Real-world insights into hemorrhagic cystitis: An etiology-specific examination of healthcare utilization patterns and patient outcomes

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ABSTRACT

Introduction: Hemorrhagic cystitis (HC) is a clinically significant condition with diverse etiologies, yet data on its healthcare burden remain limited. This study aimed to evaluate the healthcare utilization patterns and outcomes associated with HC across multiple etiologies.

Methods: We conducted a retrospective cohort analysis using the TriNetX database, identifying 177 947 patients diagnosed with HC over a 20-year period. Patients were stratified into four etiologic cohorts: radiation-induced, infection-induced, chemotherapy-related, and systemic disease-related. Outcomes included emergency department (ED) visits, repeat visits to the ED, hospital admissions, procedural interventions, and mortality rates at seven days, 30 days and 90 days. Demographic profiles and comorbidity profiles were also assessed.

KEY MESSAGES

- We conducted a large cohort study of 177 947 hemorrhagic cystitis (HC) patients across four etiologies.
- Chemotherapy-induced HC showed highest 90-day mortality (11.9%) and admission rates.
- Radiation-induced HC had the greatest procedural burden at all time points.
- Infection-induced HC accounted for most emergency department visits (47.6%).
- Propensity-matched analysis revealed better survival in radiation-induced HC vs. others.

Results: In this cohort study of HC patients, demographics and clinical characteristics varied by etiology. Radiation-induced HC patients were oldest (mean age 69.8 years), while infection-induced HC had the highest Hispanic/Latino (8.4%) and Black (18.6%) representation. Systemic autoimmune HC showed the highest comorbidity burden. ED presentations were most frequent in infection-induced HC (47.7%), while chemotherapy-induced HC had the highest admission (60% at 30 days and 64.4% at 90 days) and 90-day mortality (11.9%). Radiation-induced HC had the highest procedural rates across all time points (42.3%, 48.9%, and 54.6% at seven days, 30 days, and 90 days, respectively).
Conclusions: This study provides a comprehensive characterization of HC across etiologies, highlighting underrecognized subgroups with significant healthcare impact. Findings underscore the need for standardized treatment protocols to enhance clinical management.

INTRODUCTION

Gross hematuria, characterized by the presence of visible blood in the urine, is a clinically significant condition associated with considerable morbidity.[1,2] The differential diagnosis encompasses a broad spectrum of etiologies, with an anatomically oriented classification delineating potential sources as renal and upper urinary tract, bladder, prostatic, or urethral origins.[3] Despite its frequent occurrence in clinical practice, there remains a notable paucity of data regarding its incidence, prevalence, and optimal management strategies. The diagnostic evaluation typically integrates urinary analyses—such as urinalysis and urine culture—alongside advanced imaging modalities, including ultrasound and computed tomography (CT) urogram, as well as direct visualization via cystoscopy. Management is guided by the underlying etiology, necessitating a tailored approach to address the specific pathological process.[4-8]
Among individuals with bladder-related sources of bleeding, hemorrhagic cystitis (HC) represents one of the most complex and challenging conditions to manage. It is characterized by diffuse inflammation and hemorrhage of the bladder urothelium, leading to substantial morbidity.[9,10] The differential diagnosis encompasses a broad spectrum of etiologies, including infection, chemical exposure, radiation therapy, and systemic autoimmune disorders.[11-13] Despite extensive clinical experience, there remains no universally accepted treatment paradigm for HC.[14-16]

Furthermore, HC imposes a significant burden on patients and healthcare systems alike, contributing to high treatment costs, and substantial hospital resource utilization, with a high risk of mortality irrespective of the underlying etiology.[17-19] A recent study by Arora et al estimated that the annual inpatient treatment cost for radiation-induced HC in the United States amounts to 63.5 million USD.[20] Given the profound impact of HC, numerous studies have examined treatment patterns specific to individual etiologies, particularly radiation-induced cystitis,

chemotherapy-related cystitis, and post-transplant cystitis. While these investigations have consistently underscored the disease's morbidity, few have conducted comparative analyses of treatment strategies across different etiologies of HC.[18, 21-23]

The present study aims to quantify the burden of hemorrhagic cystitis in contemporary clinical practice, analyze need for intervention among affected individuals, and evaluate patient outcomes.

METHODS

This study utilized TriNetX, a global federated health research network that provides access to electronic medical records from large healthcare organizations. A retrospective cohort study was conducted to analyze individuals who presented to a physician with a primary diagnosis of gross hematuria with cystitis within the TriNetX database.

Patients were categorized into cohorts based on etiology, employing ICD-10 codes to identify cases of radiation-induced cystitis, infection-related, chemotherapy-related cystitis, and systemic autoimmune disease. Additionally, CPT codes were utilized to assess emergency department visits, hospital admissions, urinary procedures, and mortality rates. The codes used in the search strategy has been outlined in Appendix A.

Exclusion criteria included individuals under 18 years of age and those with a prior presentation of gross hematuria. The primary outcome was 30-day mortality following physician evaluation. Secondary outcomes encompassed emergency department visits, admission rates, and urologic procedure rates at 7-day, 30-day, and 90-day intervals, along with mortality assessments at 7 days and 90 days.

Data

This study utilized data from the US Collaborative Network on TriNetX, a large-scale federated health research database encompassing records from over 115 million patients. The dataset was systematically queried to identify cases of hemorrhagic cystitis (HC) attributed to radiation exposure, infections, chemical or chemotherapy-induced injury, and systemic autoimmune conditions. Using relevant ICD-10 codes, a total of 177,947 individuals who presented with HC between 2004 and 2024 were identified for inclusion in the analysis.

Statistics

Descriptive statistical analyses were performed to characterize baseline demographic parameters, including age, sex, race, and ethnicity. Additionally, the prevalence of key comorbidities—such as type II diabetes mellitus, hypertension (HTN), obesity, ischemic heart disease (IHD), and chronic obstructive pulmonary disease (COPD)—at the time of HC diagnosis was assessed. Further evaluations included emergency department visits, hospital admission rates, urological procedure utilization, and mortality outcomes at 7-day, 30-day, and 90-day intervals. After propensity-matching for age, sex, race, ethnicity and the key comorbidities mentioned above, a

Kaplan-Meier analysis was performed to compare ED visits, admission rates, procedure rates, and mortality rates at 90-days between radiation-induced HC and HC due to other causes.

RESULTS

A total of 177,947 adult patients diagnosed with hemorrhagic cystitis (HC) over the past two decades were included in the analysis. Baseline demographic characteristics and comorbidities are detailed in Table 1. Among the defined cohorts, patients with radiation-induced HC exhibited the highest mean age (69.8 years). The proportion of males was lowest within the infection-induced HC group (69.4%), whereas the highest proportion of Hispanic/Latino men was observed in the same cohort (8.4%).

The racial distribution across all cohorts is summarized in Table 1, with White patients comprising the predominant demographic group. Notably, the proportion of Black patients was highest in the infection-induced HC cohort (18.6%), while Asian patients were most represented in the chemotherapy/chemical-induced HC group (3.6%). The comorbidity profile of patients diagnosed with hemorrhagic cystitis (HC) is detailed in Table 1. Among the defined cohorts, individuals with systemic autoimmune disease–related HC exhibited the highest prevalence of key comorbidities, including diabetes mellitus (40.4%), obesity (45.2%), hypertension (77.4%), ischemic heart disease (34.8%), and chronic obstructive pulmonary disease (COPD) (42.5%), surpassing all other groups.

Regarding emergency department utilization, the proportion of HC patients presenting to the emergency room was lowest among those with radiation-induced HC (18.4%) and highest among individuals with infection-induced HC (47.6%). Additionally, the rate of repeat emergency visits within seven days was most pronounced in patients with chemotherapy-induced HC (7.2%), a trend that persisted across longer follow-up periods, with 30-day (21%) and 90-day (36.3%) revisit rates similarly elevated in this cohort. These findings are summarized in Figure 1. The highest 7-day admission rate was observed in the infection-induced hemorrhagic cystitis (HC) cohort (51.5%). However, patients with chemotherapy-induced HC demonstrated the highest 30-day admission rate (56.9%), a trend that persisted at 90 days, with an admission rate of 64.4% (Figure 1). Although emergency department visits and hospital admissions were comparatively lower in radiation-induced HC relative to other cohorts, procedural intervention rates were notably elevated in this group. Patients with radiation-induced HC exhibited substantial intervention rates at 7-day (42.3%), 30-day (48.8%), and 90-day (54.6%) intervals (Figure 1).

Mortality rates across the cohorts are detailed in Figure 1, illustrating trends at 7-day, 30-day, and 90-day intervals. Notably, chemotherapy-induced HC was associated with the highest mortality rate at each time point, with a 7-day mortality rate of 1%, escalating to 4.8% at 30 days and 11.9% at 90 days.

After propensity-matching for age, sex, race, ethnicity and five common comorbidities (Hypertension, ischemic heart disease, chronic obstructive pulmonary disease, obesity, and diabetes mellitus), 11,209 patients with radiation-induced HC and an equal number of patients with HC due to other causes were compared against each other. Changes in baseline demographics and comorbidities, after propensity matching, are documented in Table 2. Kaplan-

Meier survival analysis was performed to evaluate 90-day outcomes, including emergency department visits, hospital admissions, urinary procedures, and mortality. Patients with radiation-induced hemorrhagic cystitis (HC) demonstrated significantly higher 90-day emergency visit-free probability compared to those with HC from other etiologies (76.3% vs. 66.9%, $p < 0.0001$). Similarly, the 90-day admission-free probability was greater in the radiation-induced cohort (66.7% vs. 58.3%, $p < 0.0001$). This trend extended to overall survival, with radiation-induced HC patients exhibiting a higher 90-day survival probability (95.3% vs. 92.8%, $p < 0.0001$). In contrast, patients with non-radiation-induced HC had a higher 90-day procedure-free probability, suggesting a lower procedural burden in these cohorts HC (63.8 % vs 77.8%, p-value <0.0001) (Figure 2).

DISCUSSION

In this large cohort study evaluating patients with hemorrhagic cystitis (HC) across various etiologies, we observed highest 90-day mortality rates in patients with chemotherapy-induced HC (11.9%). Furthermore, we observed significant variation in admission rates, emergency department visits, procedural interventions, and mortality outcomes. While radiation-induced HC was less prevalent, it was associated with markedly higher procedural rates. In contrast, infection-induced and chemotherapy-related HC exhibited elevated admission rates but were predominantly managed conservatively, with limited invasive interventions. This trend may explain why existing literature on HC disproportionately focuses on radiation-induced cystitis, given its higher healthcare utilization and procedural burden.

This study provides a more comprehensive characterization of demographic patterns and comorbidity burdens among patients presenting with HC. Across all etiologies, a higher proportion of affected individuals were male. Hispanic/Latino men represented a relatively small fraction of each cohort, with proportions of 6.2%, 8.4%, 7.3%, and 6.3% in Cohorts A, B, C, and D, respectively. Similarly, White patients constituted the predominant racial group, followed by Black patients. Hypertension emerged as the most prevalent comorbidity across all cohorts, closely followed by obesity. These inter-cohort variations emphasize the necessity of optimizing comorbidity management in HC patients to mitigate associated complications.

Despite its clinical relevance, data on HC remain surprisingly scarce. Arora et al reported an admission rate of 82.9% for radiation-induced HC, substantially higher than our observed rate of 40.6% at 30 days. However, their findings regarding procedural intervention rates (28.2% vs. 48.8% at 30 days) and mortality outcomes (3% vs. 2% at 30 days) were comparable to our study.[20] Similarly, Neckonoff et al documented procedural rates of 50.2% and in-patient mortality rates of 1.3% for radiation-induced HC, further validating our observations.[21] Although prior studies predominantly focus on radiation-induced cystitis, our findings underscore the greater prevalence of infection-induced and systemic disease–related HC. Future research should prioritize these underrepresented subgroups to establish standardized treatment protocols. A deeper understanding of mortality risk across etiologies may better inform urologists in clinical decision-making and emergency intervention strategies.

Our study offers novel insights into real-world healthcare utilization patterns for HC across diverse etiologies. While contemporary literature has largely centered on radiation-induced HC, our findings provide a broader perspective on other clinically significant subgroups. The evidence presented herein may serve as a valuable resource for urologists in refining therapeutic strategies and improving patient outcomes. Additionally, the extensive sample size—comprising 177,947 patients over a 20-year period—enhances the robustness and generalizability of our findings.

Despite its strengths, this study has several limitations. The absence of individual-level data within the TriNetX database constrains deeper patient-specific analyses. Furthermore, the retrospective design is inherently susceptible to bias. Lastly, the lack of a distinct ICD-10 code for HC necessitated the use of multiple diagnostic codes to identify cases, introducing potential inaccuracies in classification. Future research should aim to refine diagnostic criteria and establish standardized coding practices to improve data precision and clinical applicability.

CONCLUSIONS

This study offers a comprehensive analysis of the impact of hemorrhagic cystitis on healthcare resource utilization. Our findings reveal significant variability in emergency department visits, repeat visits, hospital admissions, procedural interventions, and mortality rates across different patient cohorts. Given the rising incidence of HC, future investigation should explore its diverse etiologies to better understand its clinical trajectory. The insights derived from this real-world data can inform urologists and other healthcare professionals by highlighting patterns of healthcare utilization, ultimately aiding in more effective patient management.

AI disclosure statement: The authors did not use generative AI or AI-assisted technologies in the development of this manuscript.

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FIGURES AND TABLES

Figure 1. Comparison of emergency visits, admission rates, urogenital procedure rates, and mortality rates across various etiologies of hemorrhagic cystitis at 7-day, 30-day, and 90-day time periods.

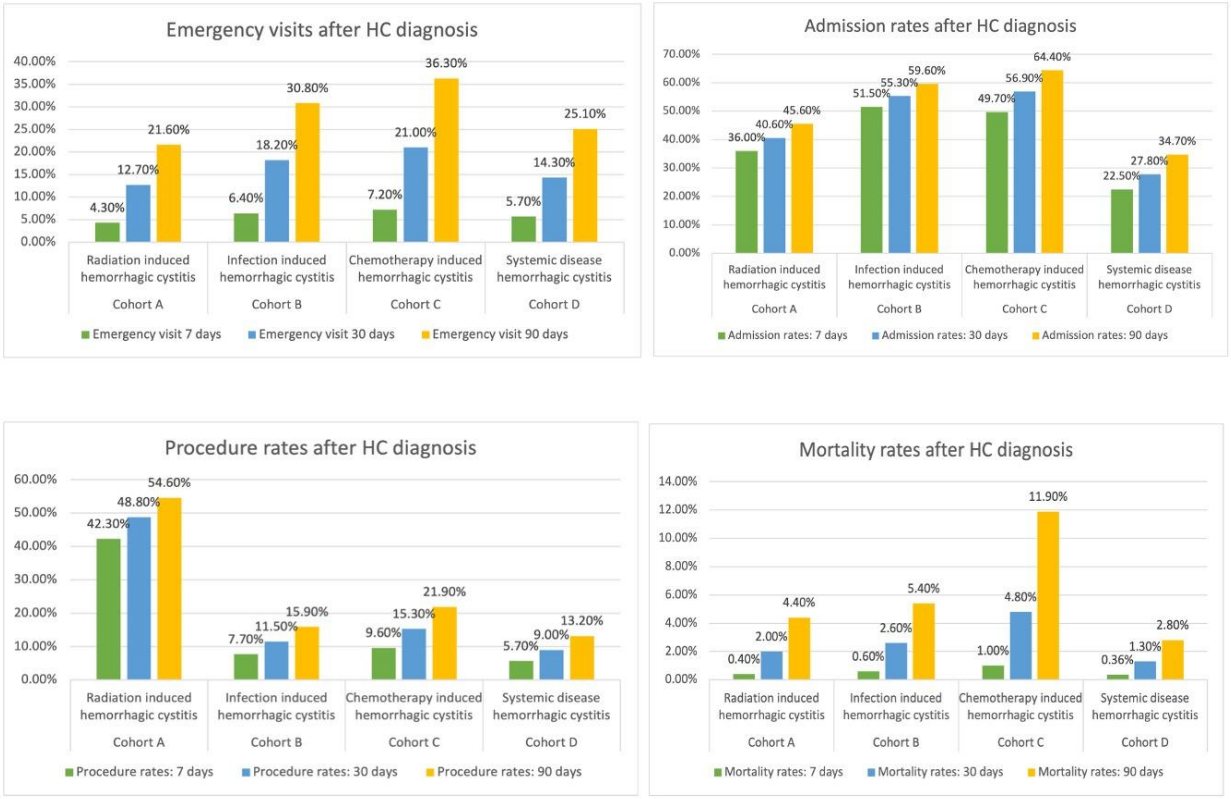

Figure 2. Kaplan-Meier analysis comparing radiation-induced HC (purple) and HC due to other causes (green). (A) Emergency-visit free probability in radiation-induced HC and HC due to other causes 76.3% vs. 66.9%, p<0.0001. (B) Admission-free probability in radiation-induced HC and HC due to other causes 66.7% vs. 58.3%, p<0.0001. (C) Urinary system procedure-free probability in radiation-induced HC and HC due to other causes 63.8% vs. 77.8%, p<0.0001. (D) Survival probability in radiation-induced HC and HC due to other causes 95.3% vs. 92.8%, p< 0.0001.

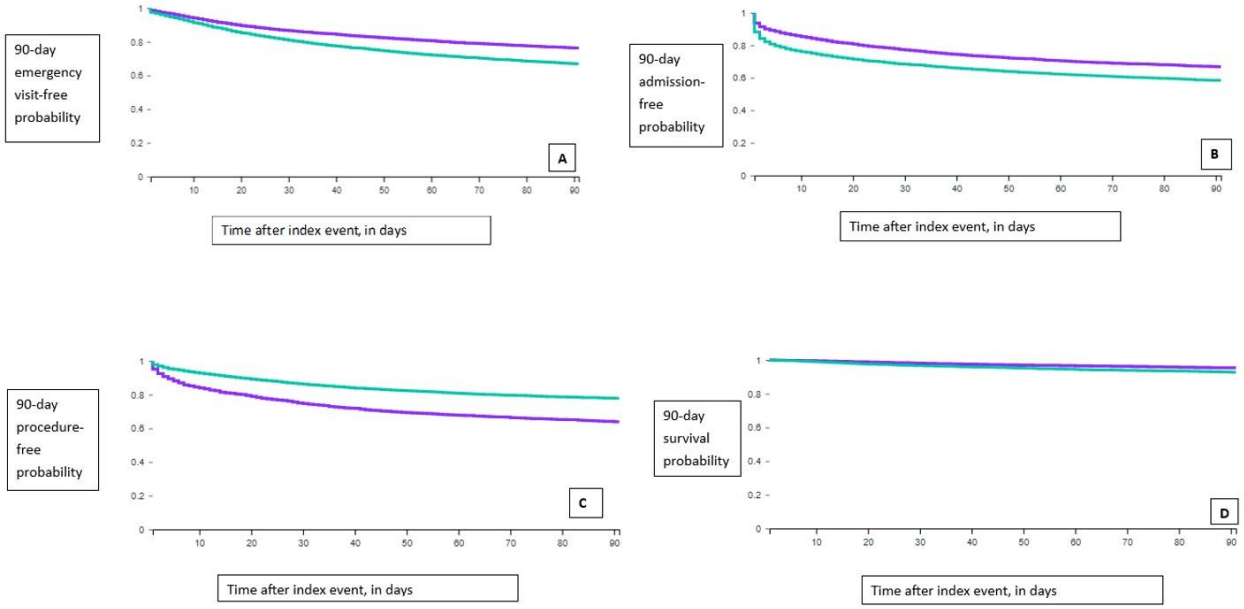

Table 1. Baseline demographic and clinical parameters of patients across various etiologies of hemorrhagic cystitis

	Cohort A: Radiation-induced hemorrhagic cystitis (n=11 657)	**Cohort B: Infection-induced hemorrhagic cystitis (n=54 784)**	**Cohort C: Chemotherapy-induced or chemical exposure-related (n=6317)**	**Cohort D: Systemic disease-related HC (n=105 189)**
Mean age in years (SD)	69.8 (10.6)	60.9 (18.9)	63.3 (15.1)	66.2 (14.3)
Males	76.0%	69.4%	69.5%	70.2%
Ethnicity Not Hispanic or Latino	71.1%	61.5%	70.5%	65.7%
Hispanic/Latino	6.2%	8.4%	7.3%	6.3%
Unknown	22.6%	30%	22.1%	27.9%
Race				
White	66.2%	65.8%	74.6%	69.9%
Black	15.1%	18.6%	14.8%	15.5%
Asian	2.8%	3.2%	3.6%	2.8%
Type II DM	27.3%	36.7%	34.3%	40.4%
Overweight/obesity	22.4%	35.4%	38.2%	45.2%
Hypertension	60.3%	63.5%	70.8%	77.4%
Ischemic heart disease	30.5%	29.4%	30.3%	34.8%
COPD	20.4%	32.6%	33.4%	42.5%

COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HC: hemorrhagic cystitis; SD: standard deviation.

Table 2. Demographic and comorbidity profile of radiation-induced HC and HC due to other causes, before and after propensity-matching				
	Before matching		**After matching**	
	Radiation induced HC (n=11 657)	**HC due to other causes (n=166 290)**	**Radiation-induced HC (n=11 209)**	**HC due to other causes (n=11 209)**
Mean age in years (SD)	69.8 (10.6)	64.3 (17.9)	69.9 (10.6)	70.1(11.2)
Males	76%	69.9%	79.7%	79.6%
Ethnicity Not hispanic or latino	71.1%	64.5%	69.6%	69.3%
Hispanic/latino	6.2%	7%	6.1%	6.5%
Unknown	22.6%	28.4%	24.1%	24.1%
Race White	66.2%	68.7%	65.9%	67.9%
Black	15.1%	16.5%	14.7%	14.8%
Asian	2.8%	3%	2.9%	2.9%
Type II DM	27.3%	39%	27.6%	27.7%
Overweight/obesity	22.4%	41.7%	22.9%	23.3%
Hypertension	60.3%	72.1%	60.3%	61.4%
Ischemic heart disease	30.5%	32.9%	30.2%	30.5%
COPD	20.4%	38.9%	20.3%	20.1%

COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HC: hemorrhagic cystitis; SD: standard deviation.