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MATRICES OF DEGREE OF ASSOCIATION OF PAIRED ANTIBIOTIC RESISTANCE OF *STAPHYLOCOCCUS AUREUS* HARVESTED FROM CANCER AND NONCANCER PATIENTS

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ABSTRACT

Background: Resistance transfer studies and plasmid screening experiments demonstrated that multi-resistance phenotype was due to transmissible plasmid and/or transposons. These strains also shown resistance to cephalosporins which is chromosome encoded. Most of hospital infections caused by multiple resistant organisms, especially multiple resistant *Staphylococcus aureus* which has been frequently isolated from patients**. Materials and Methods:** 400 patients were included and they were 200 patients with cancer diseases and 200 patients complaining of other illnesses. Swabs were taken from nares, sores and wounds and *S. aureus* was isolated and identified. Antibiotic sensitivity was carried out and paired resistance of antibiotics was recorded. **Results:** The most problematic antibiotics were penicillin G and ampicillin, showing resistance rates above 80–90%. The resistance to pairs of antibiotics like ampicillin and penicillin, penicillin and tetracycline, ampicillin and tetracycline, ampicillin and erythromycin, and penicillin and erythromycin were 146, 84, 82, 49 and 47 respectively. It was noticed that 11.8% of the isolates tested which were resistant to erythromycin being resistant to sulfonamides whereas 66.6% of isolates that resistant to sulfonamides were resistant to erythromycin. It was also concluded that 64.5% of isolates resistant to streptomycin were resistant to tetracycline, and at the same time 22.9% tetracycline-resistant isolates were resistant to streptomycin. The

McNemar Chi-square association matrix demonstrated extensive and highly interconnected multidrug resistance among *S.aureus* isolates recovered from cancer and noncancer patients. **Conclusions:** The most problematic antibiotics were penicillin G and ampicillin, showing resistance rates above 80–90%. The high multidrug resistance rate indicated strong antibiotic selective pressure and possible hospital-associated resistance circulation. Overall, cancer and noncancer isolates showed broadly similar resistance profiles, with only minor differences for selected antibiotics. The resistance to pairs of antibiotics like ampicillin and penicillin, penicillin and tetracycline, ampicillin and tetracycline, ampicillin and erythromycin, and penicillin and erythromycin were 146, 84, 82, 49 and 47 respectively. The paired antibiotic resistance analysis demonstrated extensive multidrug resistance among *S. aureus* isolates recovered from cancer and noncancer patients. The analysis showed that the strongest resistance associations occurred predominantly among β-lactam antibiotics, particularly between penicillin G and ampicillin, which exhibited extremely high paired resistance frequencies exceeding 90%. The association analysis revealed strong statistical relationships between several antibiotic pairs, indicating that resistance to one antibiotic was frequently accompanied by simultaneous resistance to another antibiotic within the same isolates.

KEYWORDS: Patients, cancer, *S. aureus*. Antibiotics resistance, matrices.

INTRODUCTION

Because of the wide usage of antibiotics in hospitals, it become a serious problem all over the world, especially in developing countries. This type of usage led to emergence of antibiotic-resistant bacteria in the hospital environment. Most of hospital infections are caused by multiply resistant microorganisms.[1-5] A significant continuous pose of threat has been made by infectious diseases on human life and property. Revealing of the true patterns of transmission of infectious diseases among society and planning a real effective prevention and control should be made to minimize the widespread of large-scale infectious disease.[6] Much of the recent literature in this context has focused on tracing of highly multidrug-resistant (MDR) which might be disseminated in hospital environment particularly through areas of highly susceptible patients like intensive care unit, burn and surgery wards and children's lounge.[6,7] The assessment of the disease burden is of priority for policymakers and public health officials to perform evidence of resource allocation and consequently to plan for the mitigation of threats to health. The Burden of Communicable Diseases in Europe(BCODE) report aimed to provide a practical policy for this burden assessment. A

policy which was followed later by many national and international studies and analyses to be built.[7-12] Resistance to penicillin G by *S. aureus* appeared rapidly after introduction the drug. Later on there was increasing proportion of *S. aureus* strains that resist streptomycin and tetracycline within the first few years of introduction of these drugs. An outbreak of infection caused by strains of *S. aureus* resistant to gentamicin and methicillin occurred in special care baby unit.[13] Methicillin- resistant *S. aureus* (MRSA) strain has been greatly increased in recent years, and patients are likely to be infected with MRSA include elderly peoples and those with postoperative infection such as orthopaedic, vascular surgery, patient with spinal injury, chronic skin ulcer, burn and chronic disease of respiratory and urinary tracts.[14] It has been found that erythromycin and clindamycin are substitutes to the use of B-lactam antibiotics or aminoglycosides, either alone or in combination with some of these drugs, however, resistance to these drugs arised as a problem during therapy, the so-called macrolide and lincosamide resistance phenotype which characterized by cross-resistance to all macrolides, lincosamides and streptogramins B. This resistance phenotype is, in many cases, plasmid and/or transposon mediated, and they found that there is no relationship between methicillin and macrolide-lincosamide resistance.[15,16] An outbreak of infection caused trimethoprim-resistant Enterobacteriaceae occurred at the University college hospital of London. It was found that geriatric patients previously treated with trimethoprim were the main source of this outbreak and this was plasmid-mediated and easily transferred from strain to another.[17] Resistance transfer studies and plasmid screening experiments demonstrated that multi-resistance phenotype was due to transmissible plasmid and/or transposons. These strains also shown resistance to cephalosporins which is chromosome encoded.[18] Most of hospital infections caused by multiple resistant organisms,[13,18,19,20] especially multiple resistant S. aureus which has been frequently isolated from patients.

MATERIALS AND METHODS

Patients

This study was carried out in hospital of atomic medicine, Al-Khansaa Hospital and general hospital of Mosul city, Iraq. 400 patients were included and they were 200 patients with cancer diseases and 200 patients complaining of other illnesses. The acceptance for participation in the present study was taken from all the participants whose native language is Arabic. They were not mentally retarded and they were completely healthy considering hearing and speaking.

Sampling

Swabs were taken from nares, sores and wounds. Swabs were rinsed with sterile nutrient broth as a transport media. 200 swabs of cancer patients and 200 swabs were from noncancer patients.[21]

Isolation

All swabs were inoculated on blood and mannitol-salt agars (Oxoid) . Inoculated plates were incubated at 37 ^{0}C for 24 hours.[21]

Identification of Staphylococcus aureus

The purified isolates of suspected S. aureus were conventionally identified following methods of workers.[22,23]

Antibiotic susceptibility testing

A loopful growth from isolates of *Staphylococcus aureus* were inoculated into nutrient broth and incubated at 37°C for 18 hours. The bacterial suspensions were diluted with ringer solution. The proportion of dilution was 1:1000.[14] Diluted bacterial suspension were poured onto the surface of the Muller-Hinton agar plates. The excess of bacterial suspensions were discarded using Pasteur pipette and plates were left for one hour at room temperature to dry. The antibiotic discs which are shown in Table 1 were selectively applied by using sterile forceps which was flamed after being cleansed with alcohol. The plates were incubated at 37 0C for overnight The size of zones of inhibition were measured from edge of disc to the edge of inhibition of growth and the result was compared with standard diameter of inhibition zones for each antibiotic utilizing the method of Bauer et al..[24,25] The following standard strain Staphylococcus aureus ATCC25923 was used as a reference strain.[18,26,27,28]

RESULTS

The figure shows that *Staphylococcus aureus* isolates from both cancer and noncancer patients had very high resistance to Penicillin G (P) and Ampicillin (AMP). Resistance to Tetracycline (TE) was moderate in both groups, while Rifampicin (RD), Cephalothin (KF), and Cloxacillin (OB) showed the lowest resistance frequencies. The highest resistance was recorded against Ampicillin, especially in noncancer isolates 93.5%, compared with cancer isolates 83.7%. Penicillin G resistance was also extremely high in both groups, with 87.7% in cancer isolates and 89.1% in noncancer isolates. Tetracycline showed almost identical resistance in both groups: 50.0% in cancer isolates and 49.3% in noncancer isolates(Tabl1 1). This suggested that tetracycline resistance was widely distributed and not strongly related to

patient category. Erythromycin resistance was higher in cancer isolates 32.6% than noncancer isolates 24.7%, suggesting a moderate increase among cancer-associated isolates. Streptomycin and Lincomycin resistance were also higher in cancer isolates, while S3, SXT, Gentamicin, Tobramycin, Cephalothin, and Cloxacillin were slightly higher in noncancer isolates. Most antibiotics did not show a statistically strong difference between cancer and noncancer groups. The resistance pattern was broadly similar between both patient categories. This indicated that most *S. aureus* isolates were resistant to more than one antibiotic. The nearly identical multidrug resistance percentages suggest that multidrug resistance is widespread and not limited to one patient group. The overall conclusion that the analysis demonstrates a high burden of antibiotic resistance among *S. aureus* isolates from both cancer and noncancer patients. The most problematic antibiotics were penicillin G and ampicillin, showing resistance rates above 80–90%. The high multidrug resistance rate indicated strong antibiotic selective pressure and possible hospital-associated resistance circulation. Overall, cancer and noncancer isolates showed broadly similar resistance profiles, with only minor differences for selected antibiotics (Figure 1).

Table 1: Frequency of resistance to various antibiotics used for *Staphylococcus aureus* isolated from cancer and noncancer patients.

Source	Isolates No.	Resistant Isolates	No.(%) resistant isolates to the following antibiotics:													Multiple resistant
		No. (%)	S3	L	S	SXT	TE	TOB	CN	AMP	RD	KF	P	OB	E	No. (%)
Cancer patients	98	90 (91.8)	3 (2.1)	10 (10.2)	20 (20.4)	0	49 (50)	4 (4.1)	4 (4.1)	82 (83.7)	1 (1.1)	1 (1.1)	86 (87.7)	2 (2.1)	32 (32.6)	88 (89.8)
Noncancer patients	77	71 (92.2)	6 (7.8)	4 (5.2)	11 (14.3)	4 (5.2)	38 (49.3)	4 (5.2)	6 (7.8)	72 (93.5)	1 (1.3)	2 (2.6)	69 (89.1)	2 (2.6)	19 (24.7)	69 (89.6)
Total	175	161 (92)	9 (5.2)	14 (8)	31 (17.7)	4 (2.3)	87 (49.7)	8 (4.6)	10 (5.7)	154 (88)	2 (1.1)	3 (1.7)	155 (88.6)	4 (2.3)	51 (29.1)	157 (89.7)

*= S3, Sulfonamide; L, Lincomycin; S, Streptomycin; SXT, Co-trimoxazole; TE, Tetracycline; CN, Gentamicin; AMP, Ampicillin; RD, Rifampicin; KF, Cephalothin; P, Penicillin G; OB, Cloxacillin.

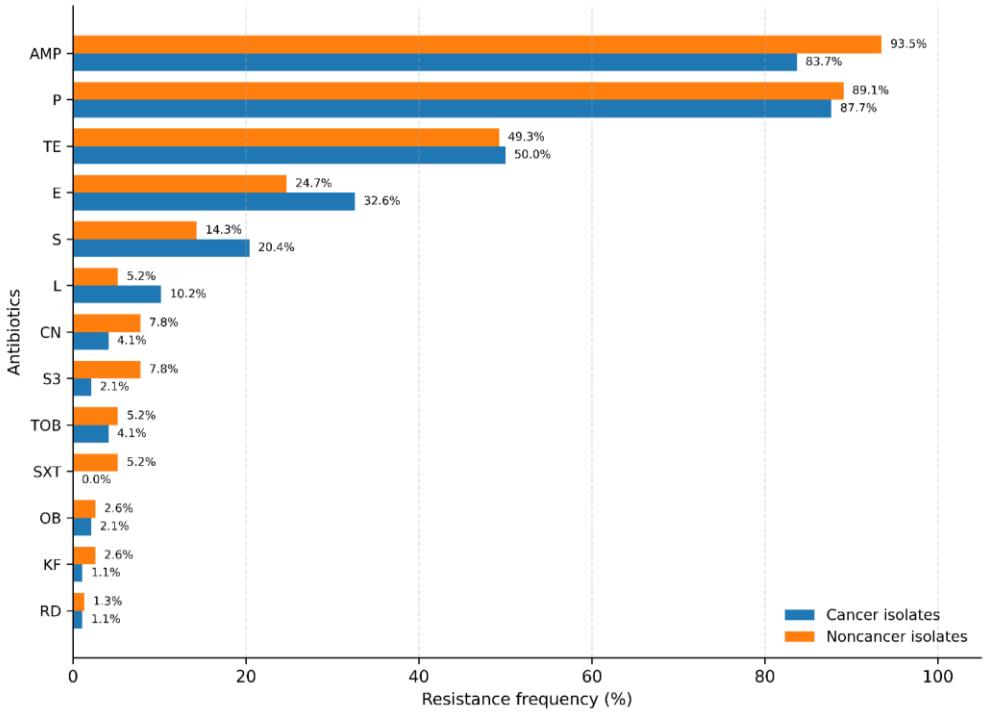

Figure 1: Comparative antibiotic resistance frequencies of *Staphylococcus aureus* isolates recovered from cancer and noncancer patients.

It was noticed that many isolates of *S. aureus* carried resistances for pairs of antibiotics at the same time (Table 2). The resistance to pairs of antibiotics like ampicillin and penicillin, penicillin and tetracycline, ampicillin and tetracycline, ampicillin and erythromycin, and penicillin and erythromycin were 146, 84, 82, 49 and 47 respectively. The paired antibiotic resistance analysis demonstrated extensive multidrug resistance among *S. aureus* isolates recovered from cancer and noncancer patients. The co-resistance matrix and publication plot revealed strong resistance associations between several antibiotics, particularly among β-lactam agents. The highest paired resistance frequency was observed between Penicillin G and Ampicillin (146 isolates), indicating a very strong co-resistance relationship. The distribution of paired resistance combinations is highly consistent with hospital-associated resistant *S. aureus* strains and reflects strong antimicrobial selective pressure within the studied population. Lower association frequencies involving gentamicin and lincomycin suggest comparatively preserved susceptibility. Overall, the findings indicate substantial antibiotic selective pressure and possible hospital-associated dissemination of resistant strains (Figure 2).

Table 2: Matrix of 175 isolates of *Staphylococcus aureus* with paired antibiotic resistance harvested from cancer and noncancer patients.

S3*	6											
L	11	3										
S	23	6	8									
SXT	3	4	0	3								
TE	34	9	9	20	4							
TOB	8	3	1	8	2	7						
CN	8	5	2	10	2	9	8					
AMP	49	9	11	27	4	82	7	9				
RD	1	0	1	0	0	0	0	0	1			
KF	2	3	2	3	1	3	2	3	3	0		
P	47	8	11	25	4	84	7	9	146	1	3	
OB	4	3	3	3	1	3	2	3	4	1	3	4
	E	S3	L	S	SXT	TE	TOB	CN	AMP	RD	KF	P

*= S3, Sulfonamide; L, Lincomycin; S, Streptomycin; SXT, Co-trimoxazole; TE, Tetracycline; CN, Gentamicin; AMP, Ampicillin; RD, Rifampicin; KF, Cephalothin; P, Penicillin G;OB, Cloxacillin.

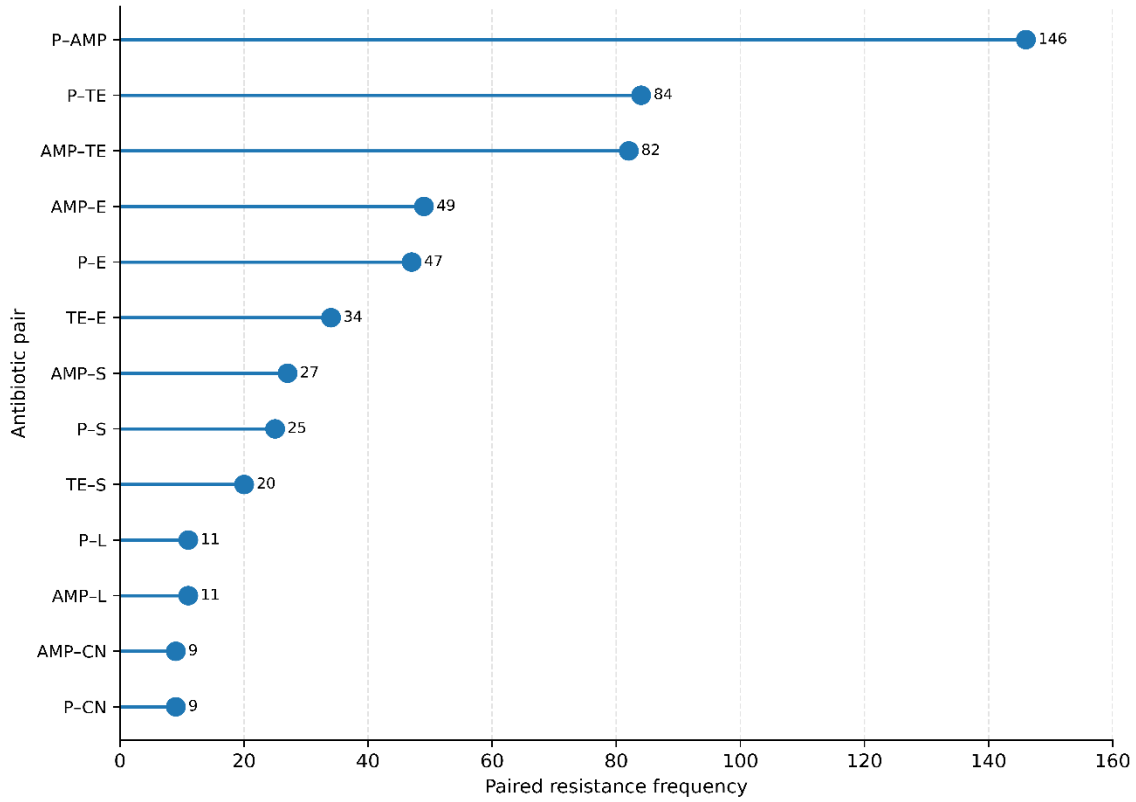

Figure 2: Scatter distribution of paired antibiotic co-resistance frequencies among *Staphylococcus aureus* isolates.

Table 3 did not show the symmetrical pattern of paired association, e.g. in the first line of the table it was noticed that 11.8% of the isolates tested which were resistant to erythromycin being resistant to sulfonamides whereas 66.6% of isolates that resistant to sulfonamides were resistant to erythromycin. It was also concluded that 64.5% of isolates resistant to streptomycin were resistant to tetracycline, and at the same time 22.9% tetracycline-resistant isolates were resistant to streptomycin. The paired antibiotic resistance frequency analysis demonstrated extensive multidrug resistance among *S. aureus* isolates recovered from cancer and noncancer patients. The bubble plot and resistance matrix revealed widespread simultaneous resistance between several antibiotic classes, indicating strong co-selection and dissemination of multidrug-resistant strains (Figure 3). The analysis showed that the strongest resistance associations occurred predominantly among β-lactam antibiotics, particularly between penicillin G and ampicillin, which exhibited extremely high paired resistance frequencies exceeding 90%. This strong relationship indicates extensive β-lactam resistance dissemination and strongly suggests the presence of common resistance mechanisms such as β-lactamase production and transferable resistance determinants. Very high resistance associations were also observed between tetracycline and several other antibiotics including sulfonamide, SXT, cephalothin, and penicillin G, with many paired combinations reaching frequencies close to or equal to 100%. These findings demonstrated that tetracycline resistance was strongly integrated into the multidrug resistance network and may coexist with multiple resistance genes carried on shared plasmids or mobile genetic elements. Dominance of β-lactam-associated resistance; Strong co-selection between multiple antibiotic classes; Possible plasmid-mediated resistance transfer; Significant antimicrobial selective pressure and Potential nosocomial circulation of resistant strains. Therefore, continuous antimicrobial surveillance, implementation of strict antibiotic stewardship programs, infection-control monitoring, and susceptibility-guided therapeutic strategies are strongly recommended to reduce further emergence and spread of multidrug-resistant *S. aureus* isolates.

Table 3: Matrix of frequency of paired antibiotic resistance of 175 isolates *of Staphylococcus aureus* harvested from cancer and noncancer patients.

	E	S3	L	S	SXT	TE	TOB	CN	AMP	RD	KF	P	OB
E	-	11.8	21.5	45.1	5.8	96.6	15.6	15.6	96.1	1.9	3.9	92.3	7.8
S3	66.7	-	33.4	66.6	100	100	33.3	55.5	100	0	33.3	88.6	33.3
L	78.6	21.4	-	57.1	0	63.3	7.2	14.3	78.5	7.2	14.3	78.5	21.4
S	74.2	19.3	25.8	-	9.7	64.5	25.8	32.2	87.1	0	9/6	80.6	9.6
SXT	75	100	0	75	-	100	50	50	100	0	25	100	25
TE	39.1	10.3	10.3	22.9	4.6	-	8.1	10.3	94.2	0	3.4	96.5	3.4
TOB	100	37.5	12.5	100	25	87.5	-	100	87.5	0	25	87.5	25
CN	80	50	20	100	20	90	80	-	90	0	30	90	30
AMP	31.8	6.5	7.1	17.1	2.6	53.2	4.5	5.8	-	0.6	1.9	94.8	2.6
RD	50	0	50	0	0	0	0	0	50	-	0	50	50
KF	66.6	100	66.6	100	33/3	100	66.6	100	100	0	-	100	100
P	3.3	5.2	7.1	16.1	2.6	54.1	4.5	5.8	94.2	0.6	1.9	-	2.6
OB	100	75	75	75	25	75	50	75	100	25	75	100	-

*= S3, Sulfonamide; L, Lincomycin; S, Streptomycin; SXT, Co-trimoxazole; TE, Tetracycline; CN, Gentamicin; AMP, Ampicillin; RD, Rifampicin; KF, Cephalothin; P, Penicillin G;OB, Cloxacillin.

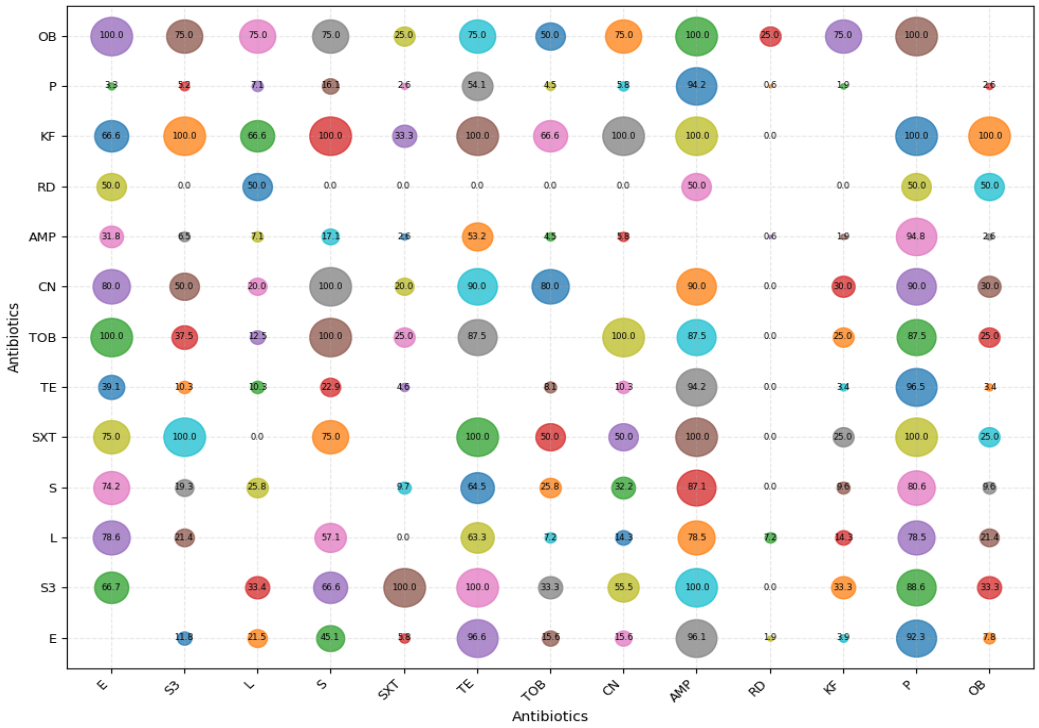

Figure 3: Bubble plot of paired antibiotic resistance frequencies among *Staphylococcus aureus* isolates recovered from cancer and noncancer patients. Bubble Size Interpretation=Very small bubble, 0–10%,Weak paired resistance association; Small bubble, 11–30%,Low co-resistance frequency; Medium bubble, 31–60%,Moderate

multidrug resistance association; Large bubble, 61–90%,Strong paired resistance relationship; Very large bubble, 91–100%,Extremely strong co-resistance association.

The McNemar Chi-square association matrix demonstrated extensive and highly interconnected multidrug resistance among *S. aureus* isolates recovered from cancer and noncancer patients (Table 4). The association analysis revealed strong statistical relationships between several antibiotic pairs, indicating that resistance to one antibiotic was frequently accompanied by simultaneous resistance to another antibiotic within the same isolates. The strongest associations were predominantly concentrated among β-lactam-related antibiotics, particularly involving penicillin G, ampicillin and cephalothin. The highest association value was observed between KF–P (150), followed closely by P-OB(149), SXT-P(149), AMP-KF(149), AMP-OB(148) and SXT-AMP(148). These extremely high McNemar association values indicate very strong paired resistance linkage and strongly suggest the presence of common resistance mechanisms shared among these antibiotics. Overall, the resistance architecture observed in Table 4 strongly indicated extensive multidrug resistance dissemination, strong β-lactam resistance dominance, shared resistance mechanisms among antibiotic classes, possible horizontal transfer of resistance genes, significant antimicrobial selective pressure and potential hospital-associated circulation of resistant *S. aureus* strains. The very high McNemar association values confirm that paired resistance among several antibiotic combinations is not random but represents biologically linked resistance patterns. These findings highlight the serious clinical challenge posed by multidrug-resistant *S. aureus* isolates and emphasize the importance of continuous antimicrobial surveillance, infection-control monitoring, and rational antibiotic stewardship programs to limit further dissemination of resistant strains (Figure 4).

Table 4: Matrix of degree of association of paired antibiotic resistance of 175 *Staphylococcus aureus* harvested from cancer and noncancer patients following Mcnemar method Chi-square test.

$$\chi^2 = \frac{(|b-c|-1)^2}{b+c}$$

Where b = isolates resistant to antibiotic A but not B and c = isolates resistant to antibiotic B but not A.

Degree of association between resistance of pairs of following antibiotics:												
	S3	L	S	SXT	TE	TOB	CN	AMP	RD	KF	P	OB
E	20.1	30.1	10.6	42.2	15.5	40.1	35.5	80.6	45.2	44.2	84.5	43.5
S3	-	1.3	4.9	2.2	75.1	0.1	0.1	142.1	3.3	4.16	142.1	2.3
L	-	-	10.3	4.5	55.1	0.5	0.5	134.3	8.6	8.6	141.3	6.7
S	-	-	-	23.3	38.8	21	19.1	78	23.7	26.1	141.3	23.3
SXT	-	-	-	-	81.1	1.1	2.5	148	0.2	0.2	149	0.2
TE	-	-	-	-	-	75.1	73.1	55.1	79.3	82.1	57.5	79.1
TOB	-	-	-	-	-	-	0.5	142.1	2.5	1.5	143.1	1.1
CN	-	-	-	-	-	-	-	140.1	4.1	5.1	140.1	3.1
AMP	-	-	-	-	-	-	-	-	148	149	4.2	148
RD	-	-	-	-	-	-	-	-	-	0	149.1	0.2
KF	-	-	-	-	-	-	-	-	-	-	150	0
P	-	-	-	-	-	-	-	-	-	-	-	149
OB	-	-	-	-	-	-	-	-	-	-	-	-

*= S3, Sulfonamide; L, Lincomycin; S, Streptomycin; SXT, Co-trimoxazole; TE, Tetracycline; CN, Gentamicin; AMP, Ampicillin; RD, Rifampicin; KF, Cephalothin; P, Penicillin G;OB, Cloxacillin.

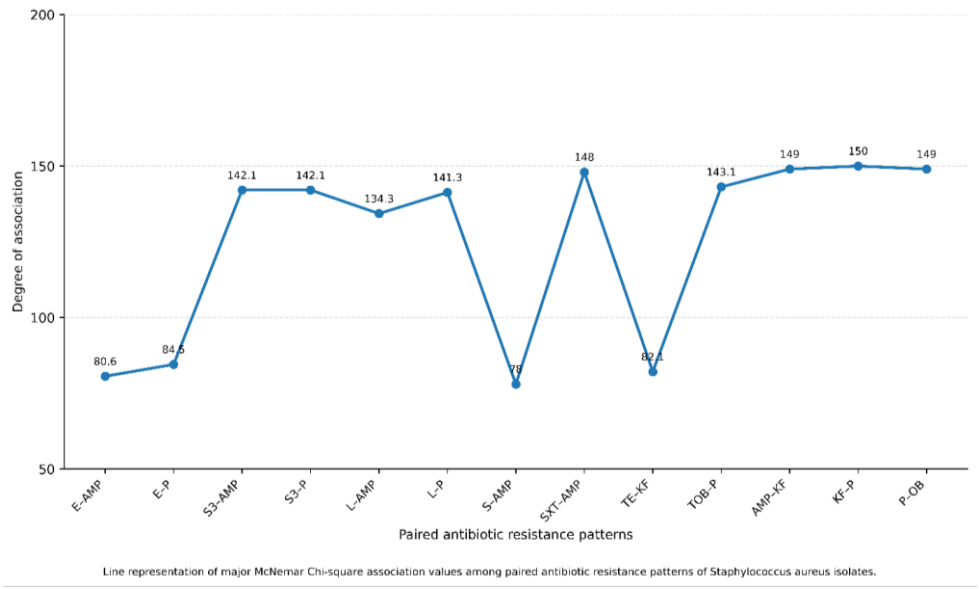

Figure 4: McNemar Chi-square association trends among paired antibiotic resistance patterns.

DISCUSSION

The figure shows that *Staphylococcus aureus* isolates from both cancer and noncancer patients had very high resistance to Penicillin G (P) and Ampicillin (AMP). Resistance to Tetracycline (TE) was moderate in both groups, while Rifampicin (RD), Cephalothin (KF), and Cloxacillin (OB) showed the lowest resistance frequencies. The highest resistance was recorded against Ampicillin, especially in noncancer isolates 93.5%, compared with cancer isolates 83.7%. Penicillin G resistance was also extremely high in both groups, with 87.7% in cancer isolates and 89.1% in noncancer isolates. Tetracycline showed almost identical resistance in both groups: 50.0% in cancer isolates and 49.3% in noncancer isolates. Bacterial resistance to antibiotics and other chemotherapeutic agents is a phenomenon that has been known for many years.[5,11,29] The mechanisms of antibiotic resistance in these variants are still under investigation. One hypothesis would be that the disinfectants altered the target site in the bacterial ribosome, making it less susceptible to neomycin and kanamycin but not to gentamicin or amikacin. Sivaji et al. and others.[30,31,32,33] observed that disinfectant derived variants of *S. aureus* became resistant to streptomycin but not to gentamicin or kanamycin. Destruction of various periplasmic enzymes by disinfectants has also been reported.[34,35,36,37] Decreased uptake of antibiotics can also be another contributory factor to the resistance. However, microorganisms exposed to subinhibitory concentrations of antimicrobials tend to adopt an adaptative response or develop resistance mechanisms in order to overcome this selective pressure.[4,38,39,40] It may occur as a horizontal gene transfer, thus enabling the spread of antimicrobial resistance genes and alteration of antimicrobial susceptibility profiles.[18,41,42,43] The present study showed that many isolates of *S. aureus* carried resistances for pairs of antibiotics at the same time (Table 2). The resistance to pairs of antibiotics like ampicillin and penicillin, penicillin and tetracycline, ampicillin and tetracycline, ampicillin and erythromycin, and penicillin and erythromycin were 146, 84, 82, 49 and 47 respectively. The paired antibiotic resistance analysis demonstrated extensive multidrug resistance among *S. aureus* isolates recovered from cancer and noncancer patients. The co-resistance matrix and publication plot revealed strong resistance associations between several antibiotics, particularly among β-lactam agents. It is noticeable that there was a strong association between pairs of resistance to many antibiotics used. Other resistance appeared to stand out as being close to independence i.e penicillin G with trimethoprim, clindamycin with gentamicin (Table 5). Other workers found that there was an association between erythro-mycin and clindamycin resistance among isolates of *S. aureus*, the so-called macrolises-lincosamides resistance but no relationship between methicillin and macrolide-lincosamide

resistance was observed.[44,45,46,47] In the present study, there was a strong association between the resistance to streptomycin and erythromycin. In contrast, Al-Ani found a weak relationship between the resistance to the same antibiotics among strains of *S. aureus* in Mosul city.[48,49,50] The present study did not show the symmetrical pattern of paired association, e.g. in the first line of the table it was noticed that 11.8% of the isolates tested which were resistant to erythromycin being resistant to sulfonamides whereas 66.6% of isolates that resistant to sulfonamides were resistant to erythromycin. It was also concluded that 64.5% of isolates resistant to streptomycin were resistant to tetracycline, and at the same time 22.9% tetracycline-resistant isolates were resistant to streptomycin. The paired antibiotic resistance frequency analysis demonstrated extensive multidrug resistance among *S. aureus* isolates recovered from cancer and noncancer patients. The bubble plot and resistance matrix revealed widespread simultaneous resistance between several antibiotic classes, indicating strong co-selection and dissemination of multidrug-resistant strains. Furthermore, Moreover, the association in antibiotic resistance in the present study is partially similar in some combinations to that found by others.[51,52,53,54] The association between pairs of resistance to many antibiotics might be explained by presence of resistance to one antibiotic induces the organism to resist another antibiotic from the same group even if not exposed to it, this is known as cross-resistance. In addition, presence of multiple antibiotic resistance at the same time might be due to the presence of multiple R-determinants on the same plasmids carried by the organism.[41,42] It is natural for bacteria to develop antibiotic resistance which is encoded by the antibiotic resistance genes (ARGs) which is not more than production of billions of years of evolution. It has been found that bacteria living in the environment already possess ARGs which are responsible for resistance to newly approved antibiotics before using of these drugs.[8,15] Inherited structural and / or physiological properties lead to intrinsic resistance to antibiotics. These functional properties including efflux to actively eliminate antibiotics from bacterial cells which entered through porin which is the mechanism by which the antibiotics unable to pass the outer membrane and by this mechanism cannot reach the target site.[55,56] Moreover, The McNemar Chi-square association matrix demonstrated extensive and highly interconnected multidrug resistance among *Staphylococcus aureus* isolates recovered from cancer and noncancer patients(Table 4). The association analysis revealed strong statistical relationships between several antibiotic pairs, indicating that resistance to one antibiotic was frequently accompanied by simultaneous resistance to another antibiotic within the same isolates. The strongest associations were predominantly concentrated among β-lactam-related antibiotics, particularly involving

penicillin G, ampicillin and cephalothin. The highest association value was observed between KF–P (150), followed closely by P-OB(149), SXT-P(149), AMP-KF(149), AMP-OB(148) and SXT-AMP(148). These extremely high McNemar association values indicate very strong paired resistance linkage and strongly suggest the presence of common resistance mechanisms shared among these antibioticsOverall, the resistance architecture observed in Table 4 strongly indicated extensive multidrug resistance dissemination, strong β-lactam resistance dominance, shared resistance mechanisms among antibiotic classes, possible horizontal transfer of resistance genes, significant antimicrobial selective pressure and potential hospital-associated circulation of resistant *S. aureus* strains. The very high McNemar association values confirm that paired resistance among several antibiotic combinations is not random but represents biologically linked resistance patterns. These findings highlight the serious clinical challenge posed by multidrug-resistant *S. aureus* isolates and emphasize the importance of continuous antimicrobial surveillance, infection-control monitoring, and rational antibiotic stewardship programs to limit further dissemination of resistant strains. Moreover, the change in susceptibility does not imply development of resistance.[42,43] because tolerance or adaptation as a phenotypic display may be considered instead.[57,58,59] Hence, cross-resistance can be proposed when the use of biocides drives selective pressure toward antimicrobial resistance regarding some microbial subpopulations.[60,61,62] The involved stress induces an adaptative response that protects pathogens, producing cellular changes that may affect the native antimicrobial susceptibility pattern.[26] This situation is particularly important in healthcare settings and infrastructures where contamination plays a significant role in healthcare-associated infections.[30] However, comprehensive efforts, including basic infection control education, improved selection, use of products and practical training are required to minimize harmful cleaning and disinfection exposures without reducing the effectiveness of infection prevention.[42,43,63,64,66] Furthermore, the evolution of antibiotic-resistant healthcare acquired microorganisms after treatment with sub-MICs of different disinfectants has been investigated elsewhere.[46,47,67,68,69]

CONCLUSIONS

The most problematic antibiotics were penicillin G and ampicillin, showing resistance rates above 80–90%. The high multidrug resistance rate indicated strong antibiotic selective pressure and possible hospital-associated resistance circulation. Overall, cancer and noncancer isolates showed broadly similar resistance profiles, with only minor differences for selected antibiotics. The resistance to pairs of antibiotics like ampicillin and penicillin,

penicillin and tetracycline, ampicillin and tetracycline, ampicillin and erythromycin, and penicillin and erythromycin were 146, 84, 82, 49 and 47 respectively. The paired antibiotic resistance analysis demonstrated extensive multidrug resistance among *S. aureus* isolates recovered from cancer and noncancer patients. The analysis showed that the strongest resistance associations occurred predominantly among β-lactam antibiotics, particularly between penicillin G and ampicillin, which exhibited extremely high paired resistance frequencies exceeding 90%. The association analysis revealed strong statistical relationships between several antibiotic pairs, indicating that resistance to one antibiotic was frequently accompanied by simultaneous resistance to another antibiotic within the same isolates.

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Statement of Ethics

All the procedures involving human participation were conducted in strict accordance with ethical standards of Institutional Research Committee, Department of Scientific Research, Mosul University as well as the 1964 Helsinki Declaration and its subsequent amendments or equivalent ethical norms.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest Statement

The author declares that he has no conflicts of interest, financial or otherwise.

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