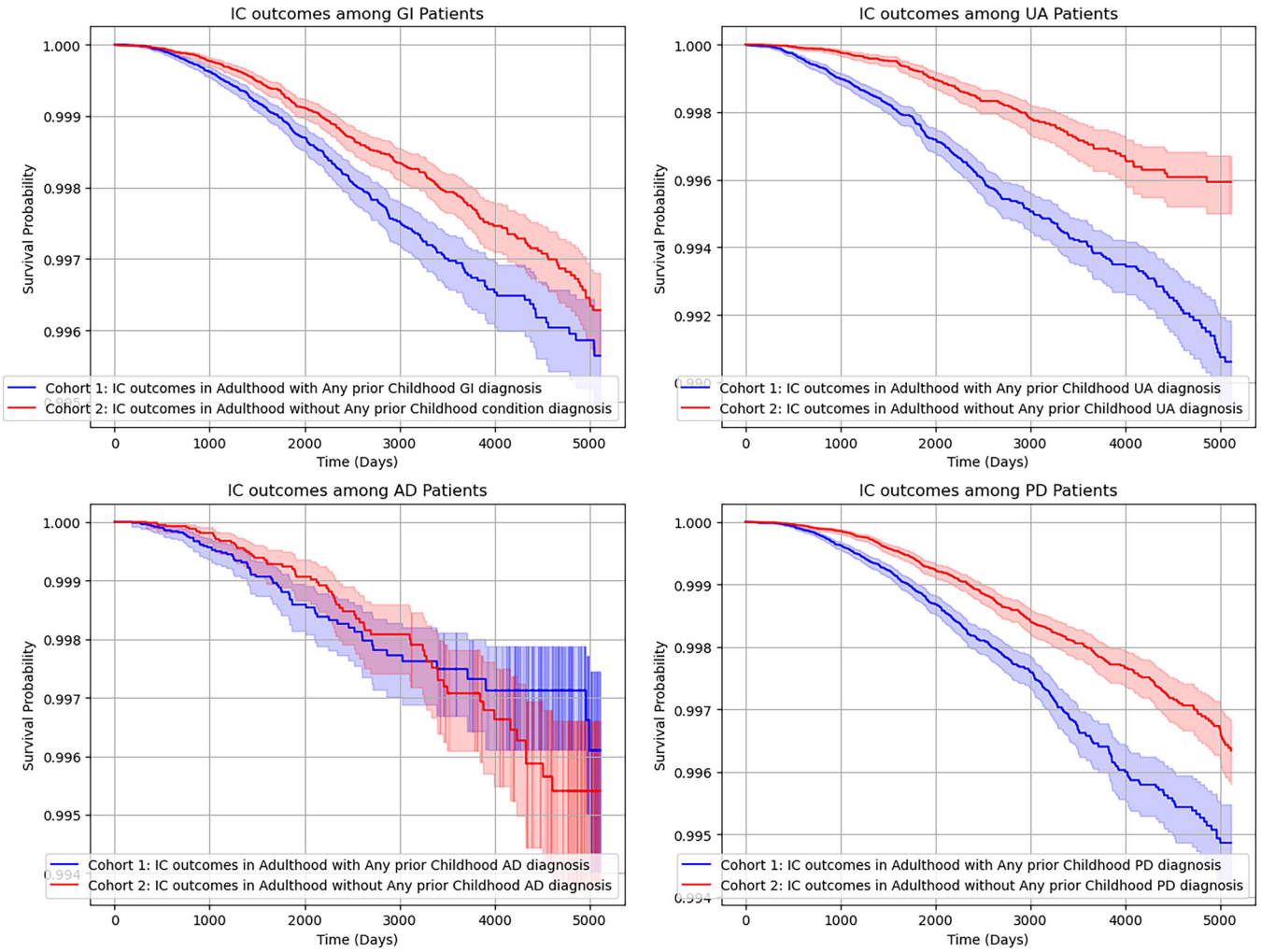

FIGURE 1 | Survival curves of patients with or without different childhood conditions including, gastrointestinal conditions, urological anomalies, autoimmune diseases, and psychiatric disorders.

Depression, however, showed a clearer association with IC, likely due to its known link with chronic pain [31, 32]. As IC can be qualified as a type of chronic pain, depression might exacerbate pain symptoms or lead to earlier IC diagnosis because of more frequent healthcare interactions.

Comorbidity patterns observed among the childhood conditions studied suggest a complex interplay of health issues that may influence the development of IC later in life. Although our analysis did not specifically investigate the combined effects of multiple conditions across the four major disease categories, the higher prevalence of IC among those with a history of urinary ailments highlights the potential role of early-life urinary conditions in the etiology of bladder disorders. Additionally, children with UA conditions often presented with concurrent GI symptoms, and a significant number of displayed symptoms related to PD, suggesting multisystem involvement that could escalate their risk for further complications, including IC. These findings emphasize the need for further research into how combinations of childhood conditions might interact to shape health outcomes in adulthood, particularly for understanding the pathways linking early-life disorders to later-life chronic conditions like IC. Addressing these complex comorbidity patterns early could enable healthcare providers to develop targeted preventive strategies that account for the broader spectrum of child health issues, potentially slowing the progression of these comorbidities. This approach is particularly crucial for children with both physical and psychiatric symptoms, which can complicate diagnosis and management, increasing the risk for chronic conditions like IC.

Due to the nature of the inclusion and exclusion criteria in the study, the exploration of several conditions diagnosed in childhood resulted in very small sample sizes, limiting our ability to interpret diagnosis-level results presented in Table 1. The specific selection criteria we applied further reduced the population size, making it challenging to examine low-prevalence diseases like IC. Additionally, conditions such as ADs and certain PDs (including BD) can be challenging to diagnose in childhood and impact diagnostic rates. This, combined with the low prevalence of IC, resulted in a small number of incident cases in both the study and control groups rendering the findings inconclusive for these conditions. Among the conditions with more robust sample sizes, childhood UTI showed the highest risk ratio for developing IC. This finding reinforces one of the primary conclusions of the study: childhood UAs, particularly UTI, serve as strong predictors of bladder disorders in later life.

4.1 | Strengths and Limitations

This study drew from an initial sample of around 4 million patients, allowing for a representative national population sample. The retrospective nature of this study and sampling from existing medical records allowed for the mitigation of several aspects of bias that can be present in prospective studies. Limitations also exist when sampling from electronic medical record datasets including uncertainty related to diagnostic and coding rigor. Additionally, the use of the TriNetX limited the ability to track patient activity outside of healthcare organizations whose records feed into the database. Therefore, the accuracy of risk ratios may be impacted by the potential lack of inclusion of diagnoses in the control group. Furthermore, attrition was a significant limitation related to the 14-year timeframe designated in this study; thus, the occurrence of IC may be underestimated in both the control and study groups, as data points are right-censored. Finally, as noted above, given the low occurrence of IC, some cohorts examined in this study are very small rendering some risk calculations inappropriate to interpret or infeasible.

5 | Conclusions

The findings of this study make a substantial contribution to the existing literature on the complexities of IC. By examining the relationship between childhood-diagnosed disorders and the development of IC, this study offers valuable insights into identifying at-risk populations. It underscores the need for early and ongoing interventions during adolescence and early adulthood to prevent or mitigate the onset of IC. Given the nature of these results, we recommend enhanced education and awareness surrounding IC, along with collaborative care across multiple medical specialties—including, but not limited to, urology, psychiatry, rheumatology, gastroenterology, and general pediatrics. Additionally, future research should consider prospective cohort studies or the use of larger datasets to provide more robust evidence--especially for low-prevalence conditions such as AD, PTSD, and ADHD. In our study, fewer than 10 patients within this group developed IC, highlighting the challenges of drawing definitive conclusions for these populations. Expanding such research will deepen our understanding of IC and improve strategies for its prevention and management.

Author Contributions

Study concept and design: Mohammad Alipour Vaezi, Huaiyang Zhong, Daniel B. Rukstalis. Drafting of the manuscript: Mohammad Alipour Vaezi, Huaiyang Zhong. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Mohammad Alipour Vaezi, Huaiyang Zhong. Interpretation of data: All authors.

Ethics Statement

This retrospective study was conducted in accordance with the ethical standards of our institutional review board (IRB) and deemed exempt from further review due to the use of deidentified medical records collected as part of routine clinical practice. All patient data was anonymized before analysis, ensuring patient privacy was protected throughout the study.

Consent

This paper includes an observational retrospective study using deidentified data. No direct contact has been made with any patient. This manuscript does not contain any reproduced material from other sources. All content, including text, figures, and tables, is original and created by the authors.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings will be available in TriNetX at https://live.trinetx.com/ following an embargo from the date of publication to allow for commercialization of research findings.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.