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Molecular detection of microorganism in prostate cancer and urinary tract infection in Iraq

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ABSTRACT
Infections associated with mortality in cancer patients are mainly attributed to bacteria, and since infections in cancer patients may disrupt the treatment pattern and increase or decrease the survival rate of patients, The current study aimed to identify virulence and antibiotic resistance factors of the predominant bacteria associated with prostate cancer and urinary tract infection. Isolates were collected from urine samples of prostate cancer and urinary tract infection patients from Imam Hassan Al-Mujtaba Hospital and Imam Zain Al-Abidin Hospital Hospital. These specimens were cultured on conventional and specific agars and were confirmed by morphological and biochemical tests and the automated method (VITEK®2). Antimicrobial susceptibility testing was performed on the isolates by the disk diffusion method.Multiplex PCR was used to assess the presence of eight virulence genes fimH, hly, papC, cnf1, int A, aer. and resistance genes include the bla-TEMand qnrgenes.
RSULTS:The most frequent bacteria linked to prostate cancer that causes UTIs is Escherichia coli.
Among bacteria recovered from individuals with prostate cancer, IntA was the most prevalent virulence factor (54.5%), followed by pap C (45.4%), fimH(36.3%), cnf1 (36.3%), hly (36.3%), and aer (27.2%). whereas bla-TEM (45.4%) and qnr (54.5%) were the most common resistance genes. Cnf1 (63.6%), fimH, hly, and int A (54.5%) were the most common virulence factors in UTI patients, but papC and aer produced (45.4%), qnr, and bla-TEM (63.6%) were also common.

Keywords: resistance, virulence, survival, Hospital.

INTRODUCTION

Compared to other diseases, cancer accounts for the largest percentage of deaths worldwide and is currently a serious public health concern (Bray et al., 2018). The most prevalent cancers include breast, lung, bronchus, prostate, rectum, melanoma, liver, cervical, and prostate cancers (De Magalhães andJoão Pedro, 2013). Although prostate cancer diagnosis and therapy have advanced significantly, the disease's origins are intricate and multifaceted. Numerous diseases, including those of the urinary tract, have been identified as potential sources of prostatic inflammatory stimuli. Urine flowing back into the prostatic duct or bacteria passing through the urethra can both infiltrate the prostate gland (Karamiet al., 2022).Because drugs do not sufficiently reach the prostate tissue, treating prostate infections is challenging. Prostate inflammation may result from this (Sfanoset al., 2013). A person's microbiome may have an impact on determining the causative agents of bacterial prostatitis and the early treatment of the infection, which may be essential in preventing prostate cancer (Al-Karawiet al.,2024).
Urinary microbial ecology, a unique environment for various species, plays a critical role in maintaining urological health and potentially developing various urological diseases.(Colellaetal.,2023;Perez-Carrasco etal.,2021).Urinary microbiota, including bacterial, fungal, and viral species, can impact genitourinary system processes, potentially leading to pro-inflammatory states, immunometric diseases, and tumorigenic prostate gland environments. (Grobeisen-Duque etal.,2023).Adhesins (P fimbriae, mannose-resistant adhesins, and type I adhesins), hemolysin, potassium capsule, aerobactin system, and resistance to serum killing are important virulence factors that cause UTI (Maheswariet al., 2013). By attaching themselves to cells, avoiding the host's immune system, and reducing immunity, the bacteria aid in the colonization of a particular niche within the host. getting nourishment from the host and suppressing the immunological response(Flores-Mireleset al.,2015). These factorscan also be horizontally transferred between these organismscausing multi-drug resistance and therapeutic failure.(Adenipekunet al.,2021).
Antibiotic resistance in cancer patients is a significant global issue, with inadequate initial antibiotic therapy often leading to poor outcomes, increased mortality, and prolonged hospitalization.Clinically treating diseases

caused by bacteria that are resistant to many drugs can be difficult, particularly when it comes to Gram-negative bacilli, for which there are frequently limited alternatives. The safe treatment of cancer patients with multidrug-resistant bacterial infections requires a thorough understanding of the key properties of antibiotics, as they have several drawbacks, including limited clinical experience, a high incidence of side effects, and a lack of knowledge about drug pharmacokinetics. Establishing infection control procedures and antibiotic stewardship programs is crucial for preventing the emergence and spread of multidrug-resistant organisms (Gudiol and associates ,2014).

METHODS

Between January and September 2024, urine samples were taken from men over 45 who had prostate cancer and urinary tract infections (UTIs) at Imam Hassan Al-Mujtaba Hospital and Imam Zain Al-Abidin Hospital. The distribution of the samples was as follows: Thirty urine samples from patients with prostate cancer and thirty urine samples fromurinary tract infections. The samples were included in the study once a pure culture of greater than 10^5 CFU/ml was obtained. Traditional biochemical assays (oxidase, Gram stain, and IMVIC) were combined with an automated method (VITEK® 2 BioMérieux) to identify the isolates. Twenty-two bacterial isolates (dominant bacteria) were chosen in order to identify the genes responsible for antibiotic resistance and pathogenicity.

The antimicrobial susceptibility of the isolates was evaluated using the Kirby-Bauer disk diffusion method on Müller-Hinton Agar medium, in line with the Clinical and Laboratory Standards Institute (CLSI) standards (Relleret al., 2009). A discrete colony of an overnight bacteria isolate was inoculated into sterile 0.9% normal saline and matched to the turbidity of 0.5 McFarland standard. Sterileswabs were used to streak the bacteria suspension onMueller Hinton. agar.The antibiotic discs used in this investigation (Bioanalyse, Turkey) was: Fourteen antibiotics were used: ciprofloxacin (5), levofloxacin (5), ampicillin (10),gentamicin (10), amikacin (30), amoxicillin-clavulanic acid (30), ceftriaxone (30), imipenem (25), meropenem (10), trimethoprim sulfamethoxazole (25), tetracycline (30), doxycycline (30), cefotaxim (30)and nitrofurantoin (100). Disks were placed at equidistance to each other and pressed firmly on the plate. The plates were then incubated at 37oC for 18–24 h. The zones of inhibition of each antibiotic were measured in millimeters against the bacteria and recorded.Clinical Laboratory Standards International (2024) were followed in the interpretation of the results.

Molecular detection of virulence factor and antibiotic-resistance genes

For identifying genes whose sequences were amplified by particular primers, fimH, intA, papC, cnf1, aer, blaTEM, and qnr operons, a traditional polymerase chain reaction (PCR) was used. Table (1) provides information on primer sequences and the expected sizes of the amplified products (Wang G et al., 2002; Yun KW et al., 2013; Yamamoto S t al., 1995; Johnson et al., 2000).

Primers used for PCR

Gene name	PCR type	Primer sequence (5’ - 3’)	Size of the amplicon (bp)	References
fim H	Standard PCR	TGCAGAACGGATAAGCCGTGG GCAGTCACCTGCCCTCCGGTA	508	Yamamoto etal(1995)
int A	Standard PCR	GGCTGGACATCATGGGAACTGG CGTCGGGAACGGGTAGAATCG	300	Yun etal.(2013)
pap C	Standard PCR	GTGGCAGTATGAGTAATGACCGTTA ATATCCTTTCTGCAGGGATGCAATA	200	(Johnson and Stell, 2000)
cnf1	Standard PCR	AAGATGGAGTTTCCTATGCAGGAG CATTCAGAGTCCTGCCCTCATTATT	498	Yamamoto et al.(1995)
hly	Standard PCR	AACAAGGATAAGCACTGTTCTGGCT ACCATATAAGCGGTCATTCCCGTCA	1177	Yamamoto et al.(1995)
aer	Standard PCR	TACCGGATTGTCATATGCAGACCGT AATATCTTCCTCCAGTCCGGAGAAG	602	Sawma-Aouad et al., (2009)
blaTEM	Standard PCR	ATGAGTATTCAACATTTCCGTG TTACCAATGCTTAATCAGTGAG	861	Mathlouthietal.,(2016)
qnr	Standard PCR	AAG GAA GCC GTA TGG ATA TT AGC TAA TCC GGC AGC ACT AT	670	Yan Jiang etal.(2008)

Results

Urine samples from research participants of prostate cancer patients, revealed that E. Coli was the most prevalent isolate, accounting for 52% followed byKlebsiella pneumonia (19%), Staphylococcus aureus (10%), Enterococcus faecalis (9%), and Enterobacter cloacae (5%), as illustrated in Figure (1).

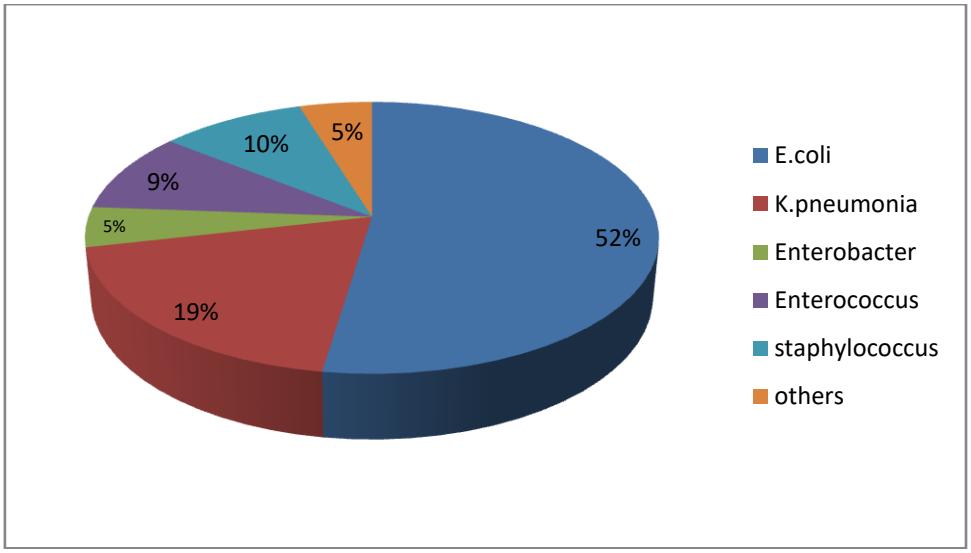


Figure 1: Distribution of bacteria in patients with prostatecancer

E. coli was the most common isolate found in urine samples from UTI patients (63%), followed by Klebsiella pneumonia (21%), Pseudomonas aeruginosa (8%), Proteus mirabilis (3%), and Serratiamarcescens (3%). as show in figure (2):

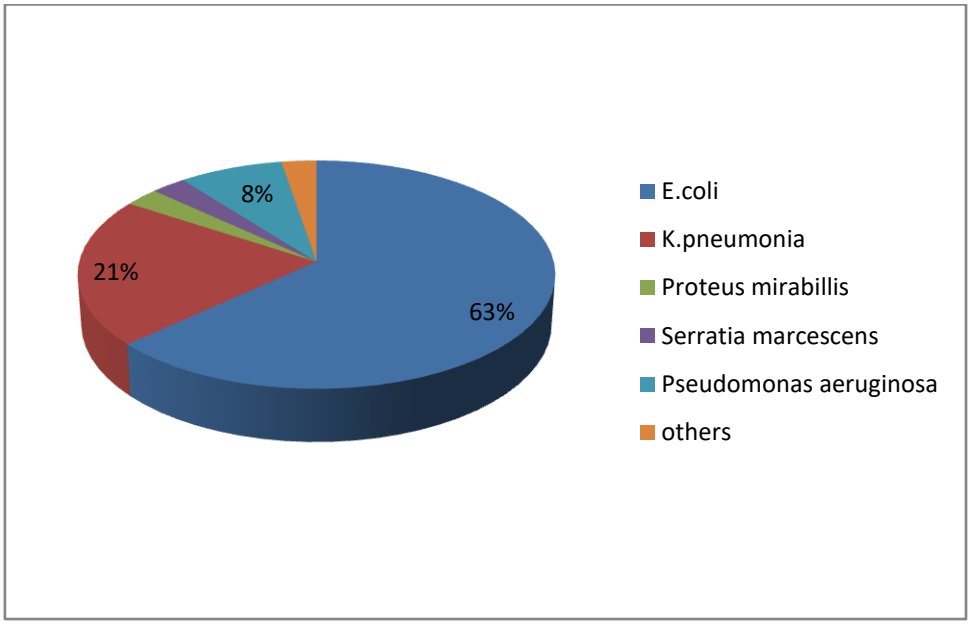


Figure 2: Distribution of bacteria in patients with UTI

Tests of antibiotic susceptibility revealed that all isolates from prostate cancer patients were resistant to ciprofloxacin, levofloxacin, ampicillin, gentamicin, tetracycline, ceftriaxone, and amoxicillin-clavulanate. In contrast, E. Coli was very sensitive to imipenem (72.7%), nitrofurantoin (72.7%), and meropenem (100%). The resistance rates to amikacin, doxycycline, and trimethoprim-supermethoxazole were 45.4%, 54.5%, and 36.3%, respectively, as shown in Figure (3).

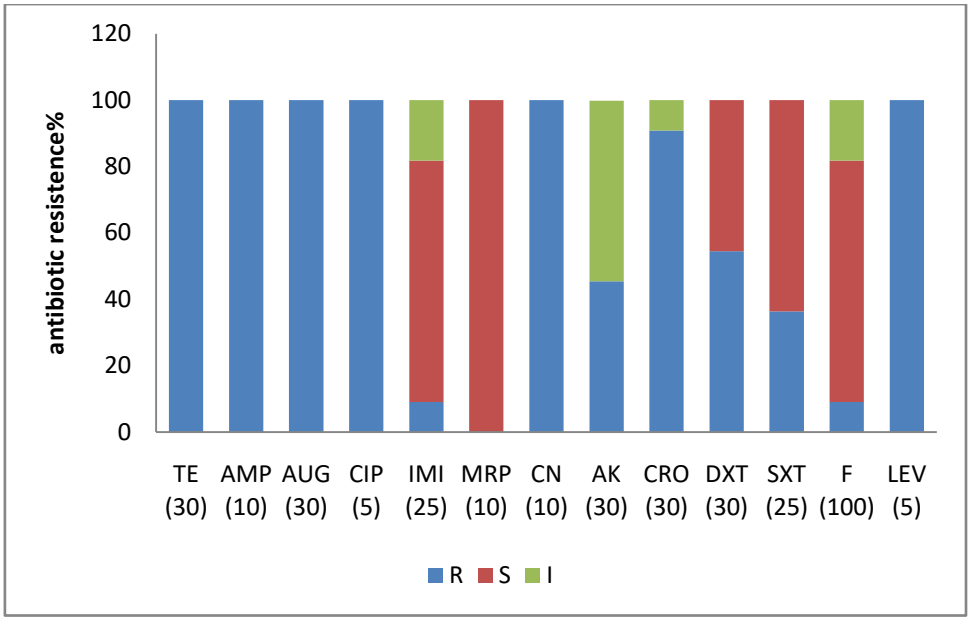


Figure 3: Pattern of antibiotic susceptibility in E. Coli isolates from PC patients

Furthermore, the study discovered that all isolates from UTI patients exhibited high resistance to ampicillin and tetracycline(100%), while the isolates exhibited various levels of resistance to doxycycline (90.9%), amoxicillin-clavulanate (81.8%), ciprofloxacin (72.7%), levofloxacin (72.7%), ceftriaxone (63.6%), trimethoprim-sulfamethoxazole (63.6%), cefotaxime (54.5%), and imipenem (54.5%). the isolates also demonstrated great sensitivity to nitrofurantoin (90.9%), amikacin (90.9%), and meropenem (100%) As seen in Figure (4).

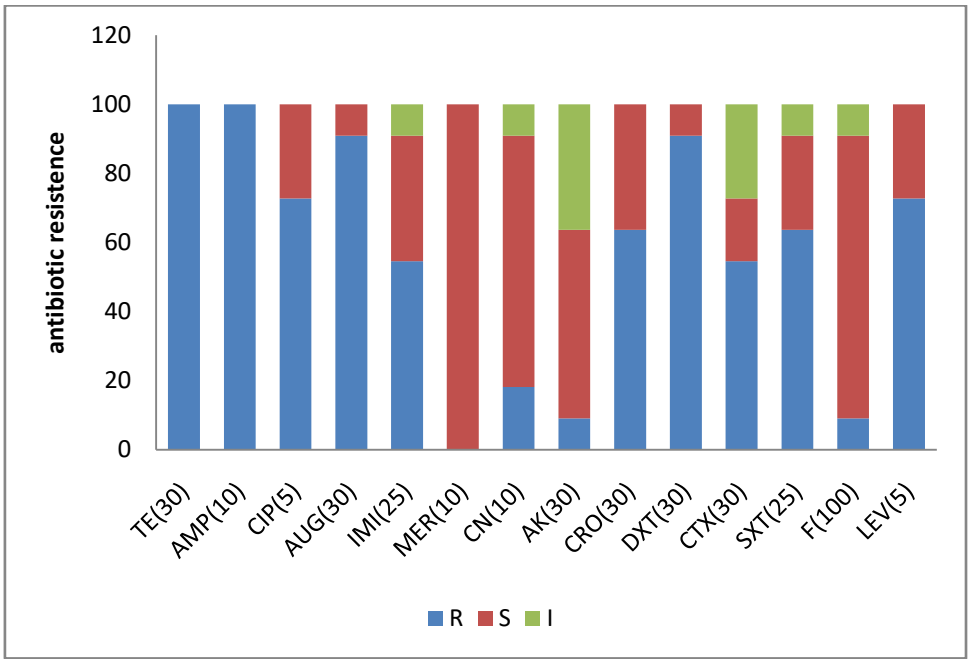


Figure 4:Antibiotic susceptibility pattern ofE. coli isolates from UTI patient

Among the bacteria found in patients with prostate cancer, IntA was the most prevalent virulence factor (54.5%), followed by pap C (45.4%), fimH (36.3%), cnf1 (36.3%), hly (36.3%), and aer (27.2%). whereas bla-TEM (45.4%) and qnr (54.5%) were the most common resistance genes.The most prevalent virulence factors in UTI patients were Cnf1 (63.6%), fimH, hly, and int A (54.5%), but papC and aer generated (45.4%), qnr, and bla-TEM (63.6%) were also prevalent. The distribution of Escherichia coli resistance and virulence genes in patients with prostate cancer and UTIs is as follows:

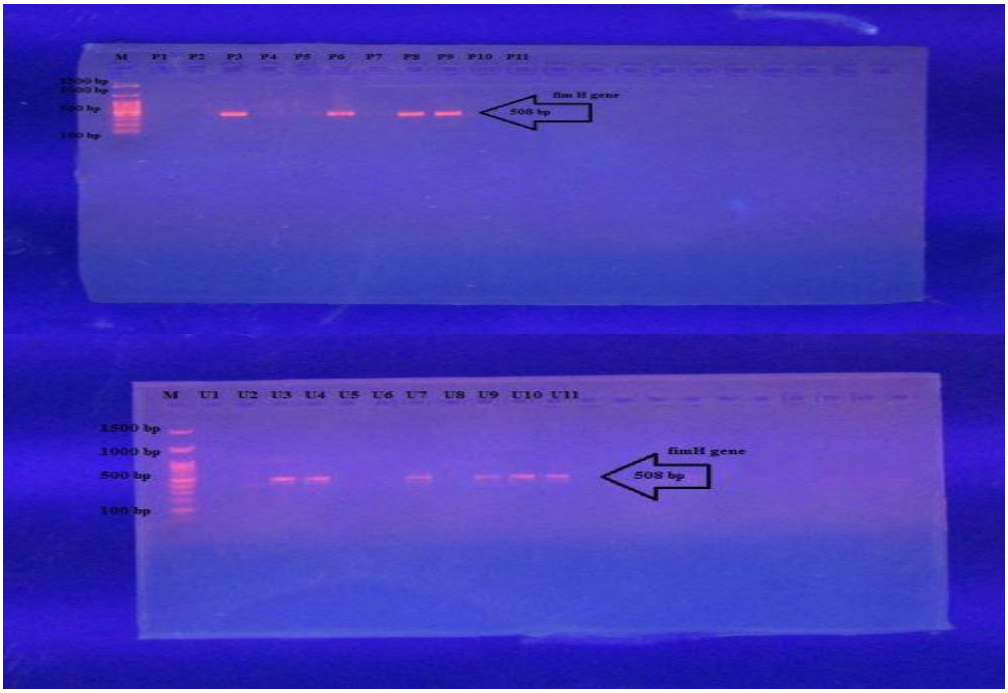


Figure 5: Escherichia coli fimH gene (508 bp) amplified by PCR in PC and UTI patients.

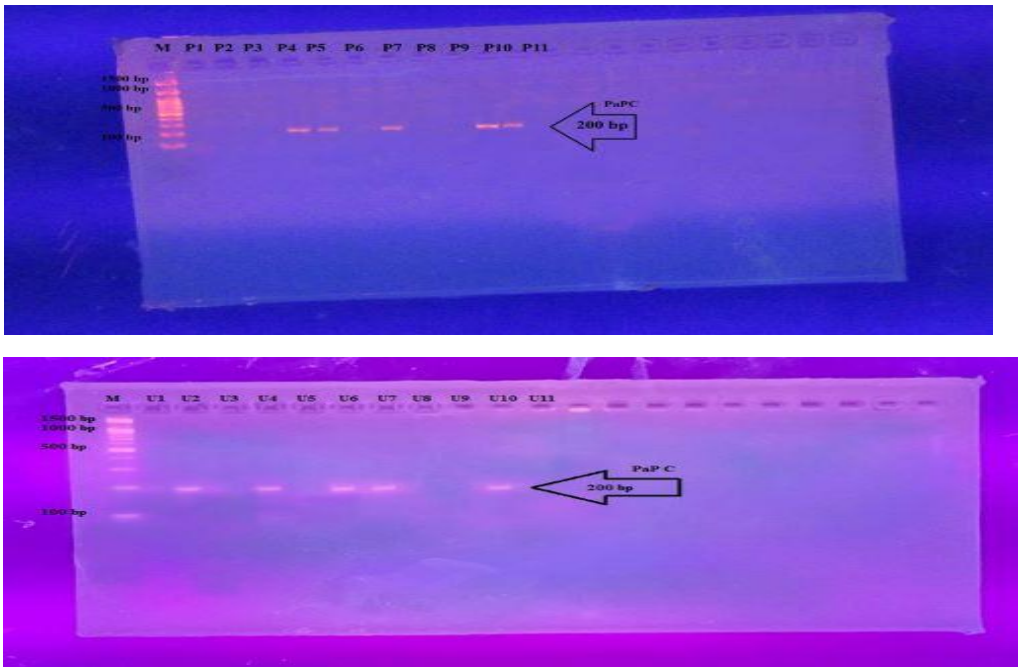
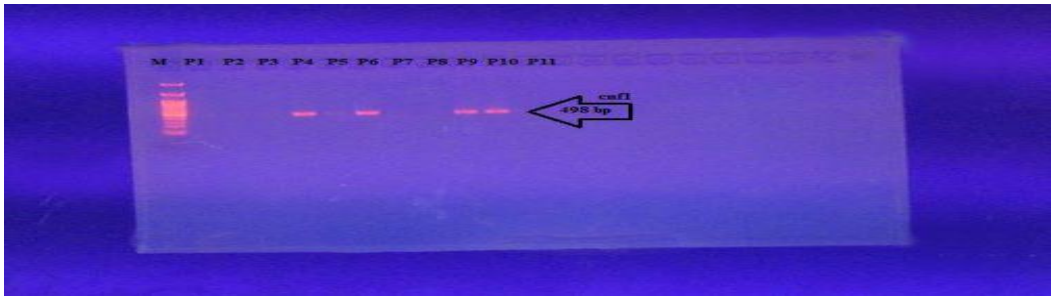


Figure 6:E. coli pap C gene (300 bp) amplification by PCR in PC and UTI patients.



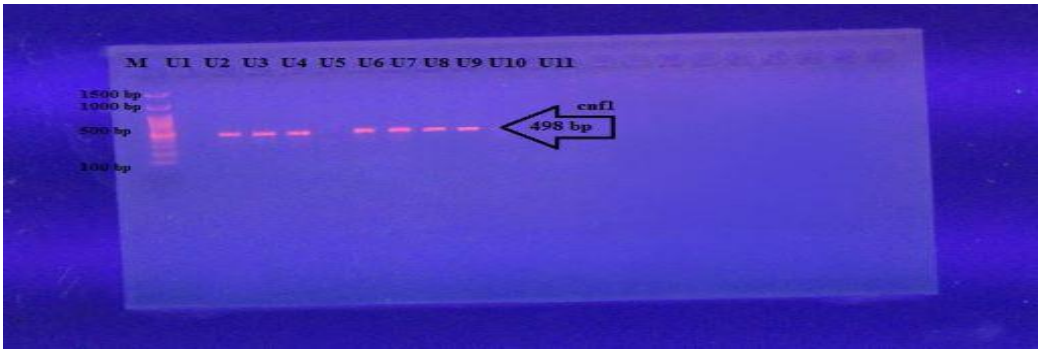


Figure 7:E. Colicnf 1 gene (408 bp) amplification by PCR in PC and UTI patients**.**

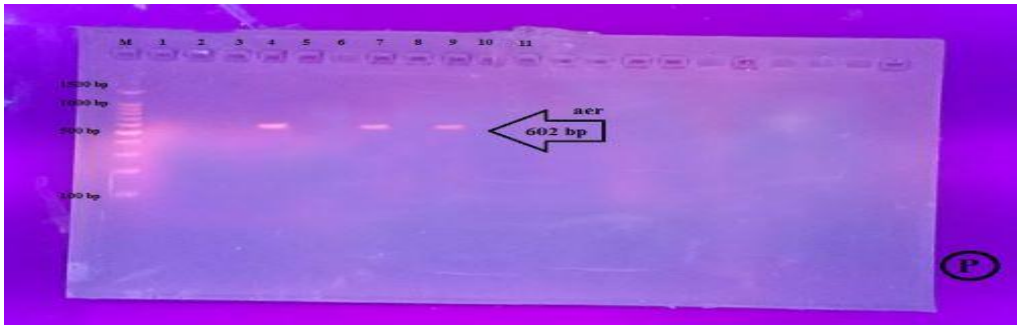
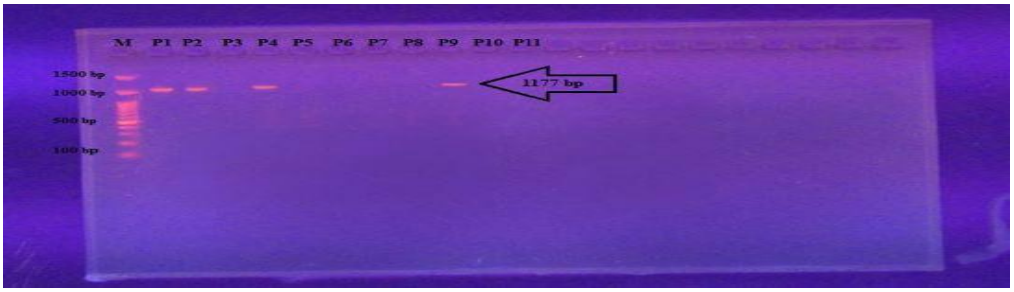


Figure 8: E. Coliaergene (602bp) amplification by PCR in PC and UTI patients.



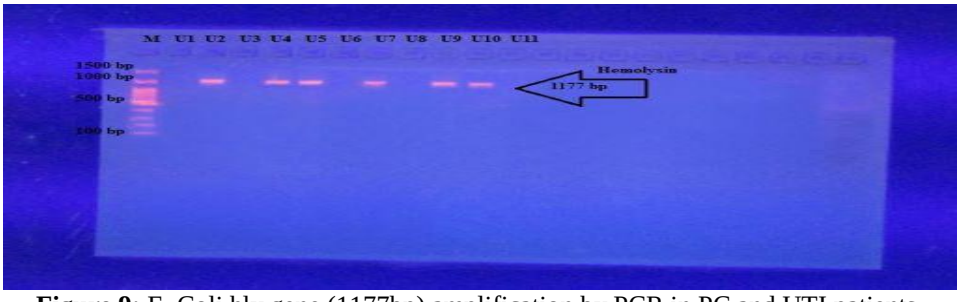


Figure 9: E. Coli hly gene (1177bp) amplification by PCR in PC and UTI patients.

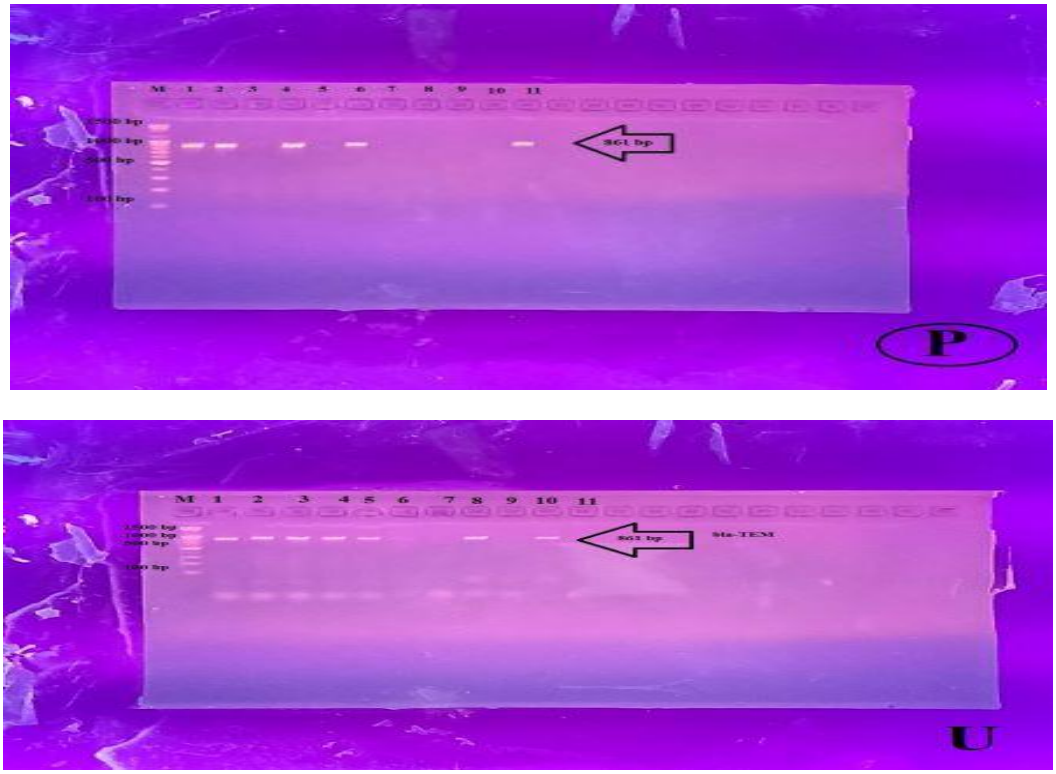


Figure 10: E. Coli $_{blaTEM}$gene (861bp)amplification by PCR in PC and UTI patients

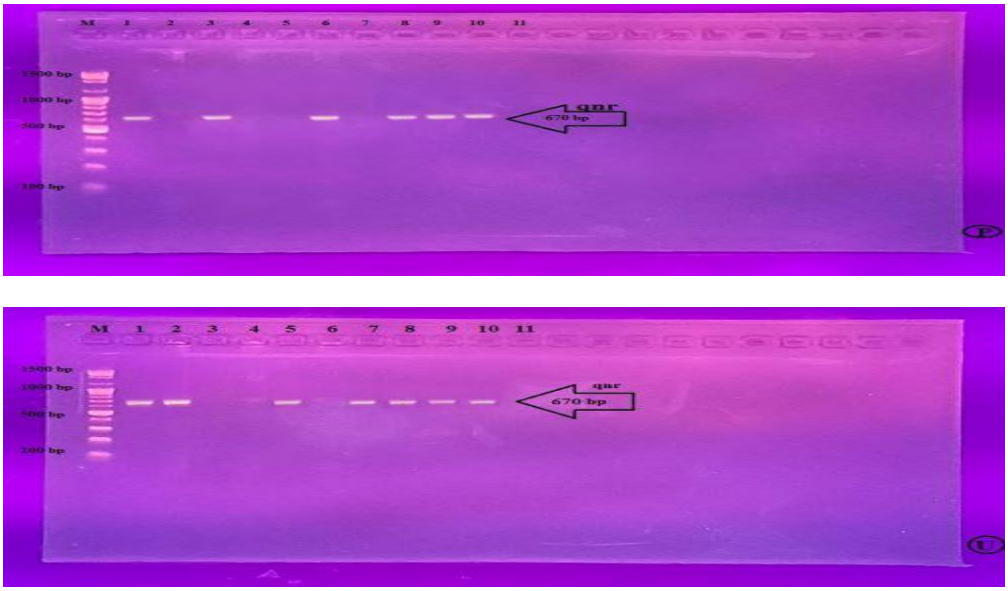


Figure 11:E. Coli qnr gene (670 bp) amplification by PCR in PC and UTI patients

DISCUSSION

Enterobacteriaceae were isolated from the studied communities showing high prevalence.Opportunistic pathogens of enteric bacteria have been documented as the source of infections among cancer patients. (Adenipekunet al., 2021). Patients with cancer suffer from immunodeficiency and Enterobacteria associated with virulence factors complicate their treatment (Tabasi M. et al.,2015).A similar study by Yuw et al. (2015) and Adenebekonet al. (2009) identified the Enterobacteriaceae family as the source of infection among cancer patients, specifically the genus Escherichia was found to have the highest relative abundance of 95%. This was also reported by Al-Karawi et al. (2024) in their study. Thus, it is in agreement with this study where E. coli was the most common organism accounting for about 52% and in agreement with Akinpelo et al. (2024) where Escherichia coli accounted for (50.0%).

Urinary stasis, poor bladder emptying, and the use of urinary devices like catheters and cystoscopies increase the incidence of bacteriuria in these populations. Additionally, bacterial colonization of the urinary system may be influenced by age-related decreases in zinc-related antimicrobial components and An elevation in the prostatic fluid's alkalinity (Agbuguiet al., 2016; Adesinaet al. 2015).

Escherichia coli is the most frequent cause of urinary tract infections. ccounting for approximately 63% of bacteria isolated from patients with UTIs, which is consistent with a study by Delcaruet al. (2017) where the percentage of E. coli was 60% and is consistent with most of the studies conducted by Danana, Hussein, and AzharNoori Hussein (2024) and Jalali et al. (2015) where E. coli was the dominant genus causing UTIs.

The study showed that all bacteria isolated from prostate cancer patients showed very high resistance to tetracycline, ampicillin, amoxicillin-clavulanate, ciprofloxacin, gentamicin, levofloxacin and cefotaxime. This is due to indiscriminate use of antibiotics and lack of antibiotic administration in hospitals (Aibinu et al., 2011). At the same time, the isolates showed high sensitivity to meropenem, imipenem and nitrofurantoin, which is consistent with the study by Parikh and Bhatt (2015) where the sensitivity of Gram-negative bacteria to carbapenems was (72%) and resistance was found to behigh to the cephalosporins(67%) and fluoroquinolones (90%).The results are in consistent with the studies that wasconducted by Alghamdi (2021),Raoetal.(2014) andShashwatietal.(2015) where the results showed a higher resistance of E. coli against third-generation cephalosporinsincluding cefotaximeand ceftazidime as well as beta lactamase inhibitors.In contrast to the study by (Akinpelo et al. (2024): Kano et al. (2016) :Nwokolo et al. (2022) indicated a high susceptibility of urinary pathogensto aminoglycosides and quinolones.As resistance to these cephalosporins develops among patients, clinicians resort to the last-line drug, carbapenems.

The study showed that all isolate were resistance to eight or more drugs and each one had one or more virulence factors. Similar trends have been reported by other studies. This suggests an increase in multidrug resistance among bacterial samples and therefore less available antibiotic treatment for patients already living with comorbid disease(Adenipekun, et al., 2021).

Bacteria isolated from UTI patients showed low resistance to nitrophoantin, amikacin, and gentamicin (9.09%, 9.09%, 18.1%) respectively which is consistent with studies conducted by others (Allami et al., 2022) in southern Iraq showed resistance to amikacin (11%)) and gentamicin (28%) and also agree with (Ahmed et al., 2019;Katongole et al. 2019) showed high sensitivity to amikacin and meropenem. Studies from India (Mukherjee et al., 2013) and Iran (Neamati et al., 2015) have highlighted low resistance to nitrofurantoin and high resistance to ampicillin, which is consistent with the findings of this study.Sensitivity to meropenem may occur due to the decreased frequency of use of this drug.

The study's findings showed that E. coli isolated from patients with prostate cancer had high frequencies of the intA and papC genes. The intAgene is crucial for Escherichia colito absorb iron, which is the pathogen responsible for the majority of community-acquired urinary tract infections (UTIs), (Garciaetal., 2011). whilepap Cgenes coding for adhesion.E. coli create two different kinds of toxinscnf 1 and hly. Haemolysin, sometimes referred to as the pore-forming toxin, enters the host's cell membrane and causes cell lysis, which makes it easier for iron and nutrients that are essential for the growth of bacteria for being released(Miranda-Estradaet al.,2017)Nevertheless, it is always possible that the corresponding gene will undergo a mutation, which would prevent its identification. Accordingly,The presence of the virulence genes is indicated by a positive PCR, while the absence of the relevant operon is not indicated by a negative PCR (Tarchounaet al., 2013).

Escherichia coli is the predominant pathogen causing urinary tract infection (UTI). The virulence of the causative strains and the host's sensitivity determine the severity (Tarchouna etal.,2013).Fimbriae or pili, which facilitate uroepithelial cell adhesion, are resistant to the bactericidal activity of human serum, formation of hemolysin, and elevated levels of K capsular antigen are among the unique virulence characteristics of uropathogenic E. coli strains (Emodyet al., 2003). Additionally, the development of UTIs is significantly influenced by the virulence factors and are critical components for colonization, extraintestinal survival, and cytopathic impact production. Additionally, uropathogenicity may be exacerbated by the development of unique virulence factors. (Hojati, Zohreh, et al.2015).

According to our findings, cnf1 and hly were more common than the other genes.These toxins linked to tissue damage and immune response dysfunction in the local area. and the abundance of aerobactin, also known as operon aer, which provides the capacity to absorb iron(Jalalietal.,2015:Farelletal.,2003).Our isolate count exceeded that of other researchers(Allamiet al., 2022) demonstrated cnf 1 (16%) and hly (15%), Miranda-Estrada et al. (2017) demonstrated cnf 1 (16.8%) and hly (17.8%), and Tarchounaetal. (2013) reported 19% and 3% for both hly and cnf genes. The severity of the UTIs may be correlated with the presence of hly (Bien etal., 2012). The phylogenetic groups, host clinical circumstances, and geographic location all affect the prevalence of these genes (Oliveira etal.,2011).Although significant differences in gene frequencies were additionally observed, the frequency of aerobactin was comparable to that seen in other investigations.

Distribution of other genes in our strains is includingfim H gene and pap gene were(54%) and (45%)respectively, genes coding for fimbrial adhesive systems, agreement with other Similar studies

Tarchounaet al.(2013) was detected 68% of fimH gene and 41% of pap gene, while Jalaliet al.(2015) was recorded 73.% and 46% of fim andpap genes respectively.These genes' prevalence in our findings This would imply that E. coli's virulence genes are crucial for UTIs.

The increasing rates of resistance to antimicrobials, especially beta-lactams and fluoroquinolones, have led to challenges in clinical practice. In this study, the majority of isolates in patients with UTI and prostate cancer were resistant to most of the antimicrobials examined. bla-TEM has been widely reported to be associated with broad-spectrum beta-lactamase activity. The occurrence of bla-TEM in urinary isolates described by Bevan et al. (2017) is consistent with our findings and reaffirms the ongoing role of genes in thwarting beta-lactamase therapy.The study found that E. coli from patients with prostate cancer had bla-TEM genes encoding antibiotic resistance (45.4%) and UTI patients had 63.3%, compared to 35.6% found by Mathlouthi et al.(2016).

Because of their broad-spectrum antibacterial activity, fluoroquinolones, which are synthetic chemical agents, are among the most often prescribed antimicrobials. Due to the widespread use of fluoroquinolones in medicine, pathogenic microorganisms now exhibit high levels of resistance to these drugs(Ginsburg et al.,2003).Escherichia coli strain that was discovered in Japan and showed resistance to many fluoroquinolones was described by Yamane et al. (2007). as in this study prevalence of qnr gene in patients with prostate cancer and UTI respectively .

Understanding E. coli virulence and antibiotic resistance in UTIs is crucial for physicians to offer alternative treatments, reduce risks, and improve infection management, requiring epidemiological data.

CONCLUSION

According to the study, Escherichia coli is the main pathogen linked to prostate cancer-causing urinary tract infections with resistance genes and virulence factors. Cephalosporin and fluoroquinolone resistance in the majority of isolates necessitates rapid detection and treatment to stop the spread.

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