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Original Article

Characterization of urosepsis in a tertiary hospital: 5-year retrospective study on prevalence and risk factors in Palestine

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Abstract

Introduction: The objective of this study was to characterize the occurrence of urosepsis in oncology patients and to explore the potential factors influencing its development and outcomes. Urosepsis is a serious systemic infection originating from a urinary tract infection. Its management is particularly challenging in immunocompromised oncology patients.

Methodology: A retrospective review of 337 oncology patients diagnosed with urosepsis between 2019 and 2023 was conducted. Various clinical and demographic factors were examined, including patient gender, type of tumor (solid or liquid), nephrostomy, presence of a double J (DJ) stent, diabetes mellitus, length of hospital stay, and use of central lines. Statistical analysis was performed to assess associations between these variables and urosepsis.

Results: Males were found to be at higher risk to develop urosepsis (*p:* 0.039). *Escherichia coli* was the most commonly identified pathogen. However, none of the analyzed factors, including tumor type (*p*: 0.432), nephrostomy (*p*: 0.503), DJ stent (*p*: 0.325), diabetes mellitus (*p*: 0.637), length of hospital stay (*p*: 0.185), or presence of a central line (*p*: 0.122), showed a statistically significant association with the occurrence of urosepsis.

Conclusions: This study is the first to examine urosepsis in oncology patients in Palestine. The findings highlight the increased risk for developing urosepsis in male gender; however, the other factors studied were not significant. The results cannot be generalized to all hospitalized patients as the studied population was in a tertiary hospital, and a bigger sample size is recommended for future studies to allow generalizability of the results.

Key words: urosepsis; oncology; risk factors; infection; retrospective; Palestine.

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Introduction

Urosepsis is a severe systemic infection resulting from a urinary tract infection (UTI) that has spread to the bloodstream, and represents a critical healthcare challenge worldwide. It is characterized by a dysregulated host response to infection, leading to organ dysfunction and high mortality rates. Despite advances in medical knowledge and technology, urosepsis remains a significant cause of morbidity and mortality, especially in vulnerable populations such as the elderly and immunocompromised individuals, such as cancer patients taking chemotherapy and transplant patients [1]. Cancer patients are at increased risk of sepsis due to several factors; especially immunosuppression caused by malignancy, hematological treatments causing immunosuppression, and invasive procedures including long-term central venous catheters and urinary catheters. However, there is a great variation in the degree of immunosuppression in the cancer population. Hematological patients are considered to be at highest risk for sepsis. These are mostly cases of acute leukemia due to prolonged and profound neutropenia, which is one of the most important risk factors for sepsis and mortality [2]. The infection originates from a UTI in 20–30% of sepsis cases [3], and the most common causes are members of the Enterobacterales family including *Escherichia coli* (with a prevalence of 52%), *Proteus* species, *Enterobacter* species, *Klebsiella* species, and *Pseudomonas aeruginosa* [4]. The mortality rate is 20–42% in severe sepsis cases [3]. Sepsis is one of the frequent complications in cancer patients, which leads to increased morbidity and mortality, and it is more challenging to manage especially due to emerging antimicrobial resistance. Studies have found that patients with sepsis who have an underlying malignant

disease have a 30% increase in mortality compared to other sepsis patients [5]. It was found that most urosepsis cases occur due to urolithiasis (42.9% of cases), followed by prostatic adenoma (24.9%) and urologic cancer 18%; other cases had urologic diseases that led to sepsis [6]. Duygu *et al.,* studied the risk factors of UTI in cancer patients and reported that nephrostomy; duration of catheterization, and active chemotherapy were risk factors for catheter related UTI. *E coli* extended-spectrum beta-lactamases (ESBL), and *K. pneumoniae* ESBL were found to be the most common microorganisms [7]. A systematic review by Brian *et al*., studied risk factors of urosepsis in elderly people, including the presence of a urinary catheter and the number of comorbidities. One of the articles they referred to was by Sari *et al*., which reported that cases with a chronic urinary catheter had cultures that were less sensitive to antibiotics commonly used for the treatment of UTI, including ciprofloxacin and gentamicin [8,9].

The diagnosis of sepsis includes two main criteria, which include demonstration of an infection through clinical picture or microbiological testing, and systemic inflammatory response syndrome (at least 2 of the following: body temperature ≥ 38 °C or ≤ 36 °C, tachycardia ≥ 90 bpm, tachypnea ≥ 20 breaths per min, respiratory alkalosis $paCO_2$ ≤ 32 mm Hg, leukocyte count: leukocytosis ≥ 12/nL or leukopenia ≤ 4/nL). Demonstration of an infection based on general signs includes fever > 38.3 °C; hypothermia < 36°C; tachycardia > 90/min; tachypnea > 30/min; impaired neurological status; edema or positive fluid balance (> 20 mL/kg/d); hyperglycemia (blood sugar >120 mg/dL) in the absence of previously diagnosed diabetes mellitus (DM); and organ dysfunction that can be demonstrated through any of the following: arterial hypoxemia (paO_2/FiO_2 < 300), acute oliguria < 0.5 mL/kg/hour (≥ 2 hour), creatinine increase by ≥ 0.5 mg/dL, coagulopathy international normalized ratio (INR) > 1.5, thrombocytopenia < 100/nL, and hyperbilirubinemia (total bilirubin >4 mg/dL, Ileus) [4].

In this study, the potential risk factors of urosepsis in cancer patients were explored. The factors included demographic factors such as gender and age, type of tumor (liquid or solid), nephrostomy, double J (DJ) stent, DM, length of stay, and presence of a central line.

Methodology

Study design

This retrospective quantitative research aimed to determine the prevalence of certain microorganisms in cancer patients with urosepsis. The study was conducted at the Augusta Victoria Hospital, Jerusalem.

The inclusion criteria were hospitalized patients diagnosed with urosepsis and who had positive urine cultures, regardless of whether their blood cultures were positive or negative. The exclusion criteria were patients with positive blood cultures for microorganisms different from those identified in urine cultures, as well as patients with polymicrobial positive urine cultures. These cases were excluded in order to study which microorganisms had the highest risk of causing sepsis in patients with UTI.

A total of 400 patients with positive urine cultures from May 2019 to December 2023 were included initially. However, after excluding cases that had a positive blood culture with a different microorganism than the urine culture, the final sample size used in the analysis was 337.

Data were extracted from patient files through a comprehensive review and following a pre-defined data collection form. This form included detailed guidelines on how to record each variable to minimize subjective interpretation and ensure consistent data collection. Data on suspected predisposing factors such as age, gender, cancer type (solid or liquid), DM, Foley catheterization, length of stay in hospital, nephrostomy, central line, microorganisms causing sepsis, and DJ stent were collected from patient files. The analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 26.0 [10].

Urine and blood cultures

Urine and blood cultures were performed according to the recommendations of the American Society for Microbiology (ASM) proceedings. Urine was cultured on 5% sheep blood agar and MacConkey agar. Pathogens with a colony-forming unit (CFU) count greater than 50,000 CFU/mL were identified using the VITEK automated bacterial identification system. (bioMérieux, Marcy-l'Étoile, France) Antimicrobial sensitivity testing was conducted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. Blood cultures were processed using the VersaTrek automated blood culture system. (Thermo Fisher Scientific, Tucson, AZ, USA) [11,12].

Data analysis

Descriptive statistics (frequencies, percentages) and inferential statistics (Chi-square test, logistic regression, confidence interval, and multivariate analysis) were performed using SPSS. The following factors were studied to assess their possible effect on increasing the risk of urosepsis, through analysis of the

same microorganism cultures in both urine and blood: age, gender, microorganisms causing urosepsis, cancer type, DM, foley catheterization, length of stay in hospital, nephrostomy, central line, and DJ stent. Multivariable logistic regression was utilized to control for potential confounding factors by adjusting for variables such as age, gender, and underlying comorbidities. A comprehensive analysis was conducted by incorporating all measured risk factors into the model and assessing the combined influence of these factors on outcomes.

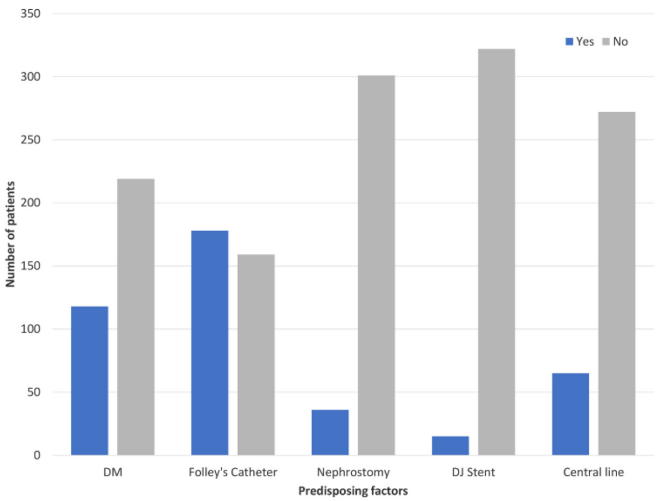
Ethical considerations

The study received approval from the Ethics Committee of Augusta Victoria Hospital with an IRB number 42/GLD/2024, which ensured adherence to all relevant ethical guidelines. Informed consent was not required because the study involved the use of fully anonymized retrospective data extracted from the hospital's records. However, strict measures were implemented to ensure patient confidentiality and compliance with data protection regulations. All data were stored securely, and access was limited to research authorized personnel only.

Limitations

The retrospective design and reliance on available data in patient files may introduce potential confounding factors. Steps were taken to adjust for known confounders in the statistical analysis to mitigate these limitations, and data quality control measures were implemented throughout the data collection process. Future studies should be cross-sectional, and focus on a single factor, such as patients with a Foley's catheter, and no other suspected risk factors, in order to obtain more significant results.

Figure 1. Suspected predisposing factors.



The predisposing factors including diabetes mellitus (DM), Foley catheter, nephrostomy, double J (DJ) stent, and central line were reviewed. A total of 118 patients had DM vs 219 with no DM; 178 had Foley catheter vs 159 without a Foley catheter; 36 had nephrostomy vs 301 without nephrostomy; 15 had DJ stent vs 322 without DJ stent; and 65 had a central line vs 272 without a central line.

Table 1. Demographic characteristics of the patients.

Demographic factors	Percentage
Gender	
Female	46%
Male	54%
Age group	
≥ 60 years	43.6%
≤ 59 years	56.4%
Length of stay	
< 14 days	41.5%
≥ 14 days	58.5%
Malignancy	
No malignancy	29.1%
Liquid	10.1%
Solid	60.8%

Results

The study aimed to determine the prevalence of microorganisms in cancer patients with urosepsis and their association with possible risk factors that predispose to bacteremia.

The total number of patients with positive urine cultures from May 2019 to December 2023 was 400. The sample size used in this analysis was 337, as cases with a positive blood culture of a different microorganism were excluded. Out of the 337 cases, there were 155 males and 182 females (Table 1). The participating patients were divided into 2 groups based on their age: (1) 190 patients who were < 60 years old; (2) 147 patients who were ≥ 60 years old. The effect of age as a risk factor was analyzed through the Chi-square test, which indicated that patients who were ≥ 60 years old were at a higher risk of urosepsis; however, this effect was not statistically significant (Table 1).

The patients were divided into 2 groups based on length of stay: (1) 197 cases had a hospital stay of < 14 days, and (2) 140 cases had length of stay of ≥ 14 days (Table 1).

The patients were also grouped based on their malignancy status: solid, liquid, and no malignancy. There were 205 cases with solid tumor, 34 with liquid tumor, and 98 with no malignancy (Table 1).

The predisposing factors including DM, Foley catheter, nephrostomy, DJ stent, and central line were reviewed. A total of 118 patients had DM vs 219 with no DM; 178 had Foley catheter vs 159 without a Foley catheter; 36 had nephrostomy vs 301 without nephrostomy; 15 had DJ stent vs 322 without DJ stent; and 65 had a central line vs 272 without a central line

(Figure1).

The 9 suspected predisposing factors are summarized in Table 2, along with the percentages of cases with the same microorganism in blood and urine.

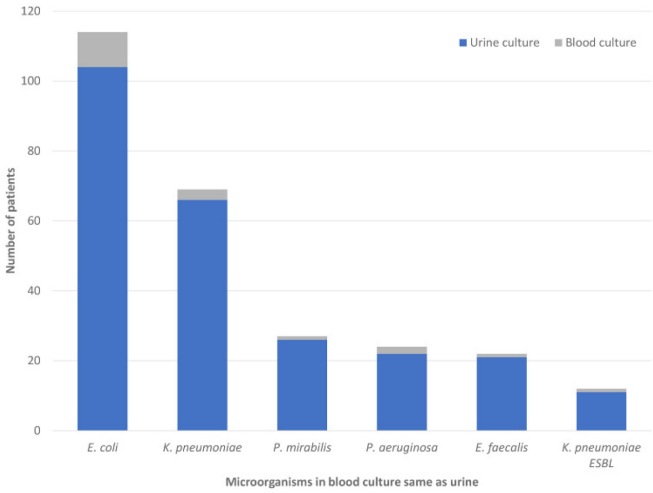
Figure 2 presents the count of positive blood culture vs positive urine culture for the 6 most common microorganisms found in the study sample.

Discussion

Urosepsis is a common healthcare problem with a major impact on the healthcare system, affecting millions each year. After extensive analysis, it appears that there is little literature regarding the prevalence of this condition in the Palestinian territories, which negatively impacts the assessment of the effect of this infection. The management of urosepsis requires a multidisciplinary approach, involving prompt recognition, appropriate antimicrobial therapy, and supportive care. However, the diagnosis and treatment of urosepsis are often complicated by various factors, including the increasing prevalence of antibiotic-resistant bacteria, delayed recognition of the condition, and challenges in implementing evidence-based guidelines in clinical practice.

Urosepsis is a serious condition that can affect individuals of all ages; but older adults, particularly those over 65 years old, are more susceptible to it.

Figure 2. Six most common microorganisms found in urine culture and in blood culture.



The count of positive blood culture vs positive urine culture for the 6 most common microorganisms found in the study sample.

Table 2. Suspected predisposing factors of having the same microorganism in blood as in urine.

Suspected predisposing factors	Percentage of cases with the same microorganism in blood as in urine	*p* value	Unadjusted odds ratio and 95% Confidence interval
Gender		0.039	2 (1–5)
Male	11%		
Female	4.9%		
Age group		0.132	1.8 (0.8–4.1)
≤ 59 years	5.8%		
≥ 60 years	10.2%		
Length of stay		0.185	1.7 (0.8–3.8)
< 14 days	6.1%		
≥ 14 days	10%		
Malignancy status		0.432	**
Liquid	2.9%		
Solid	9.3%		
No malignancy	6.1%		
DM		0.637	0.8 (0.3–1.9)
Yes	6.8%		
No	8.2%		
Foley catheter		0.354	1.4 (0.6–3.3)
Yes	9%		
No	6.3%		
Nephrostomy		0.503	1.5 (0.5–4.9)
Yes	11.1%		
No	7.3%		
DJ stent		0.325	1.9 (0.4–9)
Yes	13.3%		
No	7.5%		
Central line		0.122	2 (0.8–4.8)
Yes	12.3%		
No	6.6%		

** Risk estimated statistics can't be computed, they are only computed for 2*2 table. DM: diabetes mellitus; DJ: double J.

The average age of individuals affected by urosepsis ranges from 59.85 to 72 years, with a significant percentage being over 65 years old [4,7,13,14]. As the population ages, the incidence of urosepsis is expected to rise due to factors such as urological comorbidities associated with aging and indwelling bladder catheter use [4,13]. Additionally, the combination of being over 65 years old and female is highlighted as a significant risk factor for developing urosepsis [8,15].

A study reported that 79.21% of patients with urosepsis were female, highlighting that gender is a notable factor in this condition. Additionally, the study showed that older age (average of 72.02 years, and a high percentage of patients over 65 years old (76.24%)) was a common characteristic among individuals diagnosed with urosepsis [14,16]. The categories of male UTIs include prostatitis, epididymitis, orchitis, pyelonephritis, cystitis, urethritis, and infected urinary catheters. Infections in males may be associated with anatomic abnormalities due to the anatomy of the urinary system in males, which often require surgical correction, and might increase the risk for complicated UTIs and urosepsis [9,17].

The length of stay in the hospital is a crucial factor in the context of urosepsis. Studies have shown that the incidence of urosepsis is correlated with the length of stay in the intensive care unit, with an average of 16.3 ± 1.9 days for patients affected by this condition [10,18].

In the case of healthcare-associated urinary tract infections (HAUTI), it was found that the expected extra length of stay due to these infections was around 4 days, indicating a significant impact on hospitalization duration [11,19]. Additionally, a study highlighted that the longer the length of stay, the higher the UTI rate, with infected patients having a median length of stay of 18 days, compared to 10 days for non-infected patients [20].

Malignancy status can be a contributing factor to urosepsis. Patients with cancer are among those more likely to develop urosepsis, highlighting the importance of considering malignancy status in the context of this severe condition [1].

The literature does not provide direct information on the relationship between liquid and solid tumors and the incidence or outcomes of urosepsis. However, patients with solid tumors, particularly those involving the urogenital tract, can be at increased risk for urosepsis due to factors such as obstructive uropathy, which is common in patients with solid tumors. Obstructive uropathy can lead to urinary stasis, bacterial colonization, and potentially the development of complicated UTIs that may progress to urosepsis [21].

In contrast, liquid tumors, or hematological malignancies such as leukemia, non-Hodgkin lymphoma, and multiple myeloma, are associated with an increased risk of sepsis due to the immunosuppressive effects of the malignancy itself and the treatments used, such as chemotherapy [5]. Although literature lacks any details about the relationship of liquid tumors and urosepsis specifically, the general increased risk of sepsis in these patients suggests that they may also be more susceptible to urosepsis.

DM is associated with an increased susceptibility to infection and sepsis, including urosepsis [16]. The pathogenesis of sepsis in diabetic patients involves abnormalities in the host immune response, particularly in neutrophil function and humoral immunity, which are often attributed to the effects of hyperglycemia [22]. These immune defects can predispose diabetic patients to a higher risk of infections that can progress to sepsis.

The use of Foley catheters, or indwelling urinary catheters, is significantly associated with an increased risk of developing catheter-associated urinary tract infections (CAUTIs), which can progress to urosepsis. Patients with CAUTIs are nearly three times more likely to develop bacteremia than those without CAUTIs [9].

Rosser *et al.* found out that 15.8% of patients admitted to trauma intensive care units with a urinary catheter developed urosepsis. Urosepsis was more likely to occur in patients aged 60 years and above, with extended hospital stay and extended period of catheterization [23].

A retrospective observational study reported the incidence of urosepsis in patients with nephrostomy tubes to be 14.2%, which is significantly higher compared to 2.62% in patients without nephrostomy tubes. This indicates that the presence of a nephrostomy tube is a significant risk factor for the development of urosepsis in patients with chronic kidney disease (CKD) and UTIs [24].

A study on the risk of central line associated bloodstream infections found that there were 2–14 episodes per 1000 hospitalization days, and on average 3 to 5 per 100 central venous uses. However, no studies have linked the risk of developing urosepsis in patients with a central line [25].

This research included all patients who had a positive urine culture over a 5-year period. A urine culture was considered positive in case of growth of

50,000 CFUs or more. Only those who had positive blood cultures with the same isolates as urine culture were selected. Several independent and co-dependent factors were studied, but only gender was found to have a significant association with urosepsis. Chi-square test was used to study the association of gender with the risk for developing bloodstream infection of urinary origin. Male patients developed bloodstream infections originating from the urinary tract more frequently (p = 0.039). In contrast to this study, female gender was considered to have an independent association with the development of urosepsis in a Japanese study from 2021, which showed a significantly higher incidence in females [27]. However, a Nigerian study from 2021, agreed with this study and contrasted the general consensus by concluding that males were at a higher risk for invasive UTIs. This might be attributed to the additional risk imposed by benign prostatic hyperplasia and strictures [27]. In addition, UTI in males is considered complicated in all cases, which may also explain their increased risk of urosepsis.

The patients were divided into two groups based on their age: (1) patients younger than 60 years old, and (2) patients aged ≥ 60 years. The age factor was analyzed through the Chi-square test, and the results showed that patients in group 2 had a higher risk of urosepsis, but the difference was not statistically-significant. Interestingly, Fabbian *et al.* reported that females were more prone to having urosepsis, with that tendency increasing after the age of 60 years. Older women, however, had fewer complications when compared to men of the same age [28].

Multivariate analysis to assess the association between multiple risk factors (gender, age group [< 60 years or ≥ 60 years], length of stay, DM status, Foley catheter, nephrostomy, central line, and DJ stent), indicated no significant results. However, after exploring possible causes for p value deviation, it was found that dividing the patients based on age into "less than 60" and "60 years and above" resulted in a significant gender disproportion between the two age groups (60% of patients under 60 years old were female, with a p value of 0.012). Therefore, new age groups were created (≤ 50 years vs. > 50 years), which resulted in a more balanced gender distribution across the age groups. The multivariate analysis with the new age groups showed a significant association between gender and urosepsis, with p value of 0.034, odds ratio of 2.6, and 95% CI of 1.1–6.3.

The patients were divided into two groups based on their length of stay: patients with a length of stay ≥ 14 days, and patients who spent < 14 days. The Chi-square test indicated that there was no statistically significant difference between the two categories (p = 0.185), but patients with a longer length of stay had an increased risk of urosepsis. This may be attributed to the small sample size. These observations are in contrast to a Canadian study that reported multiple cases of sepsis in patients hospitalized for a prolonged period of time (> 29 days) [29].

This study concluded that the type of malignancy (hematological vs solid) or lack of malignancy did not constitute a risk factor for developing urosepsis (p = 0.432). Huang *et al.* found no statistically significant association between being immunocompromised due to the presence of malignancy and the risk for encountering urosepsis. Marin *et al.* conduced a prospective study with bloodstream infection to identify the different characteristics among patients with neutropenia with solid malignancies vs those with hematologic malignancies. They concluded that patients with hematological malignances were significantly younger, they were more prone to infections in case they had a vascular access or indwelling urinary catheter, and had received previous antibiotic therapy more frequently. However, comorbidities were seen more frequently in patients with solid tumors. Therefore, the urinary tract was more frequently seen as a source of bloodstream infection in patients with solid tumors, while those with hematologic malignancies were more susceptible to infection due to venous access [30].

In this research, 9.3% of the studied sample had the same organism isolated from both urine culture and blood culture, compared to 2.9% of those with hematological malignancy and 6.1% of patients without any kind of malignancies. Gudiol *et al.* found that the urinary tract is the most common source for bloodstream infection in patients with solid tumors, especially Gram-negative bacilli. However, the incidence of bloodstream infection is still lower than that in patients with hematologic malignancies [31]. A systematic review by Peach *et al.* found that, out of 6 reviewed studies, only 1 study reported significant association between DM and urosepsis [9]. This is in agreement with this study which found no significant association between DM and the risk of acquiring a bloodstream infection through the urinary tract.

Kizilbash *et al.* found that patients with urinary catheters were 3 times more vulnerable to acquiring bloodstream infections of urinary origin. The probability was half as likely in patients with external catheters, that is, nephrostomy tubes, compared to those with indwelling catheters [32]. Shigemura *et al*. found

that indwelling catheters increased the risk for urosepsis by 4 folds [33]. A study in Indonesia concluded that the risk for acquiring urosepsis in patients following DJ stent placement increased in females and older patients, and it was directly associated with the length of installation [34]. The association between having a urinary catheter and developing urosepsis was analyzed using the Chi-square test; while the association between nephrostomies and DJ stents on one hand, and urosepsis on the other was studied using the Fischer test. Even though all these factors increased the risk of developing urosepsis, no statistical significance was found through these analyses.

Gudiol *et al.* reported that Gram-negative bacilli were the most common cause of bloodstream infections of urinary origin, with *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* being the most common isolates. Resistant organisms were seen more frequently in patients with urinary instrumentation [31]. In this study, the Mann-Whitney U test was used to analyze the distribution of isolates in positive urine culture compared to those found in both urine and blood cultures. The most common isolate was *Escherichia coli*, followed by *Klebsiella pneumoniae* and *Proteus mirabilis*. *Escherichia coli* was more likely to spread to the bloodstream, compared to other isolates.

This study's results cannot be generalized on all hospitalized populations, due to the specific characteristics of the sample. Most patients had malignancies, or were at a long-term care facility, due to the nature of the admissions that the tertiary care hospital receives which included cancer patients, nephrology patients, and cases requiring long-term care. Therefore, further research with a bigger and more diverse population will be needed for more generalizable results.

Conclusions

In this study, male gender was the primary risk factor for blood-stream infection of urinary origin. Gram-negative bacilli were the main culprit, with *Escherichia coli* being the most common isolate. Since these findings contradict previous studies, further studies with larger population and randomization are recommended to avoid possible confounders. In addition, other factors including urinary catheterization and solid versus liquid tumors can be studied in a larger sample size.

Ethics approval

Ethical approval was obtained from Augusta Victoria Hospital Ethical Committee on 5 September 2024, with IRB number 42/GLD/2024.

Consent to participate

Consent to participate was waived due to the retrospective nature of the study.

Availability of data and material

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

IB, study design, data analysis, manuscript draft; DS, study design, data collection, data interpretation, manuscript draft; AS and HR, data collection; MY, data analysis; MH, manuscript writing and review; AS, critical revisions, approved the final version of the manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interests

No conflict of interests is declared.

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