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The Prevalence of blaCTX-M, blaTEM Genes in Bacteria Isolated From Bladder Cancer Patients with UTI

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***Abstract*— Urinary tract infections (UTIs) are among the most prevalent infections in cancer patients . Two hundred urine samples were taken from patients with bladder cancer in the period between the first of April 2021 and 15 of October 2021 while they were enrolled in the third floor of Ghazi Al-Hariri Hospital, Medical City, Baghdad Province, and private clinics in Nasiriyah Province (100 from patients treated with Mitomycin C (MMC) and 100 from patients treated with Bacillus Calmette-Guérin (BCG). Forty urine samples were taken from patients with UTI without Bladder Cancer (control). The most commonly pathogens were Escherichia coli ,followed by Klebsiella pneumoniae, Pseudomonas aeruginosa and Staphyllococcus aureus and other genera of UTI bacterium. The total ESBLs Producers in the current study from of 40 isolates was represented 27(72.5%) of tested cases .The highest ESBLs Producer in all Groups was E.coli (44.44%, 23.07% ,33.33%) followed by K.pneumoniae (27.7% ,15.38%, 22.22%) and P.aeruginosae recorded (16.6%,7.69%,22.22%) .According to PCR out of 38 Clinical specimen from all groups ,the results of the bla CTX-M gene indicated its presence in 21 isolate (55.2%),while the presence of bla TEM gene was 26(68.4%) of total isolates.**

Keywords— ESBLs genes ,Bladder Cancer ,UTI ,16srRNA

I. INTRODUCTION (*HEADING 1*)

The urinary bladder is a hollow, viscous, pyramid-shaped pelvic organ. The bladder's role is to store urine and aid in the evacuation of urine during micturition. It is located near other pelvic organs, such as the distal bowels (rectum) and organs from the male and female genital tracts (1). As the ninth most prevalent type of cancer overall, bladder cancer (Bca) is still the most common malignancy of the urinary system (2). With an anticipated 81,400 new cases and 4.5% of all new cancer cases in the US in 2020, it is the sixth most prevalent malignancy. It is thought to be one of the most expensive malignancies to treat on a per-patient basis in the United States . One of the most dangerous side effects and the main factor in both morbidity and mortality in cancer patients are infections. Urinary tract infections (UTIs) are among the most prevalent infections in cancer patients (3). UTIs can range from asymptomatic bacteriuria to mild uncomplicated cystitis, potentially serious pyelonephritis, and even life-threatening sepsis. A urinary tract infection (UTI) is described as an inflammatory reaction of the urothelium to the invasion of germs, typically bacteria, also known as uropathogens. A number of microorganisms, primarily the *Enterobacteriaceae*, are responsible for UTIs (4). The most common bacterium is *Escherichia coli*, Other significant Gram-negative bacterial species include *Klebsiella* and *Proteus* spp., *Pseudomonas* sp., and Gam-positive strains like *Enterococcus faecalis*, as well as a few *Staphyllococci* species, such as *Staphyllococcus epidermidis*, *Staphyllococcus aureus*, and *Staphyllococcus saprophyticus*, the latter is restricted usually on female UTIs (5).The most common antibiotics that doctors recommend are beta lactams. A four-member, nitrogen-containing, β-lactam ring is the structural basis of beta-lactam antibiotics. The ring structure and connected chemical groups of the antibiotics vary. Penicillins, Cephalosporins, Carbapenems, and Monobactams are examples of -lactam drug types.Even while urinary tract infections (UTIs) are treatable, antibiotic resistance among urinary tract bacteria has been on the rise, making it harder to keep under control. The synthesis of hydrolytic enzymes, known as "β-lactamases," is the most prevalent method of resistance among *Enterobacteriaceae* (6). The term "β-lactamases" refers to enzymes that break down the amide link in the β-lactam ring, inactivating the medicine and ending the treatment. Based on genetics, biochemical characteristics, and substrate affinity for a β-lactamase inhibitor, β-lactamases are classified in a complicated way (7). According to their molecular makeup, β-lactamases can be divided into four different groups called classes A through D. Because Classes A, C, and D have a serine residue at the active site that causes bond hydrolysis, they are also known as serine β-lactamases (SBLs). Class B β-lactamases, on the other hand, are known as metallo—β-lactamases (MBLs) because the hydrolytic action is boosted by one or two necessary zinc ions in the active sites (8).

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Class C comprises the AmpC -lactamases, while classes A and D contain the classic and extended-spectrum β-lactamases (ESBLs) (ACBL) (9). Class A enzymes include the following: (1) TEM, which is the first plasmid-encoded β-lactamase identified in Gram-negative bacteria and is named for a patient by the name of Temoniera; (2) Sulfhydryl variant (SHV), an enzyme with similar activity to TEM; (3) Cefotaximase (CTX-M); and (4) *K. pneumoniae* carbapenemase (KPC), which is in charge of carbapenem (10).The Recent study aimed to the isolation , identification of the gram negative bacteria from bladder cancer pateints with UTIs treated with Bacillus Calmette-Guérin BCG or Mitomycin C (MMC) and characterized the presence of *bla* $_{CTX-M}$ and *bla* $_{TEM}$ phenotypically and by PCR in the isolated bacterium .

II. MATERIALS AND METHODS

A. The Isolation and Detection of Gram Negative Bacteria

Two hundred urine samples were taken from patients with bladder cancer one hundred from bladder cancer patients treated with BCG (Group-1) and one hundred treated with Mitomycin C (Group –II) in the period between the first of April 2021 and 15th of October 2021 while they were enrolled in third floor of Ghazi Al- Hariri Hospital, Medical City, Baghdad Province, and private clinics in Nasiriyah Province. Forty urine samples were taken from patients with UTI without Bladder Ca (Control ,Group -III). Bacterial strains were identified using the Indole test ,Oxidase test , β-hemolytic activity, API20 E test and by 16sRNA (11) .

B. Combined Disc Test for the Phenotypic Detection of Extended-Spectrum β-Lactamases

The phenotypic identification of ESBLs was performed using the Double Disc Synergy Test. Amoxicillin-clavulanic acid discs (containing amoxicillin 20 g/clavulanic acid 10 g) were positioned in the middle of the inoculated plates in accordance with the CLSI, (2020)(12) instructions. Cefotaxime (30 g) and Ceftazidime (30 g) were each positioned 20 mm from the Amoxicillin-clavulanic acid disc in the middle. The plates were then kept at 37°C for a further 24 hours. The development of ESBLs was confirmed in organisms when the zone of inhibition around any cephalosporin increased by around 5 mm toward the amoxicillin-clavulanic acid disc (13).

C. Polymerase chain reaction (PCR)

Conventional PCR test were used to amplify the target DNA using specific primer pairs for Molecular identification of *E.coli* ,*K.pneumoniae* and *P.aeruginosa* and ESBLs genes Table(1) .

Table(1):Primers that used in this study

Target Gene	Oligonucleotide Sequence (5'-3')	Amplicon Size (bp.)	Conditions	References
16srRNA *E. coli*	F: AGAGTTTGATCMTGGCTCAG R: CCGTCAATTCATTTGAGTTT	919 bp	Step 1: 94ºC, 30 sec.. Step 2: 94ºC, 15- 30 sec. Step 3: 57 ºC, 15- 60 sec. Step 4: 68ºC, 1 min/kb. Step 6: 68 ºC, 5 min. Step 7: 4-10 ºC, forever	(Momtaz *et al.*, 2013)(14)
16srRNA *K. pnuemuniae*	F:GCAAGTCGAGCGGTAGCACAG R: CAGTGTGGCTGGTCATCCTCTC	216bp	Step 1: 94ºC, 30 sec.. Step 2: 94ºC, 15- 30 sec. Step 3: 55ºC, 15- 60 sec. Step 4: 68ºC, 1 min/kb. Step 6: 68 ºC, 5 min. Step 7: 4-10 ºC, forever	(Miller *et al.*, 2013)(15)
16srRNA *P.aeruginosa*	**F:**TGCCTGGTAGTGGGGGATAA **R:**-GGATGCAGTTCCCAGGTTGA `	505 bp	Step 1: 94ºC, 30 sec.. Step 2: 94ºC, 15- 30 sec. Step 3: 57ºC, 15- 60 sec. Step 4: 68ºC, 1 min/kb. Step 6: 68 ºC, 5 min. Step 7: 4-10 ºC, forever	**(** Shaebth ,2018)(16)
***Bla* $_{TEM}$**	*Bla* $_{TEM}$ -F: ATGAGTATTCAACATTTCCGTG *Bla* $_{TEM}$ -R: TTACCAATGCTTAATCAGTGAG	861	Step 1: 94ºC, 30 sec.. Step 2: 94ºC, 15- 30 sec. Step 3: 57 ºC, 15- 60 sec. Step 4: 68ºC, 1 min/kb. Step 6: 68 ºC, 5 min. Step 7: 4-10 ºC, forever	**(** Mathlouthi *et al.*,2016)[(17)]
***Bla* $_{CTX-M}$**	*Bla* $_{CTX-}$ .5´TTTGCGATGTGCAGTACCAGTAA-3´ *Bla* $_{CTX-M}$ - 5´CGATATCGTTGGTGGTGCCATA-3´	590	Step 1: 94ºC, 30 sec.. Step 2: 94ºC, 15- 30 sec. Step 3: 55 ºC, 15- 60 sec. Step 4: 68ºC, 1 min/kb. Step 6: 68 ºC, 5 min. Step 7: 4-10 ºC, forever	(Bahrami *et al* .,2018)(18)

D. Data Analysis

The Statistical Analysis System(SAS ,2012)(19) program was used to detect the effect of various factors in the study parameters. Least significant difference –LSD test was used to significant compare between means. Chi-square (χ^2) test was used to significant compare between percentage (0.05 and 0.01 probability) in this study.

III. Results

A. Bacterial isolation

The current study was conducted on 200 specimens of Bladder Carcinoma patients with Urinary Tract Infections and 40 specimens from non- bladder cancer Patients with UTIs .The results were distributed according to the patient's Bladder Ca. therapy . The incidence among patients treated with BCG was 33(33%) (Group-I) , while that for those treated with Mitomycin C(MMC.) was 23 (23%)(Group-II).The incidence in Control samples (non-Bladder Ca. Patients but have UTIs.) was 17 (42.5 %) (Group-III) as observed in the Table(2) Figure(1).The most commonly pathogens were (26) *Escherichia coli* , followed by (20) *Klebsiella pneumoniae* ,(10) *Pseudomonas aeruginosa* and (4) *Staphyllococcus aureus* and other genera of UTI bacterium from All three groups as represented in Table (3), the results showed significant differences ($p < 0.05$).

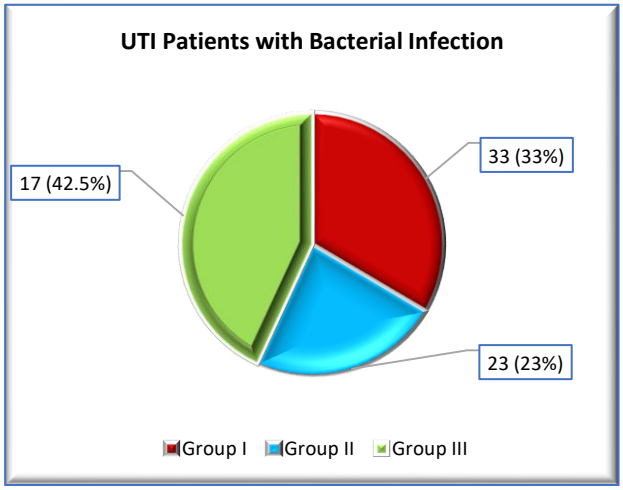
Table (2): Distribution of UTIs Patients according to the three groups

Patients with UTIs.	Isolates NO.	%
Group-I	33	33%
Group-II	23	23%
Group-II	17	42.5%

*Group-I : Bladder Cancer Patients treated with Mitomycin C (MMC)

*Group-II: Bladder Cancer Patients treated with Bacillus Calmette-Guérin (BCG)

*Group-III: Patients with UTI doesn't have bladder Cancer (Control)



Figure(1): Percentage of bacterial isolation among the three groups

Table(3): Bacterial isolates from different three groups

Fig. 1. Bacterial Species	Fig. 2. Group-I		Fig. 3. Group-II		Fig. 4. Group-III		Fig. 5. Total
	Fig. 6. No.	Fig. 7. %	Fig. 8. No.	Fig. 9. %	Fig. 10. No.	Fig. 11. %	Fig. 12. No.
Fig. 13. *E. coli*	Fig. 14. 13	Fig. 15. 13	Fig. 16. 9	Fig. 17. 9	Fig. 18. 4	Fig. 19. 10	Fig. 20. 26
Fig. 21. *K. pneumoniae*	Fig. 22. 11	Fig. 23. 11	Fig. 24. 9	Fig. 25. 9	Fig. 26. 4	Fig. 27. 10	Fig. 28. 24
Fig. 29. *P. aeruginosa*	Fig. 30. 5	Fig. 31. 5	Fig. 32. 3	Fig. 33. 3	Fig. 34. 2	Fig. 35. 5	Fig. 36. 10
Fig. 37. *S. aureus*	Fig. 38. 4	Fig. 39. 4	Fig. 40. 2	Fig. 41. 2	Fig. 42. 1	Fig. 43. 2.5	Fig. 44. 7
Fig. 45. *Morganella. morgani*	Fig. 46. 0	Fig. 47. 0	Fig. 48. 0	Fig. 49. 0	Fig. 50. 4	Fig. 51. 10	Fig. 52. 4
Fig. 53. *P. mirabilis*	Fig. 54. 0	Fig. 55. 0	Fig. 56. 0	Fig. 57. 0	Fig. 58. 1	Fig. 59. 2.5	Fig. 60. 1
Fig. 61. *E. cloacae*	Fig. 62. 0	Fig. 63. 0	Fig. 64. 0	Fig. 65. 0	Fig. 66. 1	Fig. 67. 2.5	Fig. 68. 1
Fig. 69. Total	Fig. 70. 33	Fig. 71. 33	Fig. 72. 23	Fig. 73. 23	Fig. 74. 17	Fig. 75. 10	Fig. 76. 73
Fig. 77. $CalX^2$= 24.81	Fig. 78. $TabX^2$= 21.03			Fig. 79. DF= 12	Fig. 80. p. value 0.016*		

*Group-I : Bladder Cancer Patients treated with Mitomycin C (MMC)
*Group-II: Bladder Cancer Patients treated with Bacillus Calmette-Guérin (BCG)
*Group-III: Patients with UTI doesn't have bladder Cancer (Control)

B. Bacterial Identification

On various media, including blood agar, MacConkey agar, Eosin Methylene Blue (EMB), and Mannitol salt agar, the cultural traits of 73 isolates from All Groups were examined. Results showed that 26 isolates from all groups had *E.coli* growth. Twenty-four isolates of *K.pneumoniae* from all groups .Ten isolates of *P. aeruginosa* , seven isolates of *Staphylococcus aureus* , four isolates of *M. morganii*, one strain of *Proteus mirabilis* and one isolate of *Enterobacter cloacae* . Biochemical tests were conducted on the predominant isolates in Groups I, II, and III, including *E. coli*, *K. pneumoniae*, and *P. aeruginosa*.

Additional verification was performed using the API 20E system based on 20 biochemical assays related to the activities of *E. coli* ,*K.pneumoniae* and *P.aeruginosae* metabolism after 18 hours at 35°C .After that and by using a genomic DNA minikit, genomic and according to Green and Sambrook, 2012(20) ,DNA was isolated from 40 bacterial isolates, including *E. coli* (17), *K. pneumonia* (15), and *P. aeruginosae* (8) .Such results were also observed when the DNA samples analyzed by gel electrophoresis, in which DNA bands were detected indicating purified DNA samples as shown in Figure(2).

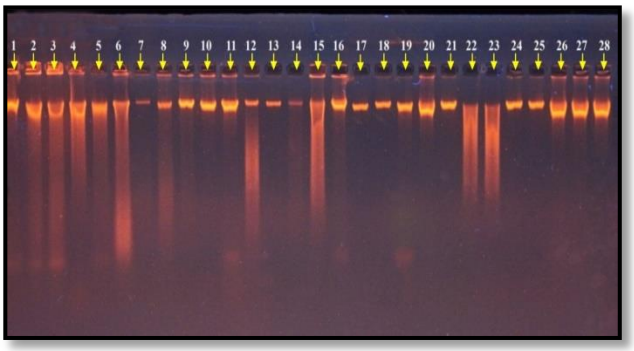
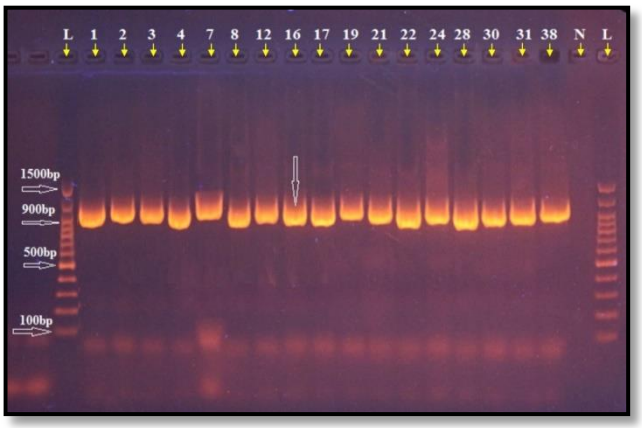


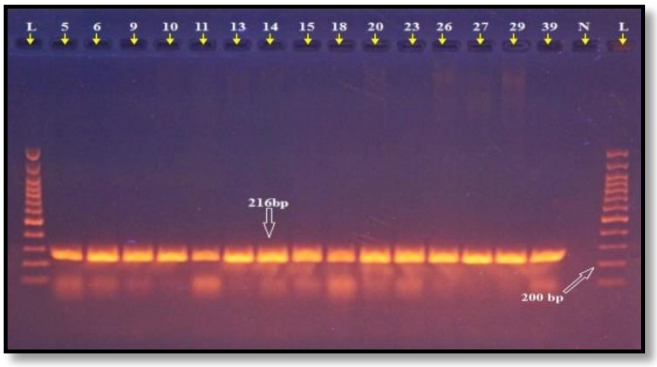
Figure (2) : Ethidium Bromide stained agarose Gel electrophoresis appearance that displays DNA from bacteria that was extracted.

C. Amplification of 16S rRNA gene

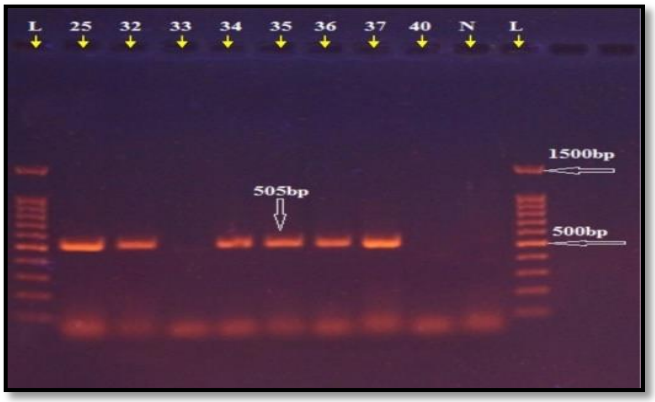
Using particular primers for the PCR amplification of *E. coli*, *K. pneumonia*, and *P. aeruginosae* 16S rRNA, 40 isolates were subjected to molecular identification. Six isolates of *P. aeruginosa* gave positive results and two yielded negative results, compared to all of the *E. coli* and *K.pneumoniae* isolates Figure(3) a,b&c.



Figure(3 a) : Gel electrophoresis for PCR product of *(Escherichia coli* primer) ,Lanes (1-38) represented positive results and Lane (N) represented Negative control .



Figure(3 b): Gel electrophoresis for PCR product of *(K. pnuemuniae* primer, Lanes (5-39) represented positive results and Lane (N) represented Negative control .



Figure(3 c) :Gel electrophoresis for PCR product of *(P.aeruginosa* primer) ,Lanes (25-35 and 34-37) represented positive results except lane (33 and 40) which represented Negative results and Lane (N) represented Negative control

D. Phenotype Screening of Extended Spectrum β-Lactamases(ESBLS)

Double Disc Synergy Test was used to detect the ability of isolates to produced ESBLs .Table(4) represent that the highest ESBLs Producer in all Groups was *E.coli* 8(44.44%), 4 (23.07%) , 3 (33.33%) followed by *K.pneumoniae* 5 (27.7%) , 2 (15.38%), 2 (22.22%) and *P.aeruginosa* recorded 3(16.6%),1(7.69%),2 (22.22%) .The total ESBLs Producers in the current study from 40 isolates was (27)72.5%. Figure (4), As represented in Table (4) ,there was a high significant differences $P \leq 0.01$.

Table (4): Distribution of ESBLs producers according to Groups

Fig. 81. **Phenotype of ESBLs %**		Fig. 82. **Positive %**	Fig. 83. **Negative %**	Fig. 84. **Total No. & %**
Fig. 85. **Group I**	Fig. 86. *E. coli*	Fig. 87. 44.4	Fig. 88. 0.00	Fig. 89. 27 (72.5)
	Fig. 90. *K. pneumonia*	Fig. 91. 27.7	Fig. 92. 11.11	
	Fig. 93. *P. aeruginosa*	Fig. 94. 16.6	Fig. 95. 0.00	
Fig. 96. **Group II**	Fig. 97. *E. coli*	Fig. 98. 23.07	Fig. 99. 15.3	
	Fig. 100. *K. pneumonia*	Fig. 101. 15.38	Fig. 102. 30.76	
	Fig. 103. *P. aeruginosa*	Fig. 104. 7.69	Fig. 105. 15.3	
Fig. 106. **Group III**	Fig. 107. *E. coli*	Fig. 108. 33.33	Fig. 109. 0.0	
	Fig. 110. *K. pneumonia*	Fig. 111. 22.22	Fig. 112. 22.22	
	Fig. 113. *P. aeruginosa*	Fig. 114. 22.22	Fig. 115. 22.22	
Fig. 116. p. value for *E. coli*				Fig. 117. **< 0.001****
Fig. 118. p. value for *K. pneumonia*				Fig. 119. **0.013***
Fig. 120. p. value for *P. aeruginosa*				Fig. 121. **< 0.001****
Fig. 122. Overall p. value				Fig. 123. **< 0.001****

*Amoxicillin-clavulanic acid (containing amoxicillin 20 g/clavulanic acid 10 g)
*Cefotaxime (30 g)
*Ceftazidime (30 g)

Figure (4) : Phenotypically ESBL producer by double-disc synergy test.

E. Genotype Screening of Extended Spectrum β-Lactamases(ESBLS)

Out of 38 Clinical specimen from all groups were examined by PCR for ESBLs genes presence , results of the *bla* $_{CTX-M}$ gene indicated its presence in 21 isolate(55.2%), 3(17.6%) ,3 (27.27%) ,2(20%) respectively in *E.coli* with total percentage about (23.6%), and about 5(29.4%),3(27.27%) ,2(20%)respectively in *K.pneumoniae* with the total percentage about (26.3%) ; 2(11.7%) , 1(9%) , 0 (0.0%) respectively, in *P.aeruginosa* which was around (7%) , the results show that the P value was Non Statics . Table(5) , Figure(5), Regarding *bla* $_{TEM}$ genes **,**the current results indicated the presence of this gene in 26(68.4%) of total isolates , *E.coli* recorded 36.8% 6(35.3%), 5(45.45%),2(30%) in all groups respectively 15.7% and 3 (17.6%), 3(27.27%) ,0.0(0.0%) for *K.pneumoniae* ,The total percentage around 15.7% and 2(11.7%),2(18.18%) ,2(20%) in *P.aeruginosae* in all groups respectively Table(6) , Figure(6) .The mentioned table described that there was a high significant differences P<0.001.

Table(5): Frequency of *bla* $_{CTX-M}$ gene in Bacterial isolates from all groups

PCR *bla*$_{CTX-M}$ Results %		**Positive %**	**Negative %**	**Total No. & %**
Group I	*E. coli*	17.6	29.4	21 (55.2)
	K. pneumonia	29.4	11.7	
	P. aeruginosa	11.7	0.0	*E. coli* 23.6% *K. pneumonia* 26.3% *P. aeruginosa* 7.0%
Group II	*E. coli*	27.27	18.18	
	K. pneumonia	27.2	9.0	
	P. aeruginosa	9.0	9.0	
Group III	*E. coli*	20.0	10.0	
	K. pneumonia	20.0	20.0	
	P. aeruginosa	0.00	0.00	
p. value for *E. coli*				**0.001****
p. value for *K. pneumonia*				**0.047***
p. value for *P. aeruginosa*				**0.003****
Overall p. value				**0.663**^{NS}

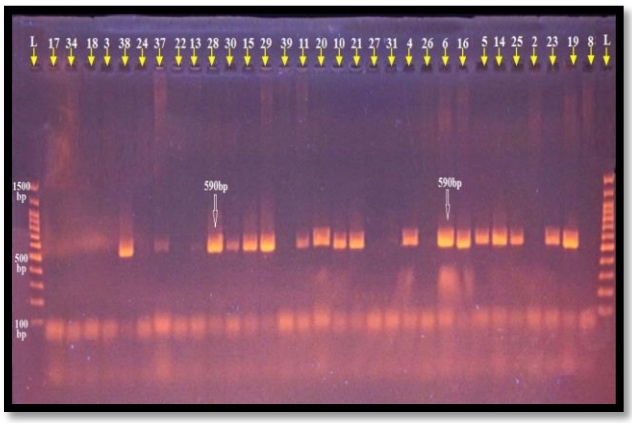


Figure (5) : Gel electrophoresis for PCR product of (CTX-M gene) which show 590bp, Lane L : DNA ladder (1500-100)bp, Lanes (28,37,13-29,11-21,31-4,6-16,5-25 and 23-19) represented positive results, Lanes (17-3,24,22,39,27,2 and 8) represented Negative result Lane (N) represented Negative control .

Table(6): Frequency of *bla* $_{TEM}$ gene in Bacterial isolates from all groups

Fig. 124. **PCR *bla* $_{TEM}$ Results %**		Fig. 125. **Positive %**	Fig. 126. **Negative %**	Fig. 127. **Total No. & %**
Fig. 128. **Group I**	Fig. 129. *E. coli*	Fig. 130. 35.3	Fig. 131. 11.7	Fig. 132. 26 (68.4)
	Fig. 133. *K. pneumonia*	Fig. 134. 17.6	Fig. 135. 36.36	
	Fig. 136. *P. aeruginosa*	Fig. 137. 11.7	Fig. 138. 0.00	Fig. 139. *E. coli 36.8%* Fig. 140. *K. pneumonia 15.7%* Fig. 141. *P. aeruginosa 15.7%* Fig. 142.
Fig. 143. **Group II**	Fig. 144. *E. coli*	Fig. 145. 45.45	Fig. 146. 0.00	
	Fig. 147. *K. pneumonia*	Fig. 148. 27.27	Fig. 149. 9.0	
	Fig. 150. *P. aeruginosa*	Fig. 151. 18.18	Fig. 152. 0.00	
Fig. 153. **Group III**	Fig. 154. *E. coli*	Fig. 155. 30.0	Fig. 156. 10.0	
	Fig. 157. *K. pneumonia*	Fig. 158. 0.00	Fig. 159. 40.0	
	Fig. 160. *P. aeruginosa*	Fig. 161. 20.0	Fig. 162. 0.00	
Fig. 163. p. value for *E. coli*				Fig. 164. **0.001****
Fig. 165. p. value for *K. pneumonia*				Fig. 166. **< 0.001****
Fig. 167. p. value for *P. aeruginosa*				Fig. 168. **Non-statistic**
Fig. 169. Overall p. value				Fig. 170. **< 0.001****

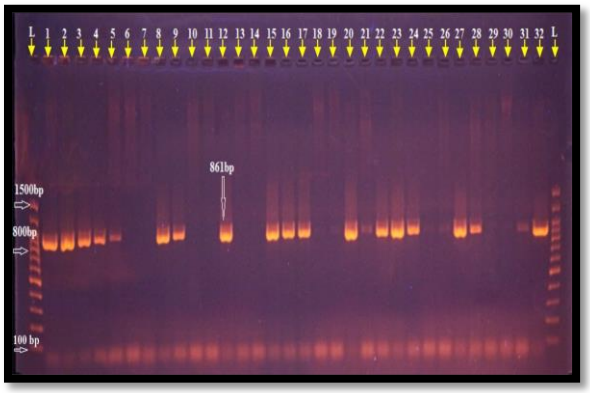


Figure (6) :Gel electrophoresis for PCR product of (TEM gene) which show 861bp, Lane L : DNA ladder (1500-100)bp ,Lanes (1-5,8-9,12,15-17,20-28 and 31-32) represented positive results,Lanes (6-7,10-11,13-14 ,18-19 and 29-30) represented Negative result Lane (N) represented Negative control .

IV. Discussion

Urinary tract infection (UTI) is one of the main causes of fever and morbidity in immune-compromised cancer patients. Atypical presentations are common in these patients, hence it's crucial to screen for UTI (21). The isolation rate from 200 patients in the recent study was concur with those of (22), who reported that 73 (24%) of the 308 urine samples from cancer patients in Nebal that had been subjected to culture contained bacterial growth. (23), similarly in line with our findings, discovered that from approximately 199 bladder ca. patients in Mexico City, 20 patients (10%) had UTI following TURBT; 100 of the 497 processed samples from cancer patients in India who were thought to have

UTIs tested positive for bacterial growth, according to (21); At Al-Diwaniya Teaching Hospital/Al-Diwaniya Governorate/Iraq, 33 urine samples from bladder Ca. were examined by (24), They identified 73% of the uropathogens isolated from those samples. In our findings *E. coli* were the most prevalent bacteria in Groups I, II, and III, respectively. These were followed by *K. pneumoniae* ,*P. aeruginosa* and *S. aureus* and Other kinds in Group-III include *Enterobacter cloacae* , *P. mirabilis* ,and *M. morgani*. The study findings were somewhat similar to those reported by (3), who stated that among the 292 urine samples from cancer patients in Ethiopia, *E. coli* was the most often identified uropathogen, followed by *K. pneumoniae* and *Citrobacter diversus*;Other Study conducted by (25) also agree with our current findings , they collected Urine samples from cancer patients in Pakistan and revealed that *E. coli* was the most prevalent followed by *Klebsiella spp*, *S. aureus* while 3 (7.1%) were *Proteus spp* and *Pseudomonas* spp.; In a Study conducted in Al- Nasiryah city by (26) also convergent with our findings ,they reported that only 90 samples from 330 urine give positive growth results and 57(63.3%) *E.coli* and 21 (23.3%) *K.pneumoniae* and 12(13.3%) From other Gram negative bacteria ; (27) reported that *K. pneumoniae* (31.2%), *S. aureus* (6.3%), *Ps. aeruginosa*, *P. mirabilis*, *Enterococcus spp*. (3.7% each), *S. saprophyticus* (2.6%), and *Citrobacter spp.* (0.4%) were the most common pathogens found in Najaf city specimens cultures , UPEC was found in 41.3% (111/269) of those specimens. According to (28), which contradicts our findings, the most prevalent isolates from cancer patients were *Klebsiella* spp. (18.30%), *Pseudomonas spp*. (17.65%), and *E. coli* (14.71%), followed by *S. aureus* (13.72%).The screening of ESBL producers in our finding was done by Double Disc Synergy Test. The total ESBLs producers in the result of the recent study were Similar to that reported in other studies : (29) ; (30); (31) ,the disagreement with our finding reported by (32). The highest ESBLs Producer in all Groups was *E.coli* . This findings in line of many studies : (33) , (34) . The ESBL *K. pneumonia* producers in the present study were in agreement with (35) ; 36) ; and disagree with (37) . *P.aeruginosae* recorded ESBLs producing in all groups was comparable to the occurrence reported previously by (38) ; (39); (40) ; higher than the rate recorded in United Kingdom by (41). Although DDST is thought to be a reliable method for detecting ESBLs, it has been shown to have problems due to the non-standardization of the disc placement distance(42). Another possibility is that clavulanate, which induces AmpC enzymes but does not effectively inhibit them, may cause these enzymes to attack cephalosporins, obscuring the synergy brought on by the suppression of the ESBL)(43). Along with geographical differences, this may be the reason why the current study and the ones that came before it disagree. Antibiotic-resistant ESBL-producing bacteria have been shown to exhibit regional differences in antibiotic resistance rates in the past. This is because antibiotic usage and infection control practices differ in various places (44). In the current study, the results revealed that the prevalence of ESBL genes *bla* $_{CTX-M}$ gene by using PCR in line with (45) they observed *bla* $_{CTX-M}$ β-lactamases genes in 46.7% of isolates ; (46) reported that the percentage of *bla* $_{CTX-M}$ was (65%) in Bacteria Isolated from Urinary Tract Infections in Bangladesh; (47) stated that the presence of *bla* $_{CTX-M}$ in *Enterobacteriaceace* family in Brazil is about 55.55% ; (48) disagree with our findings and recorded low percentage for *bla* $_{CTX-M}$ (15%) from Patients Infected with Urinary Tract Infections in Al-Najaf City.

The presence of bla_{CTX-M} enzyme among ESBL-producing in *K.pneumoniae* , in some extent near the study of (49) ,they stated that 24% of *K. pneumonia* was harbored the bla_{CTX-M} gene in a study conducted in Iran ; (50) found that the prevalence of *bla* $_{CTX-M}$ in *K. pneumonia* in of North Sumatera isolates was 36.47 % ; Hihger percentage than our findings were reported by (51) in Al-Madenah Al-Monawwarah with a significant ratio (74.1%) and very low percentage around 2.7% conducted in health centers in Ouagadougou, Burkina Faso by (52) . Regarding *E.coli* isolates in the recent study ,the bla_{CTX-M} percentage was compatible with Ahsan and Islam ,2019 ,they recorded that 24.2% of *E.coli* contained bla_{CTX-M} ; (53) reported that the *bla* $_{CTX-M}$ in *E.coil* from UTI was 27% ; In a study conducted by (52) , that Approximately 39.6% *E. coli* harbored *bla* $_{CTX-M.}$was recorded ; (54) reported very high rate of this gene in *E.coli* around 80.15% .*P.aeruginosae* in our study produced *bla* $_{CTX-M}$ gene in all groups in accordance with a study conducted by (55) , they recorded that 3.4% of *P.aeruginosa* was harbored *bla* $_{CTX-M}$; (56) in a research in the hospital of Makkah ,they stated that the frequencies of *bla* $_{CTX-M}$ in *P.aeruginosae* was only 10.7% ; In another study conducted by (57) ,they revealed that *bla* $_{CTX-M}$ was found in 17.5% of *P. aeruginosae* in urine samples ;Study conducted by (58) , incompatible with our result ,they revealed higher result around 31.7% of *bla* $_{CTX-M}$ in *P.aeruginosae*

Bla $_{TEM}$ in the present study in accordance with several previous studies , in a study conducted for Clinical Isolates of *Enterobacteriaceae* in different Regions of Sudan by (59) ,they revealed that 61% were positive for bla_{TEM} genes; (60) reported that bla_{TEM} genes percentage was about 63% in *Enterobacteriaceae* among Patients in Ethiopia ;Other study conducted in Egypt on *Enterobacteriaceae* isolated from hospital acquired infections and community by (61) , they reported that bla_{TEM} genes was about 73% in all isolates ; (62) in compatible with our results ,they record low percentage for bla_{TEM} genes about 10.9 % in India .The recent study reported that bla_{TEM} from all *E.coli* isolates is in agreement with (63) in Maiduguri reported bla_{TEM} about (31.4%) ; Another study supported the findings was done by (52) found an overall 24.6% prevalence of TEM encoding genes in *E. coli* ; (64) They recorded that 38% of *E coli* isolates had the bla_{TEM} gene ; (52) in agree with our finding and record high percentage for this gene about 89% in *E .coli* Isolated From Urinary Tract Infections in Iran . The presence of bla_{TEM} in *K.pneumoniae* isolates is in agreement with (65) they reported in a study conducted in Iran that bla_{TEM} in *K.pneumoniae* isolates was about (12.4%), (66) reported the prevalence rates for bla_{TEM} (12.35%), in urinary *K. pneumonia* strains ; (67)revealed that 16.1% of *K.pneumoniae* isolates produced bla_{TEM}

while higher percentage than our finding recorded by (68) about 83% . *P.aeruginosae* in our study produced *bla* $_{TEM}$ gene in accordance with a study conducted by (69) they reported that 15% of *P.aeruginosae* isolates were carry *bla* $_{TEM}$ gene ; (70) investigated that 26.7% of *P.aeruginosae* strains were have *bla* $_{TEM}$; (71) , revealed that 27.72% of *P.aeruginosae* isolates were harbored *bla* $_{TEM}$ gene ; while in a study conducted in Chinese teaching hospitals , (72) reported that very low percentage 4.5% of *P.aeruginosae* expressed *bla* $_{TEM}$ gene .

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