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"To Study the Uropathogenic Profile and its Antibiotic Susceptibility Pattern among Immunocompromised Patients at a Tertiary Care Centre in Kashmir, India".

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KEYWORDS
Antibiotic Susceptibility Testing (AST), Antibiotic resistance, Diabetes Mellitus, Immunocompromised, Post renal transplant, Post cancer chemotherapy, Urinary tract infection (UTI), CLSI.

ABSTRACT:
Introduction: Immunocompromised patients have a higher tendency of developing all infections, especially infections of the genitourinary tract. Urinary tract infections cause considerable morbidity in immunocompromised patients, and if complicated, increase in the mortality. In Kashmir, the magnitude of immunocompromise-associated urinary tract infections have increased in the past few years. The successful management of urinary tract infections depends upon the identification of risk factors in the immunocompromised population.
Aim and Objectives: To study the uropathogenic profile and its antibiotic susceptibility pattern among immunocompromised patients at a tertiary care centre in Kashmir.
Material and Methods: This was a facility based cross-sectional study carried out in the Department of Microbiology, conducted on 405 immunocompromised patients visiting the study centre from April, 2021 to 31st March, 2022. Demographic data was collected through structured face-to-face interview. The Standard microbiological methods were used for identification of uropathogens and the antibiotic susceptibility testing was done by the Modified Kirby–Bauer disk diffusion technique according to the CLSI guidelines 2020. The study participants were stratified into 6 categories in order to evaluate the patternof antibiotic resistance among the heterogeneous immunocompromised patient population. Univariate logistic regression was used assess the significance of each factor level with respect to UTI positivity with p-value<0.05 as statistically significant. Adjusted and unadjusted odds ratios for risk factors along with 95% confidence intervals were reported.
Results: In the present study a total of 405 immunocompromised patients were screened with the overall prevalence of UTI 34.81% (141/405). The mean age was observed to be 33.09 ± 23.73 years, with the maximum number of patients in the age group of 51-60 years of age group with the highest proportion of the immunocompromised UTI positive patients (29/141; 20.56%). Females accounted for

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58.2% (82/141) of the patients with UTI as compared to 41.8% (59/141) of males.Amongst the 141 samples testing positive for UTI, 61 (43.26%) tested positive for bacterial isolates whereas, 80 (56.73%) tested positive for candida species. Among the bacterial isolates 46 (75.40%) were gram negative and 15 (24.59%) gram positive. The results also reflected high prevalence of UTI (68/141; 48.22%) among the diabetes mellitus category of immunocompromised patients

The most typically grown organisms were *E.coli* (26%) followed by *E.faecalis* (14%) and *K.pneumoniae* (10%). The antibiotics Amikacin, piperacillin/tazobactam, cefoperazone/sulbactam, and carbapenems were all effective against Gram-negative isolates, while nitrofurantoin, linezolid, and vancomycin were effective against Gram-positive cocci.

Conclusion: For empirical treatment, we cannot rely on commonly used oral antibiotics and specific groups such as fluoroquinolones, cephalosporins (excluding those containing sulbactam), and ampicillin. Those organisms were found in both controlled and uncontrolled diabetic groups and showed a similar pattern of antibiotic resistance. These findings emphasise the necessity of glycemic control in diabetic patients to minimise UTIs, independent of age or gender.

INTRODUCTION

Immunocompromised patients have a high prevalence of serious opportunistic infections [1]. Conditions such as diabetes mellitus, cancer chemotherapy and radiation therapy, post-transplant immunosuppressant therapy and surgery put patients at significantly highrisk of acquiring opportunistic infections and subsequent infection-related mortality [2,3]. Furthermore, indiscriminate use of antibiotics and prolonged hospital stays make immunocompromised patients vulnerable to multidrug-resistant (MDR) bacterial strains[4].Urinary tract infection (UTI) is one of the most common infections among immunocompromised patients due to their prolonged immunosuppression, complex treatment and catherization [5,6,7]. The prevalence of UTI in immunocompromised patients has been reported to range between 20% to 50 in India. There are many issues which need to be addressed while dealing with UTIs in immunocompromised patients which include interaction of antibiotic medication with immunosuppressive drugs, infection with drug-resistant bacteria, fungal UTI, and recurrent UTI.

The microorganisms that cause urinary infections in immunocompromised patients seem to differ between regions, but the most common causative microorganisms uniformly throughout the world are gram-negative bacteria, with *Escherichia coli* (30–80%), *Klebsiella pneumoniae* (10%), *Proteus* (5%) and *Pseudomonas* (5%) being the most frequent species. Among the gram-positive bacteria *Enterococcus sp*. and *Staphylococcus aureus* are also more common in this patient population [8,9,10]. The increasing prevalence of multidrug-resistant microorganism (MDRO) is one of the major challenges in management of UTI in immunocompromised patients [8,11,12].

Among immunocompromised patients bacteriuria is often found in urine samples during routine microbiology testing which if left unattended can lead to complicated UTIs. It is vital to detect these infections early in the primary care setting for prompt management and prevention of complications[13,14]. Most of the UTIs are treated empirically on the basis of the pathogen epidemiology and its expected resistance pattern in a geographical area.

Understanding the patterns of uropathogens and their antimicrobial resistance is imperative to facilitate the clinicians in rational and optimal empirical treatment. To the best of our knowledge, there is no comprehensive study in Kashmir region assessing this pattern among the immunocompromised patients. Compilation of such data is essential to develop the evidence based management guidelines, as well as to provide recommendations for AMR stewardship program and support the National Action Plan on AMR. Therefore, the present study was undertaken to evaluate the uropathogenic profile and AMR among the immunocompromised patients with suspected UTI, in Kashmir region.

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MATERIAL AND METHODS

Study design and setting

This was a Hospital based Cross sectional study carried out in the Department of Microbiology at ‘Dr Qadqri’s Hematology Centre and Clinical Laboratory, Srinagar, Kashmir, for a period of one year i.e,April, 2021 to 31st March, 2022. The study center caters to the patient population of the Srinagar city in particular. Being one of the leading microbiology centers in the Kashmir valley and due to the overwhelmed tertiary healthcare facility in Kashmir region, most of the immunocompromised patients visit the center for routine follow-up. The principles of Declaration of Helsinki and ICH-GCP guidelines were followed during the study. As the study was conducted during COVID-19 pandemic period, COVID-19 preventive guidelines were followed strictly.

Inclusion Criteria: Immunocompromised patients diagnosed with; solid and blood malignancies, post organ transplant, diabetes mellitus, SLE and HIV; patients on immunosuppressant drugs and patients willing to provide informed written consent were included in the study.

Exclusion Criteria: Children less than 10 years of age, pregnant females, history of prolonged catheterization (more than 2 days) or intake of antimicrobials within the past 2 weeks, patients hospitalized or unable to respond to the questions, and not consenting to participate in the study were excluded.

All patients attending the center for routine follow-up irrespective of the UTI symptoms were screened randomly for their eligibility.A total of 405 freshly voided midstream urine samples from the immunocompromised people whose initial routine urine tests were positive for pus cells and albumin were collected in a sterile wide mouth container, only after obtaining informed written consent. Within an hour of being collected, all urine samples were processed for aerobic bacterial culture. In case of any delay, the samples were refrigerated and processed within 4 to 6 hours.

Data collection

A face-to-face structured interview with the patient for collecting demographic and baseline data was conducted and information captured in a systematic case record form. The structured interview was drafted in English, then translated to Kashmiri the local language for actual data collection and finally translated back to English to maintain data uniformity. The microbiological data to diagnose UTI was collected by the standard microbiological testing protocol followed in the study center.

To assess the actual frequency of renal tract infection amid the heterogeneous immunocompromised patient population, the study participants were stratified into 6 categories; diabetes mellitus, post renal transplant, post cancer chemotherapy, diabetic mellitus and post renal transplant, diabetic mellitus and post cancer chemotherapy and others (SLE, ulcerative colitis, rheumatoid arthritis and multiple sclerosis patients on immunosuppressants).

Specimen processing

Urine specimen collection: Urine specimens were collected aseptically by standard mid-stream “clean-catch” method in sterile wide mouth leak proof bottles and processed within 2 hours after collection. All subjects were directed to wash the urethral area before urine collection to avoid contamination. The female subjects were also asked to hold the labia wide apart during urine collection.

Identification of uropathogen and diagnosis: Microscopic examination of urine specimens was done at low and high power to detect the epithelial cells, casts, crystals, pus cells, bacteria and yeast cells. A colony count of ≥10 5 CFU/ml was considered positive for UTI [15]. For classification of bacteria, gram staining of the specimen smears was carried out. Samples with colony count of ≥10 5 CFU/ml were sent for urine culture for further identification of the uropathogens and confirmation of diagnosis. Midstream urine samples were inoculated on HiCrome UTI agar without centrifugation for suspected bacterial infections [16] and incubated at 37°C aerobically for 24 hours [17].

The specimens werefurther sub-cultured on MacConkey agar media. Presence of 100,000 colony-forming units (CFU) per milliliter in the urine culture was reported as

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UTI positive[18]. Standard identification procedures were followed for gram-negative bacteria with a subculture on chromatic differential medium (Liofilchem, Italy) and use of Analytical Profile Index (API) [19]. The gram-positive isolates were identified based on the phenotypic parameters like growth on mannitol salt agar (Oxoid, UK), chromatic agar, colony morphology, and gram staining, which was followed by microscopic analysis and specific biochemical test. For identification and examination of morphologic characteristics of important yeast species, germ tube test, corn meal agar and HiChrome^{TM} Candida Differential Agar culture were used [20].

Antibiotic Susceptibility Testing (AST): The antibiotic susceptibility pattern of the isolates was determined by the Kirby–Bauer disk diffusion method according to Clinical and Laboratory Standards Institute (CLSI) guidelines [21]. The results were recorded as susceptible (S), intermediate (I) and resistant (R). However, during data analysis, intermediate results were merged with the susceptible category. The antibiotics purchased from HiMedia (India) were used for drug susceptibility test. The reference strain used as quality control was *E. coli* (ATCC 25922) for gram negative and *S. aureus* (ATCC 25923) gram positive bacteria.

Operational definition

After culture of an appropriately collected sample, a patient was considered positive for UTI if there were more than 100,000 CFU of bacteria per milliliter. Contamination was defined as the presence of more than two bacterial species [18]. Resistance to more than one antimicrobial agent in three or more antimicrobial categories was defined as multidrug resistance (MDR) infection [22].

Statistical analysis

Patient demographic characteristics and clinical data (immunocompromised category) were analyzed by using descriptive statistics. Statistical analysis was done using SPSS- 20 program (SPSS Inc, Chicago, IL, USA). Univariate logistic regression was used to assess the significance of each factor level with respect to UTI positivity. Multivariate binary logistic regression analysis was employed to overcome the impact of confounding factors associated with UTI. For the risk factors, adjusted and unadjusted odds ratios with 95% confidence intervals were calculated. p-value was <0.05 was taken as statistically significant.

RESULTS

In the present study a total of 405 immunocompromised patients visiting the study center were screened during the stipulated period and the overall prevalence of UTI were found to be 34.81% (141/405). The mean age of the study participants was found to be 33.09 ± 23.73 years. As appreciated in Table 1, the highest proportion of the immunocompromised UTI positive patients (29/141; 20.56%) were in the age group of 51-60 years of age group. Females accounted for 58.2% (82/141) of the patients with UTI as compared to 41.8% (59/141) of males.Amongst the 141 samples testing positive for UTI, 61 (43.26%) tested positive for bacterial isolates whereas, 80 (56.73%) tested positive for candida species. Among the bacterial isolates 46 (75.40%) were gram negative and 15 (24.59%) gram positive. The results also reflected high prevalence of UTI (68/141; 48.22%) among the diabetes mellitus category of immunocompromised patients

Table 1: Socio-demographic and baseline characteristics of UTI positive immunocompromised patient population (n=141).

Demographic & baseline characteristics		**UTI Positive N (%)**
Age	18-20	**4 (2.83)**
	21-30	**19 (13.47)**
	31-40	**28 (19.85)**
	41-50	**27 (19.14)**
	51-60	**29 (20.56)**
	61-70	**27 (19.14)**
	>71	**7 (4.96)**

Gender	Male	**59 (41.84)**
	Female	**82 (58.15)**
Immunocompromised category	Diabetes mellitus	**68 (48.22)**
	Post renal transplant	**53 (37.58)**
	Cancer chemotherapy	**7 (4.96)**
	Diabetes mellitus & post renal transplant	**9 (6.38)**
	Diabetes mellitus & post cancer chemotherapy	**1 (0.70)**
	Others	**3 (2.12)**
Bacterial UTI		**61 (43.26)**
	Gram positive bacteria	**15 (24.59)**
	Gram negative bacteria	**46 (75.40)**
Fungal UTI		**80 (56.73)**

Table 2: Distribution of isolated uropathogens as a function of age (n=141).

Uropathogen isolated	Age N (%)							Total N (%)	P-value
	18-20	21-30	31-40	41-50	51-60	61-70	>71		
FUNGAL									
Candida albicans	1 (25)	9 (47.37)	11(39.29)	8 (29.63)	9 (31.03)	7 (25.93)	2 (28.57)	**47 (33.33)**	**0.048**
Candida glabrata	0 (0)	1 (5.26)	0 (0)	4 (14.81)	5 (17.24)	1 (3.7)	2 (28.57)	**13 (9.21)**	**0.055**
Candida krusei	0 (0)	1 (5.26)	2 (7.14)	1 (3.7)	0 (0)	0 (0)	0 (0)	**4 (2.83)**	**0.370**
Candida parapsilosis	0 (0)	1 (5.26)	1 (3.57)	0 (0)	0 (0)	1 (3.7)	0 (0)	**3 (2.12)**	**0.677**
Candida spherica	0 (0)	0 (0)	0 (0)	1 (3.7)	0 (0)	0 (0)	0 (0)	**1 (0.70)**	**0.423**
Candida tropicalis	1 (25)	0 (0)	1 (3.57)	1 (3.7)	2 (6.9)	4 (14.81)	3 (42.86)	**12 (8.51)**	**0.353**
BACTERIAL									
GRAM NEGATIVE									
E.coli	2 (50)	2 (10.53)	3 (10.71)	7 (25.93)	6 (20.69)	6 (22.22)	0 (0)	**26 (18.43)**	**0.084**
K. pneumonia	0 (0)	0 (0)	4 (14.29)	1 (3.7)	4 (13.79)	1 (3.7)	0 (0)	**10 (7.09)**	**0.032**
M. morganii	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.7)	0 (0)	**1 (0.70)**	**0.423**
P. aeruginosa	0 (0)	4 (21.05)	2 (7.14)	0 (0)	1 (3.45)	1 (3.7)	0 (0)	**8 (5.67)**	**0.081**
Acinetobacter	0 (0)	0 (0)	1 (3.57)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (0.70)**	**0.423**
GRAM POSITIVE									
Staph. aureus	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.45)	0 (0)	0 (0)	**1 (0.70)**	**0.423**
E. faecalis	0 (0)	1 (5.26)	3 (10.71)	4 (14.81)	1 (3.45)	5 (18.52)	0 (0)	**14 (9.92)**	**0.062**
Total	**4 (100)**	**19 (100)**	**28 (100)**	**27 (100)**	**29 (100)**	**27 (100)**	**7 (100)**	**141 (100)**	
p-value	**0.215**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.017**		

From Table 2 it can be inferred that the most common pathogen was *Candida albicans*(fungal) isolated in 47 (33.33%) patients, followed by *Escherichia coli*(gram negative) in 26 (18.43) and *E. faecalis* (gram positive) in 14 (9.92) isolates. Based on the age groups once again *Candida albicans* was the most common organism isolated in the age groups ranging from 21 to 70 years, with significant p value of 0.048 across the age groups and p value of <0.001 within each of age group of the specified range. E.coli was the most frequent isolate in 18-21 age group.

Figure 1: Prevalence of isolated uropathogens with respect to gender (n=141).

Uropathogens isolated	Gender N (%)		Total N (%)	p-value
	Female	Male		
FUNGAL				
C. albicans	29 (35.36)	18 (30.50)	**47 (33.33)**	**<0.001**
C.glabrata	7 (8.53)	6 (10.16)	**13 (9.21)**	**0.004**

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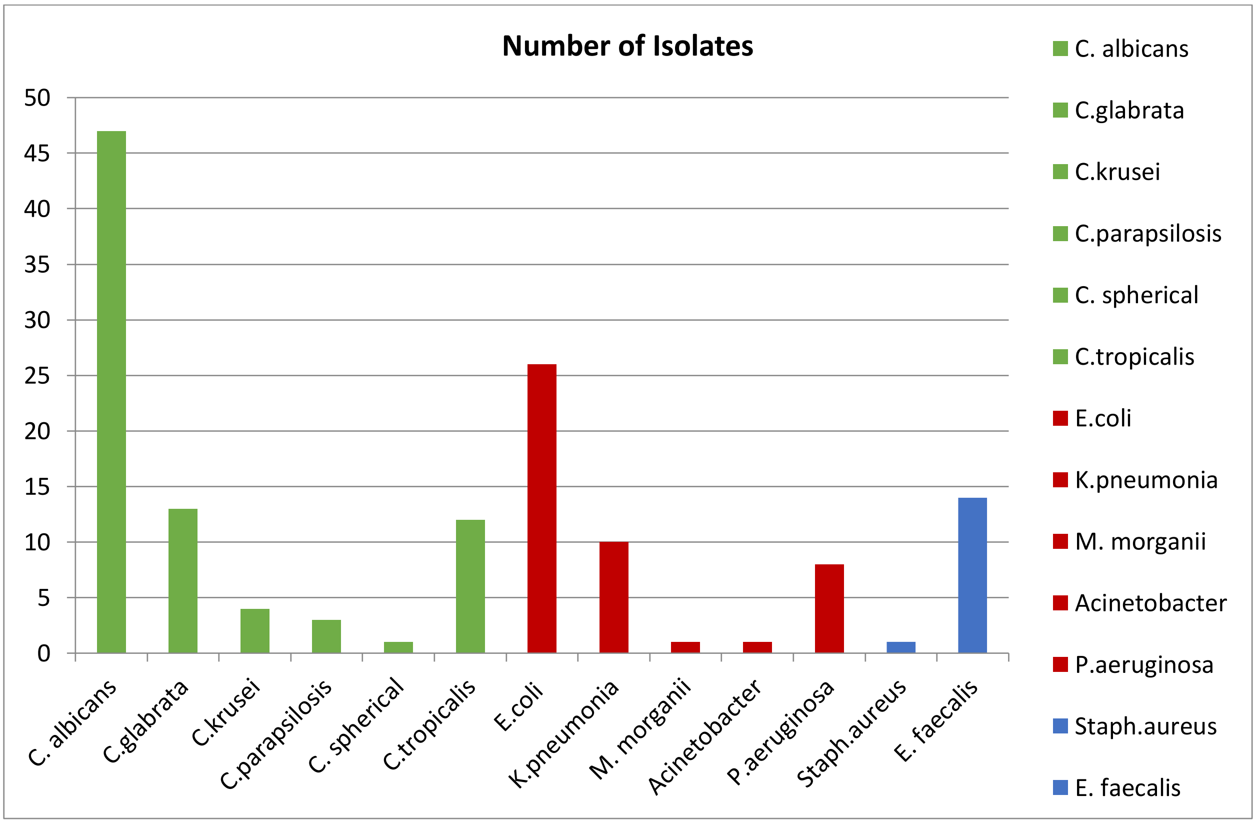
C.krusei	2 (2.43)	2 (3.38)	**4 (2.83)**	**0.156**
C.parapsilosis	0 (0.00)	3 (5.08)	**3 (2.12)**	**0.221**
C. spherical	0 (0.00)	1 (1.36)	**1 (0.070)**	**0.416**
C.tropicalis	4 (4.87)	8 (13.55)	**12 (8.51)**	**0.023**
BACTERIAL				
GRAM NEGATIVE				
E.coli	22 (26.82)	4 (6.77)	**26 (18.43)**	**<0.001**
K.pneumonia	3 (3.65)	7 (11.86)	**10 (7.09)**	**0.010**
M. morganii	1 (1.21)	0 (0.00)	**1 (0.70)**	**0.416**
Acinetobacter	0 (0.00)	1 (1.36)	**1 (0.70)**	**0.416**
P.aeruginosa	3 (3.65)	5 (8.47)	**8 (5.67)**	**<0.001**
GRAM POSITIVE				
Staph.aureus	0 (0.00)	1 (1.69)	**1 (0.70)**	**0.416**
E. faecalis	11 (13.41)	3 (5.08)	**14 (9.92)**	**0.003**
TOTAL	**82 (100)**	**59 (100)**	**141 (100)**	

As depicted in figure 1, the most frequent organism isolated among females was *candida albicans*(29; 35.36%) with significant p value of <0.001, followed by *E.coli* (22; 26.82%) again with p value of <0.001 and *E.fecalis* (11; 13.41%) with p value of 0.003.

Whereas, in males the order was *C.albicans* (18; 30.50%) followed by C.tropicalis (8; 13.55%) with p value of 0.023 and *K.pneumonia* (7; 11.86%) with p value of 0.010.



Graph No. 1: Graphical representation of Prevalence of isolated uropathogens

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Table 3: Prevalence of isolated uropathogens among immunocompromised patient population (n=141).

Uropathogen isolated	Immunocompromised Category N (%)						Total N (%)	Stats For a pathogen across IC categories
	Diabetes mellitus	Post renal transplant	Post cancer chemotherapy	Diabetes mellitus & post renal transplant	Diabetes mellitus &post cancer chemotherapy	Others		
FUNGAL								
Candida albicans	25 (35.21)	15 (30.00)	2 (28.57)	3 (33.33)	0 (0.00)	2 (66.67)	47 (33.33)	<0.001
Candida glabrata	6 (8.82)	5 (9.43)	0 (0.00)	2 (22.22)	0 (0.00)	0 (0.00)	13 (9.22)	0.004
Candida krusei	2 (2.94)	2 (3.77)	0 (0.00)	0 (0.00)	0 (0.00)	0(0.00)	4 (2.84)	0.156
Candida parapsilosis	1 (1.47)	2 (3.77)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (2.12)	0.221
Candida spherica	1 (1.40)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.70)	0.416
Candida tropicalis	5 (7.35)	4 (7.55)	3 (42.85)	0 (0.00)	0 (0.00)	0 (0.00)	12 (8.51)	0.023
BACTERIAL								
GRAM NEGATIVE								
E.coli	17 (25.00)	6 (11.32)	0 (0.00)	1 (11.11)	1 (100.00)	1 (33.33)	26 (18.43)	<0.001
K. pneumonia	4 (5.88)	5 (9.43)	0 (0.00)	1 (11.11)	0 (0.00)	0 (0.00)	10 (7.09)	0.010
M. morganii	1 (1.47)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.70)	0.416
P. aeruginosa	0 (0.00)	7 (13.21)	0 (0.00)	1 (11.11)	0 (0.00)	0 (0.00)	8 (5.67)	<0.001
Acinetobacter	0 (0.00)	1 (1.89)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.70)	0.416
GRAM POSITIVE								
Staph. aureus	0 (0.00)	0 (0.00)	1 (14.29)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.70)	0.416
E. faecalis	6 (8.82)	6 (11.32)	1 (14.29)	1 (11.11)	0 (0.00)	0 (0.00)	14 (9.92)	0.003
Total	68 (100)	53 (100)	7 (100)	9 (100)	1 (100)	3 (100)	141 (100)	
Stats within IC category across all pathogens	<0.001	<0.001	0.053	0.212	0.446	0.097		

Table 3 reflects *C.albicans* the most common organism isolated in diabetes mellitus group (25; 35.21%) followed by *E.coli* (17; 25%) with p value of <0.001 within the group.*C.albicans* was also the most frequent organism isolated in Post renal transplant group (15; 30%) followed by *P. aeruginosa* ((7; 13.21%) with p value of <0.001 within the category. *C.albicans* was the most common organism isolated in Diabetes mellitus & post renal transplant group (3; 33.33%). *C.albicans* was overall the most frequent isolate with a p value of <0.001 across all the immunocompromised study groups.

Figure 2: Comparative resistance pattern among the Gram positive and Gram negative bacterial isolates in the immunocompromised UTI positive patients (n=61).

Antimicrobial Agent	No. of resistant Gram – isolates (N=46)	Resistance (%)	No. of resistant Gram + isolates (N=15)	Resistance (%)	p-value
Ciprofloxacin	31/46	67.4	14/15	93.3	0.006
Levofloxacin	22/46	47.8	12/15	80.0	0.011
Cotrimoxazole	31/36	86.1	0	0.00	
Imipenem	26/46	56.5	0	0.00	
Ceftriaxone	40/45	88.9	0	0.00	
Piperacillin/Tazobactam	16/46	34.8	6/15	40.0	0.718
Amikacin	12/46	26.1	0	0.00	
Gentamicin	23/46	50.0	8/15	53.3	0.881
Meropenem	29/46	63.0	0	0.00	
Ceftazidime	36/46	78.3	0	0.00	
Vancomycin	0	0.00	4/15	26.7	
Ampicillin	36/37	97.3	8/14	57.1	0.003
Tigecycline	27/46	58.7	0	0.00	
Linezolid	0	0.00	1/15	6.7	
Cefoperazone-Sulbactam	36/46	78.3	0	0.00	
Nitrofurantoin	22/45	48.9	10/15	66.7	0.213
Norfloxacin	30/45	66.7	9/15	60.0	0.645
Trimethoprim/Sulfamethoxazole	22/38	57.9	0	0.00	
Fosfomycin	18/45	40.0	0	0.00	
Ertapenem	23/44	52.3	0	0.00	
Aztreonam	0	0	0	0.00	

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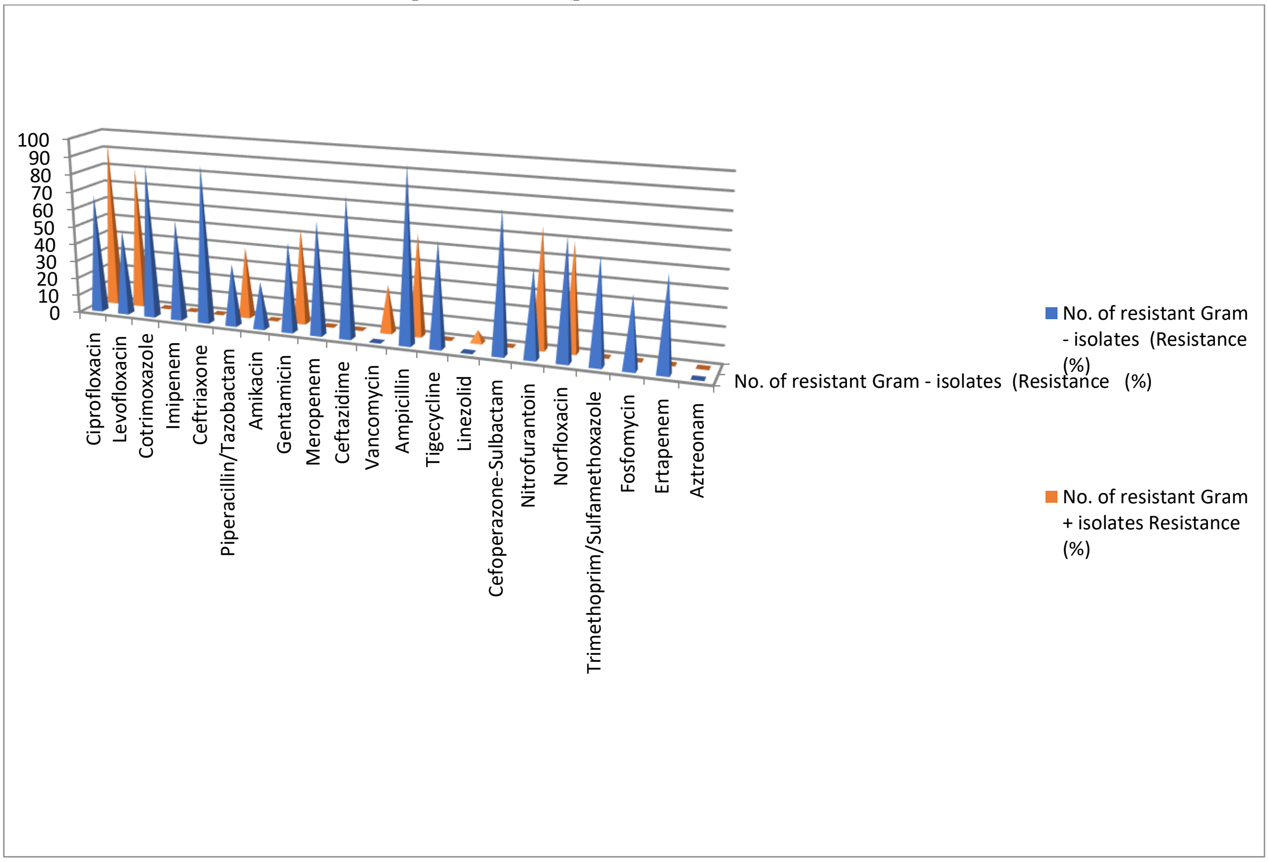
p-value	<0.001	<0.001	

Figure 2 clearly reveals that the gram negative bacterial isolates were mostly resistant to ampicillin (97.3%), ceftriaxone (88.9%), cotrimoxazole (86.1%). Whereas gram positive bacterial isolates were mostly resistant tociprofloxacin (93.3%) and levofloxacin (80%). We also note that resistance to ciprofloxacin (p value=0.005) and levofloxacin (p value=0.011) is significantly high in gram positive bacteria as compared to gram negative bacteria. On the contrary resistance to ampicillin is significantly high in gram negative bacterial isolates (p value=0.003).



Graph No. 2: Graphical representation ofComparative resistance pattern among the Gram positive and Gram negative bacterial isolates in the immunocompromised UTI positive patients (n=61).

Table 4: Overall antimicrobial resistance pattern of bacterial isolatesin the immunocompromised UTI positive patients (n=61).

Antimicrobial resistance pattern	**Gram Negative (n=46)**					**Gram Positive (n=15)**	
	E. coli (26)	**K. pneumonia (10)**	**M. morganii (1)**	**P. aeroginosa (8)**	**Acinetobacter (1)**	**Staph. aureus (1)**	**E. faecalis (14)**
Ciprofloxacin	**18(69)**	**6 (60)**	**0**	**6 (75)**	**1 (100)**	**1 (100)**	**13 (93)**
Levofloxacin	**18(69)**	**0**	**0**	**3 (38)**	**1 (100)**	**1 (100)**	**11 (79)**
Cotrimoxazole	**22 (85)**	**9 (90)**	**N.A**	**N.A**	**N.A**	**N.A**	**N.A**
Imipenem	**15(58)**	**9(90)**	**0**	**1(13)**	**1 (100)**	**N.A**	**N.A**
Ceftriaxone	**24(92)**	**7(70)**	**N.A**	**8 (100)**	**1 (100)**	**N.A**	**N.A**
Piperacillin/Tazobactam	**8(31)**	**5 (50)**	**0**	**2 (25)**	**1(100)**	**0**	**6 (43)**
Amikacin	**5 (19)**	**5(50)**	**1 (100)**	**1 (13)**	**0**	**N.A**	**N.A**
Gentamicin	**12(46)**	**6(60)**	**0**	**4 (50)**	**1 (100)**	**0**	**8 (57)**
Meropenem	**25(96)**	**3(30)**	**0**	**1(13)**	**0**	**N.A**	**N.A**
Ceftazidime	**19 (73)**	**8(80)**	**0**	**8 (100)**	**1 (100)**	**N.A**	**N.A**

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Vancomycin	**N.A**	**N.A**	**N.A**	**N.A**	**N.A**	**1 (100)**	**3 (21)**
Ampicillin	**25 (96)**	**10 (100)**	**1 (100)**	**N.A**	**N.A**	**N.A**	**8 (57)**
Tigecycline	**16 (62)**	**6 (60)**	**1 (100)**	**4 (50)**	**0**	**N.A**	**N.A**
Linezolid	**N.A**	**N.A**	**N.A**	**N.A**	**N.A**	**0**	**1 (7)**
Cefoperazone-Sulbactam	**21 (81)**	**8 (80)**	**0**	**6 (75)**	**1 (100)**	**N.A**	**N.A**
Nitrofurantoin	**7 (27)**	**10(100)**	**N.A**	**4 (50)**	**1 (100)**	**1 (100)**	**9 (64)**
Norfloxacin	**17 (65)**	**8 (80)**	**N.A**	**4 (50)**	**1 (100)**	**1 (100)**	**8 (57)**
Trimethoprim/Sulfamethoxazole	**13(50)**	**8 (80)**	**0**	**N.A**	**1 (100)**	**N.A**	**N.A**
Fosfomycin	**7 (27)**	**8 (80)**	**1 (100)**	**2 (25)**	**N.A**	**N.A**	**N.A**
Ertapenem	**7 (27)**	**8 (80)**	**N.A**	**8 (100)**	**N.A**	**N.A**	**N.A**
Aztreonam	**N.A**	**N.A**	**0**	**N.A**	**N.A**	**N.A**	**N.A**

The results of table 4 reveal that the *E.coli* isolates were mostly resistant to ampicillin (96%), meropenem (96%) and ceftriaxone (92%). Surprisingly, all *K.pnemonia* isolates were resistant to ampicillin and nitrofurantoin (100%) and 90% were resistant to cotrimoxazole and imipenem. Once again all isolates of *P.aeroginosa* were found resistant to ceftriaxone, ceftazidime and ertapenem (100%). The gram positive *E.faecalis* showed 93% resistance to ciprofloxacin and 79% resistance to levofloxacin.

DISCUSSION

A prevalent health issue in nosocomial and community settings is urinary tract infection (UTI). The bacteria that cause UTIs have more aggressive virulence characteristics compared to non-pathogenic bacteria, which improves their host cell adhesion, colonisation, and invasion capacities. Through the use of certain virulence factors, such as pili, capsules, lipopolysaccharides, and other cell surface features, these bacteria are able to avoid evading the host's immune system (Camacho *et al*, 2004) [23]. One of the most typical infections, particularly among women, is UTI. According to the National Ambulatory Medical Care Survey, UTI alone accounts for up to one million visits to hospital emergency rooms and roughly seven million outpatient department (OPD) visits, leading to approximately 100,000 inpatient stays (Foxmann, 2010) [24].

In the present study the overall prevalence of UTI was found to be 34.81% with females accounting for 58.2% of the patients with UTI. The present study was similar to the study performed by the other author where the ratio of females was more as compared to the males. This study was similar to the study by other researchers Suhail A. *et al*, and Martin Odoki *et al*., in 2019 where the ratio of females was more as compared to the males [25, 26]. Study by (Ahmed *et al*, 2019), (Odoki *et al*, 2019)were also in support to the present study [27, 26]. Higher prevalence of UTI among females is due to various factors that predispose women to UTI (August *et al*, 2012) [28]. Interestingly, in other study showed that recurrent urinary tract infections with resistant microorganisms are more common in male transplant recipients. Therefore data suggest, starting treatment with a wide-spectrum antibiotic may be warranted for UTI infections in male transplants since they tend to be caused by resistant microorganisms and have a tendency to recur. There are studies in both the general population and the transplant population to support these findings [29,30]. Urinary outflow obstruction due to prostate, possible prostatitis, and inadequate response to antibiotics due to long uroepithelial tissue in male recipients compared to females are the mechanisms that explain this situation. It is important to emphasize that, a UTI caused by ESBL-producing microorganisms carries an almost three times greater risk of recurrence [31]. Brakemeir et al reported that the recurrence rate of UTI with ESBL producing bacteria was found to be 54% [30]. Our findings were also consistent with this previously published data. These results should be interpreted with caution due to the single-center and retrospective nature of the study and the relatively small number of patients. The low number of events limits further statistical analysis for exploring the exact effect of male gender on resistant and recurrent UTIs.

In the present study the bacterial UTI observed for gram positive bacteria was 15 (24.59%), gram negative 46(75.4%) wheras fungal uti was found to be 80 (56.73%) that reflected that among the 141 UTI positive samples, 61 (43.26%) tested positive for bacterial

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isolates whereas, 80 (56.73%) tested positive for candida species.

The present study was in support with the other studies where Gondos et al. in Yemen in 2015 depicted most prevalent bacteria causing UTI as E. coli with a percentage of 44%, followed by *Staphylococcus saprophyticus* 34%, *Enterobacter* spp. 12%, *Klebsiella* spp. 6%, and finally P. aeruginosa 4% [32] Another study done by Rivera-Sanchez et al. in 2010 showed the organisms: E. coli 32%, *Candida albicans* 21%, *Enterococci* 10%, and *K. pneumoniae* 5% [33,34].

On microbiological examination,fungal species (candida) were identified in 80 (56.73%) and bacterial isolates in 61 (43.26%) out of 141 samples testing positive for UTI. It is noteworthy that higher prevalence of fungal UTI was observed as compared to bacterial UTI, in all immunocompromised patient categories. Highest prevalence of fungal UTI was recorded at 58.82% (40/68) in diabetes mellitus category and 50.94% (27/53) in post renal transplant category of patients. Furthermore, bacterial isolates based on their gram staining and reveals that the prevalence of gram negative bacteria was 3 times that of gram positive bacteria (15:46 samples). Thus, from among the 61 bacterial isolates,45 (73.77%) were identified to be gram negative and 16 (26.22%) were gram positive in a study [34].

Similar study was performed by the other research workers where among 206 bacterial isolates obtained from 417 urine samples, majority of the isolates (99%) were Gram negative bacteria (Manjula *et al*, 2016) [35].

In the current study it was observed that the most typically grown organisms were *E.coli* (26%) followed by *E.faecalis* (14%) and *K.pneumoniae* (10%) .This study was in support with the study by Manjula *et al*, 2016 where *Escherichia coli* (56.79%), *Klebsiella sps* (19.9%), *Pseudomonas sps* (6.3%), *Proteus sps* (5.8%), *Enterobacter sps* (3.8%), *Citrobacter sps* (1.4%), *Enterococcus sps* (0.9%), and other *NFGNB* (4.8%) were observed.

There were other studies which were parallel to the present study stating that *E. coli* was the predominant isolate which is compatible with a study conducted in India (E. coli (40%) and *K. pneumonia* (25%)) [36] another study in India (*E. coli* (38.1%) [37] and in Sudan (*E. coli* (39.2%) and *Klebsiella pneumonia* (19%)) . Among Gram positives, *S. aureus* was the predominantly isolated bacteria followed by Enterococcus species, which is in line with a study conducted in Tamil Nadu, India [38], and in Nigeria [39]. This variation might be due to sample size variation, and we had included all types of cancer patients in our study, but other studies include specific cases of cancer patients. There was another study performed by the research investigator Abiye Tigabu [40] et al in 2020 where the overall prevalence of asymptomatic bacteriuria in cancer patients was 23.3%. *E. coli* (32.1%) was the commonest isolated uropathogenic bacteria followed by Klebsiella species (25.0%), *S. aureus* (21.4%), *Enterococcus* species (10.7%), Serratia species (7.1%), and *Enterobacter aerogenes* (3.6%) in cancer patients. Most Gram-negative bacteria were more sensitive to ceftazidime, cefoxitin, nalidixic acid, nitrofurantoin, norfloxacin, ciprofloxacin, and tobramycin, whereas highly resistant to ampicillin, penicillin, tetracycline, and ceftazidime. S. aureus isolates were 100% susceptible to nitrofurantoin.

There were other studies which were in contrast to the present study where the frequency of Gram-negative bacteria isolated from the urine samples of cancer patients in Egypt was 17.2% [41] and in another study reported in a Japan frequency of bacteriuria (15%) for Gram-negative bacteria was observed [42].

In the present study it was found that the highest proportion of the immunocompromised patients (74/405; 18.27%) as well as UTI positive patients (31/141; 21.98%) were in the age group of 30-40 years of age group. Based on the age groups once again *Candida albicans* was the most common organism isolated in the age groups ranging from 21 to 70 years, with significant p value of 0.048 across the age groups and p value of <0.001 within each of age group of the specified range. *E.coli* was the most frequent isolate in 18-21 age group. This study was parallel to the study performed by author (Odoki *et al*, 2019) [29].

On microbiological identification, the current study revealed that the most common pathogen was *Candida albicans* (fungal) isolated in 47 (33.33%) patients, followed by *Escherichia coli* (gram negative) in 26 (18.43) and *E. faecalis* (gram positive) in 14 (9.92) isolates. As a function of gender, our results show that the most frequent organism isolated among females was

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candida albicans (29; 35.36%) with significant p value of <0.001, followed by *E.coli* (22; 26.82%) again with p value of <0.001 and *E.fecalis* (11; 13.41%) with p value of 0.003. Whereas, in males the order was *C.albicans* (18; 30.50%) followed by *C.tropicalis* (8; 13.55%) with p value of 0.023 and *K.pneumonia* (7; 11.86%) with p value of 0.010.

The findings of the present study were similar to other reports which suggest that gram negative bacteria, particularly *E. coli* was the commonest pathogens isolated from patients with UTI (Onifade *et al*, 2005), (H. Fukushima,2017 Okonofua 2005 and Okonofua, 1989) [43-45] . The incidence of *E. coli* in our study was higher when compared with the Nigerian studies reporting 42.10% (Okonko *et al*, 2009) and 51% (Nwanze *et al*, 2007) [46,47]. Most of the studies conducted in Africa and Arab countries showed less than 50% isolation of *E coli* from the UTI patients but re- ported a higher percentage (29%) of *S aureus* as second most frequently isolated bacteria from UTI cases. Reports from other developing or developed countries were the isolation of Gram positive bacteria as uropathogen is very low <10% (Akram *et al*, 2007), (Mahesh *et al*, 2010) [48,49] Similar study was also recorded by the other authors where the rate of E.coli was observed to be the maximum followed by *Klebsiella pneumonia* least for *Proteus vulgaris, Acinetobacter baumannii*, *Staphylococcus saprophyticus*.

In another study, the effect of ampicillin, augmentin, tetracycline, and penicillin were minimal while cefoxitin, nitrofurantoin, norfloxacin, nalidixic acid, and ciprofloxacin were found to be the most efficient antibiotics for bacterial isolates from both cancer patients. Among the isolates, 46.4% (13/28) showed multidrug-resistance pattern in cancer patients. The proportion of multidrug-resistant isolates among cancer patients for *E. coli* was 44.4% (4/9), Klebsiella species 57.1% (4/7), S. aureus 16.7% (1/6), Enterococcus species 100% (3/3), and Serratia species 50% (1/2). The Enterococcus species were resistant to five antimicrobials, one Serratia species isolate showed resistance to four antimicrobials, and three Klebsiella species were resistant to three antimicrobials. The MDR isolates are associated with a history of antimicrobials; this might be due to the development of specific mechanisms of resistance through time [43].

There was another study in support to our present study where the most common pathogen was *Escherichia coli*, isolated in 52 episodes (73,2%), followed by *Klebsiella pneumoniae* in 12 (16,9%) and fungal species were found as causative agents in 3 (4,2%) UTI episodes. It was also noted that Methicillin-resistant *Staphylococcus epidermidis* was isolated in one and *Enterococcus faecalis* was isolated in three UTI episodes. In total, 71 microorganisms were isolated in all patients. After excluding fungal causes, 43 out of 68 bacterial microorganisms (63.2%) were caused by ESBL producing microorganisms. In total 46 (67.6%) isolates were identified as MDROs. Multidrug resistant microorganisms (MDROs) were more frequent in male patients (32 episodes in males vs. 14 episodes in females, p = <0.001) and had more recurrent UTIs when compared to female patients. The male recipients also had more CUTI at presentation compared with female recipients.In antibiotic susceptibility tests, the majority of *Escherichia coli* and *Klebsiella pneumoniae*, 84.6% and 83.3% respectively, were resistant to TMP-SMX. Of the 52 *Escherichia* coli isolates, 78.8% were resistant to the quinolones. In *Klebsiella pneumoniae* isolates, 25% were found to be quinolone resistant. No bacteria were found to be carbapenem-resistant. Therefore, 49.2% were treated with carbapenems in our cohort [50].

Similar study was also reported by Shrestha, G et al [51] where out of 308 patients who had undergone culture, 73 (24%) of samples had bacterial growth. The most common organisms isolated were *E. coli* (58%), *Staphylococcus* (11%) and *Klebsiella* (10%). These bacteria had undergone susceptibility testing to 27 different antibiotics in various proportions. There were high levels of resistance to antibiotics in the “Access” and “Watch” groups of antibiotics (2019 WHO classification). Of the 73 samples having bacterial isolates, high levels of resistance to ampicillin, amoxicillin and cefalexin of antibiotics in the “Access” group (>80%) and to fluroquinolones in the “Watch” group (>63%) was observed. In addition, resistance in the “Reserve” group, was observed on average in 11.5% (polymyxin 15%, tigecycline 8%). MDR among 89% of the culture positive samples was reported.

On comparative analysis between the various immunocompromised groups we observed that

C.albicans the most common organism isolated in diabetes mellitus group (25; 35.21%) followed by *E.coli* (17; 25%) with p value of <0.001 within the group.*C.albicans* was also the most frequent organism isolated in Post renal transplant group (15; 30%)followed by *P. aeruginosa* ((7; 13.21%) with p value of <0.001 within the category. *C.albicans* was the most common organism isolated in Diabetes mellitus & post renal transplant group (3; 33.33%). *C.albicans* was overall the most frequent isolate with a p value of <0.001 across all the immunocompromised study groups. From the 6 major categories of immunocompromised patient population participating in the study, the highest prevalence of UTI (43.58%) was observed in the diabetes mellitus category [34].

Biswas D, et al in 2022 [52] also reported the increase in the *E.coli* cases. Studies done by Bonadio M, et al. [53] had found an increased incidence of E. coli (54.1%) in diabetic patients with bacteriuria, the next prevalent organism being Enterococcus spp: 8.3%. Similar results with this study were seen with studies done by Zhanel et al.,[54] Huvos et al.,[55] O'Sullivan et al.,[56] Vigg et al.,[57] Szucs S, et al.,[58] Geerlings SE, et al.,[59] Asghar et al. [60] Klebsiella was the second common organism isolated (16.3%) which matches with observations by Zhanel et al. [54] and Vigg et al. [57] One sample contained Candida along with *E. Coli*. Al-Khashmani et al.,[61] in their study, found that *Staphylococcus epidermidis* was the most common bacterium isolated from urine in both diabetics and non-diabetics (22.4%), and *E. coli* (19%) was the second most common isolate. Other common bacterium isolates included *Enterococcus fecalis* (13.7%), *Klebsiella pneumonia* (12%), and Enterobacter sp (12%), *Staph aureus* (10.3%).

The results of the antimicrobial susceptibility testing (AST) revealed that gram negative bacterial isolates were mostly resistant to ampicillin (97.3%), ceftriaxone (88.9%), cotrimoxazole (86.1%). Whereas gram positive bacterial isolates were mostly resistant to ciprofloxacin (93.3%) and levofloxacin (80%). We also note that resistance to ciprofloxacin (p value=0.005) and levofloxacin (p value=0.011) is significantly high in gram positive bacteria as compared to gram negative bacteria. Our results demonstrate that the *E.coli* isolates were mostly resistant to ampicillin (96%), meropenem (96%) and ceftriaxone (92%). Surprisingly, all *K.pnemonia* isolates were resistant to ampicillin and nitrofurantoin (100%) and 90% were resistant to cotrimoxazole and imipenem. Once again all isolates of *P.aeroginosa* were found resistant to ceftriaxone, ceftazidime and ertapenem (100%). The gram positive *E.faecalis* showed 93% resistance to ciprofloxacin and 79% resistance to levofloxacin.

About half of *E.coli* isolates were susceptible to Ampicillin, and around 40% each for Cotrimoxazole and fluroquinolone, and about 30% to Amoxiclav. Studies done by Bonadio M et al. [53] and Zhanel et al. [54] did correlate with the present study. In a study done by Asghar et al. [60] *E. coli* was shown to have high resistance (87%) to fluroquinolones. The probable reasons for this variation in findings can be due to the difference in the patients' drug adherence, treatment protocols/Regimens, and the availability of drugs in the different regions. A study by Koul AN in 2018 observed that Urine culture was positive in 23 (65%) cases, with bacteria in 22 (96%) and fungus in 1 (4%). Predominant bacteria grown from cultures were *Klebsiella pneumoniae* 32%, *Pseudomonas aeruginosa* 18%, *Escherichia coli* 14%, *Enterococcus faecalis* 13%, *Acinetobacter* 10%, *Staphylococcus aureus* 9%, and *Enterobacter* 4%. Antibiotic resistance profiles showed a high resistance patterns to ceftriaxone 60%, levofloxacin 53%, nitrofurantoin 53%, ciprofloxacin 40%, cotrimoxazole 40%, piperacillin–tazobactam 26%, amikacin 26%, gentamicin 26%, meropenem 26%, and imipenem 13%. The drug susceptibility profile showed high sensitivity to polymyxin 36%, piperacillin–tazobactam 32%, tigecycline 22%, amikacin 23%, levofloxacin 22%, imipenem 18%, vancomycin 18%, and nitrofurantoin 18%.Patients were followed up over a period of 4 weeks. At the 2nd week of follow-up, 2 (5%) cases were still culture positive, and the symptoms of UTI persisted in 6 (17%) cases. Of 35 cases, 25 were followed up till the 4th week. Culture positive was noted in 6 (24%) cases, and the symptoms persisted in 10 (40%) cases. In recurrent infections, relapses were noted in 3 (50%) cases and reinfections in 3 (50%) [62].

The susceptibility of various immunosuppressed patient population to a particular type of infection does not depend on a single factor in a particular patient. Rather the concept of *'triple state of immunosuppression'*, a complex function determined by the interaction of several factors; such as the main disease characteristics, the dose and duration of the prescribed immunosuppressive therapy; technical factors including the presence or absence of granulocytopenia and the integrity of the mucosal skin barrier at the beginning of the infection; metabolic factors such as protein-calorie malnutrition, uremia, and hyperglycemia; and finally the immunomodulatory effects such as viruses as cytomegalovirus, Epstein-Barr virus, the hepatitis viruses and HIV, is proposed to play a critical role [63].

To our knowledge, microbiologists are not routinely given indications by clinicians on which drugs they prefer for antibiotic drug susceptibility testing. In this situation the microbiologists choose the most available antibiotics testing discs to test resistance. Frequent shortages of drug susceptibility tests further exacerbates the situation. All these issues explain the lack of a standard pattern in antibiotic susceptibility testing and have been previously documented to interfere in antibiotic susceptibility testing [64]. This points to the need for optimal and rational use of antibiotics in cancer patients to prevent antibiotic resistance, as well as improvement of quality of antibiotic resistance testing. Currently, no guidance exists on symptoms indicating urine sample culture in cancer patients and antibiotics which require drug susceptibility testing in the cancer hospital.We believe the study findings to be reflective of ground-level reality. We recommend prospective research studies to ascertain the prevalence of UTI, current antibiotic use/prescription patterns for UTI and antibiotic resistance patterns among cancer patients in a representative sample of health facilities that provide cancer care in the country. We recommend the implementation of standard protocols for systematic testing of bacteria for antibiotic drug susceptibility testing, recording and periodic reporting of drug resistance patterns and rational use of antibiotics in cancer patients. There is urgent need for an AMR stewardship program to educate and create awareness among health care professionals and the community on the rationale use of antibiotics [64-68].

It is essential to correctly identify the pathogen that is causing UTI in order to successfully treat the affected people. Failure to do so will not only cause the patient's illness to worsen and expose them to complications, but it will also encourage bacterial resistance because of the incorrect administration of antibiotics. Due to the high level of *E. coli* antibiotic resistance in this area, beta-lactam medications in the current study had limited effects for treating UTI in patients. Due to these linked factors, such as resistance which may result in incorrect antibiotic prescription, which may in turn choose for new resistance genes, the appropriate steps may assist to reduce the risk of infection of UTIs. Hospitalised, genitourinary tract anomalies, indwelling catheter, diabetic, female gender, and married individuals are recommended to get routine UTI screenings. Regular audits are the key to controlling UTI. Therefore, to tackle this resistance, proper infection control practises, antibiotic stewardship, and hygiene should be implemented.

Limitation of the Study

There are some limitations of the study. First, only those who visited the study center throughout the study period were included in the study, hence we were unable to generalize the study findings beyond this health facility. However, we believe the study findings to be reflective of ground-level reality. Second, due to resource constraints, we could not include a qualitative component to this study to better understand and explain the study findings. Thus, most of the explanations for the study findings are anecdotal. Third, we are unable to comment on prevalence of UTI or the correlation between patient characteristics and bacterial growth in urine cultures in our setting, as large proportion of data was missing on the three most important variables that were previously known to predict bacterial growth in urine specimens, namely presence or absence of symptoms, stage of cancer and use of antibiotics prior to the time of requesting urine culture [52]. Possible reasons may be that there are no standardized guidelines for UTI screening or proforma requesting for urine cultures.

CONCLUSION

It is well known that the uropathogenic bacteria's susceptibility to antibiotics fluctuates over time and varies geographically. Here, we've discussed how the top antibiotics with low overall resistance percentage affected the study's uropathogens. The results of the present study revealed a high magnitude of UTIs among immunocompromised patients especially the diabetic population.The study suggested that sex, duration of

DM diagnosis in years, comorbidity were independent contributing factors for UTIs among immune compromised patients.

Furthermore, this study highlights the importance of monitoring the causative agents of UTIs and their resistance patterns in order to guide them onempiric treatment practices. Therefore, we strongly propose that each tertiary center catering to immunocompromised patients should evaluatetheir own UTI risk factors and develop antibiograms which are critical forpromoting rational and targeted drug treatment. Hence, to tackle this resistance, proper infection control practises, antibiotic stewardship, and hygiene should be implemented

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Author contributions

F.O. contributed to conceptualization, title and design selection, data analysis, interpretation, and article write-up. N.N. contributed to conceptualization, title and design selection, data collection, analysis, interpretation, and article write-up. P.S. contributed to conceptualization, data analysis, and interpretation. All authors have read and approved the final article.

Availability of data and materials

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

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