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ORIGINAL ARTICLE

Inducible Clindamycin and Methicillin Resistant *Staphylococcus aureus* Among Cancer Patients at University of Gondar Compressive Specialized Hospital, Northwest Ethiopia: Carriage Rate and Antibiotic Resistance Patterns

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SUMMARY

Background: **Methicillin-resistant *Staphylococcus aureus* (MRSA) is a type of *Staphylococcus aureus* strain which is resistant to a group of beta-lactam antibiotics. Methicillin-resistance is due to a penicillin-binding protein, which has a low affinity for beta-lactam antibiotics. Excess and inappropriate use of clindamycin have led to the emergence of resistant Staphylococcal strains. Cancer patients are at high risk of bacterial colonization due to cancer chemotherapy which leads to severe and prolonged immunosuppression. This study aimed to assess the carriage rate of inducible clindamycin and MRSA among cancer patients.**

Methods: **A hospital-based cross-sectional study was conducted on 200 cancer patients from January to August 2019. Sociodemographic data and nasal swab samples were collected and inoculated on mannitol salt agar and then incubated at 37°C for 24 hours. The identification of isolates was done by colony characteristics and biochemical reactions. MRSA was detected using cefoxitin disc and inducible clindamycin resistance detected using D-test. Interpretations of antibiotics susceptibility was done using CLSI 2018. Finally, data was entered, cleared, and checked using Epi-info version 7 and exported to SPSS version 20 for analysis. Logistic regression was used for statistical association. p-value ≤ 0.05 at 95% CI was considered statistically significant.**

Results: **In this study, of the 59 *Staphylococcus aureus* isolates tested, 22% (13/59) were MRSA and 78% (46/59) were MSSA. MRSA carriage rate in females was 18.6% (11/59) whereas in males it was 3.4% (2/59). MRSA carriage among urban residents (15.3% (9/59)) was higher than their rural counterparts (6.8% (4/59)). The prevalence of inducible clindamycin resistance was 17% (10/59). Multi-drug resistance patterns among *Staphylococcus aureus* isolates was 55.9% (33/59). Clindamycin (84.6%), chloramphenicol (84.6%), and ciprofloxacin (69.2%) were the most effective whereas penicillin (100%), tetracycline (76.9%), and erythromycin (76.9%) were the least effective for MRSA isolates. Urban living, being illiterate, being employed, patients with liver and lung cancer were significantly associated with MRSA carriage.**

Conclusions: **This study showed high rates of MRSA carriage and inducible clindamycin resistance with the percentages of 22 and 17, respectively. Therefore, decolonization of MRSA carriers and rational usage of antibiotics should be implemented.**

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KEY WORDS

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INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is any strain of *Staphylococcus aureus* (*S. aureus*) which is resistant to a large group of antibiotics called the beta-lactams [1]. Methicillin-resistance is largely attributed to the acquisition of the *mecA* gene which is found in the Staphylococcal cassette chromosome mec (*SCCmec*) that codes unique a penicillin-binding protein (*PBP2a*), which has low affinity to methicillin and other beta-lactam antibiotics [2,3]. MRSA has remained a significant threat to healthcare and community-associated infections worldwide. Its infection imposes an additional burden on healthcare systems leading to significant morbidity and mortality, length of hospital stays, and hospital costs [4]. It becomes a public health concern because of higher mortality, morbidity, and the significant difficulty to cure due to the limitation of therapeutic choices [5]. Prolonged hospitalization, antibiotics exposure, and the presence of other patients with MRSA colonization or infection in the hospital are major risk factors for acquiring MRSA infections [6].

Clindamycin is an important option for the treatment of both methicillin-susceptible *Staphylococcus aureus* (MSSA) and MRSA. Resistance to clindamycin in *S. aureus* derives from target site modification, mediated by *erm* genes, which lead to ribosomal methylation. Resistance may occur either in an inducible or constitutive form [7]. Resistance mediated by inducible macrolide-Lincosamides-Streptogramins B (iMLSB) phenotype leads to *in vivo* therapeutic failure even though *in vitro* they may be susceptible in Kirby-Bauer disk diffusion method [8]. MRSA isolates with inducible clindamycin resistance are resistant to erythromycin and sensitive to clindamycin on routine testing and inducible clindamycin resistance can only be identified by D-test [9-11]. Frequent use of clindamycin for staphylococcal infections has led to a large number of Staphylococcal strains resistant to it. It is very difficult to detect inducible clindamycin resistance using standard susceptibility test methods as they appear erythromycin-resistant and clindamycin sensitive *in vitro* when not placed adjacent to each other. Failure to identify inducible clindamycin resistance and *in vivo* therapy with clindamycin may select constitutive erm mutants leading to clinical failure of clindamycin therapy [12].

The development of infections caused by multidrug-resistant bacteria has become a major health problem worldwide and is of particular concern in cancer patients [13-15]. Cancer patients are at high risk of bacterial infections due to the chemotherapy for cancer patients leading to severe and prolonged immunosuppression such as neutropenia during chemotherapy, altered gut flora because of frequent antibiotic administration, and disruption of skin and damage of epithelial surfaces of the tissues by cytotoxic chemotherapeutic agents [16-19]. Decreased host immunity in cancer patients places them at increased risk for several infections, including those caused by *S. aureus* and MRSA [20]. In Ethiopia, no study had been carried out on the carriage rate of inducible clindamycin and methicillin-resistant *Staphylococcus aureus* among cancer patients. Hence, this study aimed to assess the carriage rate of inducible clindamycin and methicillin-resistant *Staphylococcus aureus* among cancer patients at the University of Gondar comprehensive specialized referral hospital, Gondar, Ethiopia.

MATERIALS AND METHODS

Study area

The study was conducted at the University of Gondar comprehensive specialized referral hospital. The hospital provides healthcare services for over five million people in Gondar town and the surrounding area, Gondar town is the capital city of central Gondar zone, in Amhara regional state. The town is 737 km away from Addis Ababa, the capital city of Ethiopia and 180 km away from Bahir Dar, the capital city of Amhara regional state. The town is located at latitude and longitude $12^{o}361N$ $37^{o}281E$ with an elevation of 2,133 meters above sea level. It has twelve sub-city, twenty-two urban and eleven rural kebeles with a projected population of 360,600. The town has 8 health centers, 21 private clinics, and one referral hospital for the population of Gondar town and surrounding three zones.

Study design and study population

A hospital-based cross-sectional study was conducted to assess the carriage rate of inducible clindamycin and methicillin-resistant *Staphylococcus aureus* among cancer patients at the University of Gondar comprehensive specialized referral hospital, Northwest Ethiopia, from January to August 2019. All cancer confirmed patients were included in the study during the study period. Cancer patients who were unable to give socio-demographic information, were currently on antibiotic treatment, and had a recent history of antibiotic treatment for the last three weeks at the time of data collection were excluded.

Sample size determination and sampling technique

A total of 200 cancer patients attending their chemotherapy in University of Gondar cancer center during the study period were included. Convenience, non-probability sampling technique was used to include 200 cancer patients.

Socio-demographic data and nasal swab specimen collection

A pre-tested questionnaire based on postulated risk factors was developed and modified to explore the objectives of the study. Then socio-demographic characteristics and other relevant information were collected. Nasal swab specimens were collected by using sterile cotton tip swabs pre-wetted with sterile saline for each anterior nares by inserting the swab and gently rotating

four to five times both in clockwise and anticlockwise direction for each study participants. The nasal swabs were collected and inoculated immediately in a properly labeled sterile Tryptic soy broth (TSB) tube (Oxoid Ltd., England) and transported using a vaccine carrier which has an icebox to maintain the temperature at 2 - 8°C until it reaches to the laboratory [21].

Laboratory inoculation and identification

Each nasal sample was inoculated onto mannitol salt agar (Oxoid Ltd., England) and the plates were incubated aerobically at 37°C for 24 hours. Samples that were positive for mannitol fermentation and golden yellow colonies on mannitol salt agar were further inoculated on blood agar plates (BAP) (Oxoid Ltd., England) and incubated at 37°C for 24 hours. The isolates obtained were identified using standard microbiological methods including colony morphology, Gram's stain reaction, and biochemical tests such as catalase and coagulase. Finally isolates that were a golden yellow colony on mannitol salt agar and blood agar pate, Gram-positive cocci in clusters, catalase and coagulase-positive were confirmed as *Staphylococcus aureus*.

Antimicrobial susceptibility testing

A suspension of a pure colony from each confirmed culture isolate was done in sterile normal saline and incubated at 37°C for at least 15 minutes. The suspension was adjusted at 0.5 MacFarland standard. A sterile cotton applicator stick was used for uniform distribution of the suspension on Muller Hinton agar (Oxoid Ltd., England). Then Modified Kirby-Bauer disk diffusion technique was implemented for antibiotic susceptibility pattern using different antibiotics such as penicillin (10 µg), erythromycin (15 µg), clindamycin (2 µg), gentamicin (10 µg), cotrimoxazole (1.25/23.75 µg), cefoxitin (30 µg), ciprofloxacin (5 µg), doxycycline (30 µg), chloramphenicol (30 µg), and tetracycline (30 µg). After incubation at 37°C for 24 hours, the zones of inhibition were measured with a ruler. Finally, the results were measured, recorded and classified as susceptible, intermediate, and resistant using Clinical and Laboratory Standards Institute (CLSI) 2018 performance standards for antimicrobial susceptibility testing interpretation [22].

Antimicrobial susceptibility testing for MRSA

Staphylococcus aureus isolates were tested for methicillin susceptibility patterns by using the modified Kirby-Bauer disc diffusion technique. A suspension of confirmed isolates was done by using 0.85% normal saline, the inocula were adjusted at 0.5 McFarland standard and streaked uniformly using sterile cotton swabs on Mueller-Hinton agar (Oxoid Ltd., England). Cefoxitin (30 µg) (Oxoid Ltd., England) discs were placed on the plates and then incubated aerobically at 37°C for 24 hours. Zone of inhibition in millimeters was measured with a ruler. Interpretations determining susceptibility of antibiotics (i.e., sensitive and resistance) done based on Clinical Laboratory Standard Institute (CLSI) 2018 [22]. Finally, those which were resistant to cefoxitin (< 21 mm) were classified as MRSA.

Antimicrobial susceptibility testing for inducible clindamycin resistance

Inducible clindamycin resistance was tested using D-test by putting erythromycin and clindamycin discs at a distance of 15 mm from each other on Muller Hinton agar plate (Oxoid Ltd., England). Then after incubation at 37°C for 24 hours, flattening of a zone (D-shaped) around clindamycin in the area between erythromycin and clindamycin discs were observed. Isolates with resistance to erythromycin and sensitive to clindamycin were interpreted as inducible clindamycin resistant [11].

Data and laboratory quality control

The questionnaire was pre-tested before the actual study began to make sure that the questionnaire was appropriate and understandable. The collected data were checked daily for consistency and accuracy. Investigators also followed standard data collection process. Five percent (5%) of the prepared culture media were randomly selected and incubated aerobically for 24 hours at 37°C to check the sterility of the prepared culture media. In addition, known strains of *Staphylococcus aureus* (ATCC 25923) and *Escherichia coli* (ATCC 25922) were inoculated to the prepared culture media to check the performance of the prepared culture media and antibiotic susceptibility test. Laboratory identification procedures like inoculation of culture media, colony characterization, and measuring of antibiotic susceptibility testing were checked. Reagents for Gram stain and biochemical tests were checked by *Staphylococcus aureus* (ATCC 25923) and *Escherichia coli* (ATCC 25922).

Data entry and analysis

Data was entered into the Epidemiological Information (EPI-Info) version-7 to check data completeness and data clearance, then transferred to SPSS version 20 for analysis. The characteristics of the study populations were summarized using frequencies, mean, and standard deviation. Binary logistic regression was used to determine the strength of the association between variables. Moreover, the adjusted odds ratio was computed using multivariate logistic regression for variables with a p-value < 0.2 to control the effect of confounding variables. p-value < 0.05 was considered statistically significant at a 95% confidence interval.

RESULTS

Socio-demographic characteristics of study participants

In this study, a total of 200 cancer patients were included. Out of these, 61% (122/200) were females and 39% (78/200) were males. The mean age of the study participants was 44 years with a range of 3 - 81 years. Most

Table 1. Prevalence of *Staphylococcus aureus*, MRSA, iMLSB and risk factors for MRSA carriage among cancer patients at University of Gondar Comprehensive Specialized Hospital, Gondar, Northwest Ethiopia, 2019.

Characteristics		Number (%)	Bacterial carriage rate					
			No. of +ve for *S. aureus*	No. of +ve for MRSA	No. of +ve for iMLSB	No. of -ve for *S. aureus*	Adjusted OR (95% CI)	p-value
Gender	Female	122 (61%)	36 (18%)	11 (18.6%)	6 (10.2%)	86 (43%)	0.741 [0.106 - 5.180]	0.763
	Male	78 (39%)	23 (11.5%)	2 (3.4%)	4 (6.8%)	55 (27.5%)	1 (ref)	1 (ref)
Residence	Urban	111 (55.5%)	36 (18%)	9 (15.3%)	7 (11.9%)	75 (37.5%)	3,593 [6.167 - 209,367]	0.018
	Rural	89 (44.5%)	23 (11.5%)	4 (6.8%)	3 (5.1%)	66 (33%)	1 (ref)	1 (ref)
Age in years	< 20 years	19 (9.5%)	1 (0.5%)	0 (0%)	0 (0%)	18 (9%)	10.074 [0.033 - 306,788]	0.083
	21 - 40 years	70 (34.5%)	23 (11.5%)	7 (11.9%)	3 (5.1%)	47 (23.5%)	3.867 [3.645 - 7.573]	0.72
	41 - 60 years	82 (41%)	25 (12.5%)	6 (10.2%)	4 (6.8%)	57 (28.5%)	0.30 [0.156 - 4.46]	0.18
	> 60 years	29 (15%)	10 (5%)	0 (0%)	3 (5.1%)	19 (9.5%)	1 (ref)	1 (ref)
Education I status	II literate	93 (46.5%)	23 (11.5%)	4 (6.8%)	3 (5.1%)	70 (35%)	19.529 [3.132 - 121.770]	0.001
	Read & write	13 (6.5%)	4 (2%)	0 (0%)	0 (0%)	9 (4.5%)	14.844 [1.615 - 136.398]	0.017
	Primary	31 (15.5%)	8 (4%)	1 (1.7%)	0 (0%)	23 (11.5%)	5.704 [0.986 - 32.996]	0.052
	Second-ary	33 (16.5%)	13 (6.5%)	7 (11.9%)	4 (6.8%)	20 (10%)	1.971 [0.458 - 8.480]	0.362
	12 and above	30 (15%)	11 (5.5%)	1 (1.7%)	3 (5.1%)	19 (9.5%)	1 (ref)	1 (ref)
Occupa-tion	Farmer	74 (37%)	22 (11%)	3 (5.1%)	3 (5.1%)	52 (26%)	1.895 [0.645 - 5.573]	0.245
	Merchant	21 (10.5%)	6 (3%)	1 (1.7%)	0 (0%)	15 (7.5%)	4.408 [0.969 - 20.044]	0.055
	Student	19 (9.5%)	3 (1.5%)	0 (0%)	0 (0%)	16 (8%)	9.240 [0.632 - 135.045]	0.104
	Employed	34 (17%)	9 (4.5%)	1 (1.7%)	0 (0%)	25 (12.5%)	19.720 [3.092 - 125.755]	0.002
	Unemploy-ed	52 (26%)	19 (9.5%)	8 (13.6%)	7 (11.9%)	33 (16.5%)	1 (ref)	1 (ref)
Income (Ethiopian birr)	Less than 500	100 (50%)	30 (15%)	7 (11.9%)	9 (15.3%)	70 (35%)	48.729 [0.118 - 20,173.29]	0.206
	501 - 1,000	54 (27%)	15 (7.5%)	3 (5.1%)	0 (0%)	39 (19.5%)	2,632.67 [0.235 - 295,544]	0.098
	> 1,000	46 (23%)	14 (7%)	3 (5.1%)	1 (1.7%)	32 (16%)	1 (ref)	1 (ref)
Marital status	Married	146 (73%)	49 (24.5%)	10 (17%)	8 (13.6%)	97 (48.5%)	0.071 [0.00 - 8,411.149]	0.657
	Unmarried	32 (16%)	4 (2%)	1 (1.7%)	1 (1.7%)	28 (14%)	434 [0.00 - 6,998.16256]	0.672
	Divorced	10 (5%)	2 (1%)	1 (1.7%)	1 (1.7%)	8 (4%)	0.02 [0.000 - 55,774.450]	0.479
	Widowed	12 (6%)	4 (2%)	1 (1.7%)	1 (1.7%)	8 (4%)	1 (ref)	1 (ref)

Table 1. Prevalence of *Staphylococcus aureus*, MRSA, iMLSB and risk factors for MRSA carriage among cancer patients at University of Gondar Comprehensive Specialized Hospital, Gondar, Northwest Ethiopia, 2019 (continued).

Characteristics		Number (%)	Bacterial carriage rate					
			No. of +ve for *S. aureus*	No. of +ve for MRSA	No. of +ve for iMLSB	No. of -ve for *S. aureus*	Adjusted OR (95% CI)	p-value
History of hospital-ization	Yes	141 (70.5%)	37 (18.5%)	10 (16.9%)	6 (10.2%)	104 (52%)	2,520 [0.010 - 62,388,7952]	0.216
	No	59 (29.5%)	22 (11%)	3 (5.1%)	4 (6.8%)	37 (18.5%)	1 (ref)	1 (ref)
History of surgery	Yes	100 (50%)	31 (15.1%)	10 (16.9%)	5 (8.5%)	69 (34.5%)	2,520 [0.5643 - 5.95892]	0.083
	No	100 (50%)	28 (14%)	3 (5.1%)	5 (8.5%)	72 (36%)	1 (ref)	1 (ref)
Type of cancer	Breast	59 (29.5%)	21 (35.6%)	3 (5.1%)	3 (5.1%)	38 (19%)	0.875 [0.156891 - 4.011]	0.333
	Colon	37 (18.5%)	10 (16.9%)	5 (8.5%)	2 (3.4%)	27 (13.5%)	2.0 [0.191 - 2,067.96978]	0.150
	Balder	11 (5.5%)	1 (1.7%)	0 (0%)	1 (1.7%)	10 (5%)	2.333 [0.439 - 1,245.398]	0.999
	Blood	16 (8%)	3 (5.1%)	1 (1.7%)	0 (0%)	13 (6.5%)	0.47 [0.094 - 2.4876786]	0.490
	Lymph node	13 (6.5%)	4 (%)	1 (1.7%)	1 (1.7%)	9 (4.5%)	0.70 [0.049 - 3.1898909]	0.640
	Thyroid	9 (4.5%)	3 (6.8%)	0 (0%)	1 (1.7%)	6 (3%)	0.6897 [0.09344 - 7.486]	0.998
	Endo-metrial	27 (13.5%)	9 (15.3%)	3 (5.1%)	2 (3.4%)	18 (9%)	0.25 [0.67542 - 1,455.58]	0.305
	Liver	8 (4%)	3 (5.1%)	0 (0%)	0 (0%)	5 (2.5%)	0.64 [1.909 - 11.889862]	0.036
	Bone	5 (2.5%)	1 (1.7%)	0 (0%)	0 (0%)	4 (2%)	0.5783 [0.38727 - 2.967]	0.995
	Lung	5 (2.5%)	1 (1.7%)	0 (0%)	0 (0%)	4 (2%)	0.714 [0.49858 - 6.4854]	0.050
	Brain	2 (1%)	1 (1.7%)	0 (0%)	0 (0%)	1 (0.5%)	3.3782 [056.542 - 815.5]	0.479
	Gastric	2 (1%)	1 (1.7%)	0 (0%)	0 (0%)	1 (0.5%)	543.32 [0.542 - 15.5786]	0.999
	Others	6 (3%)	1 (1.7%)	0 (0%)	0 (0%)	5 (2.5%)	1 (ref)	1 (ref)
Duration of cancer chemo-therapy	< 1 year	159 (79.5%)	45 (22.5%)	8 (13.6%)	8 (13.6%)	114 (57%)	35.32 [0.542 - 15.58876]	0.933
	1 - 2 years	21 (10.5%)	9 (4.5%)	5 (8.5%)	0 (0%)	12 (6%)	755.62 [0.782 - 675.588]	0.998
	> 2 years	20 (10%)	5 (2.5%)	0 (0%)	2 (3.4%)	15 (7.5%)	1 (ref)	1 (ref)

cancer patients (41% (82/200)) belonged to the 41 - 60 year group while 34.5% (69/200) of study participants belonged to the 21 - 40 year group. The majority, (55.5% (111/200)) of the cancer patients were urban residents while the rest (44.5% (89/200)) were from a rural area. Most of cancer confirmed patients (29.5% (59/200)) had breast cancer followed by colon cancer (18.5% (37/200)) (Table 1). Among the study participants, 73% (146/200) were married. Of the study participants, 79.5% (159/200) followed their cancer chemotherapy for less than one year. The majority of the study participants (96.5% (193/200)) had no history of chronic disease other than cancer; however, from the total participants a majority (70.5% (141/200)) had a history of hospitalization. On top of that, 50% (100/200) had a history of surgery and 37% (74/200) were farmers. Half

Table 2. Antibiotic susceptibility patterns of Staphylococcus aureus, MRSA, iMLSB and MDR isolates among cancer patients at University of Gondar Comprehensive Specialized Hospital, Gondar, Northwest Ethiopia, 2019.

Antibiotics	Bacterial isolates											
	MSSA (46)			MRSA (13)			iMLSB (10)			MDR (33)		
	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)
Penicillin (10 µg)	2 (4.3)	0 (0)	44 (95.7)	0 (0)	0 (0)	13 (100)	0 (0)	0 (0)	10 (100)	0 (0)	0 (0)	33 (100)
Erythromycin (15 µg)	21 (45.7)	7 (15.2)	18 (39.1)	2 (15.4)	1 (7.7)	10 (76.9)	0 (0)	0 (0)	10 (100)	3 (9.09)	5 (15.2	25 (75.8)
Clindamycin (2 µg)	41 (89.1)	0 (0)	5 (10.9)	11 (84.6)	0 (0)	2 (15.4)	10 (100)	0 (0)	0 (0)	26 (78.8)	0 (0)	7 (21.2)
Gentamicin (10 µg)	43 (93.5)	1 (2.2)	2 (4.3)	8 (61.5)	0 (0)	5 (38.5)	7 (70)	0 (0)	3 (30)	26 (78.8)	0 (0)	7 (21.2)
TMP/SMX (1.25/23.75 µg)	31 (67.4)	3 (6.5)	12 (26.1)	4 (30.8)	0 (0)	9 (69.2)	6 (60)	0 (0)	4 (40)	13 (39.4)	2 (6.06	18 (54.5)
Doxycycline (30 µg)	28 (60.9)	5 (10.9)	13 (28.3)	4 (30.8)	1 (7.7)	8 (61.5)	4 (40)	0 (0)	6 (60)	9 (27.3)	4 (12.1	20 (60.6)
Ciprofloxacin (30 µg)	43 (93.5)	1 (2.2)	2 (4.3)	9 (69.2)	2 (15.4	2 (15.4)	8 (80)	0 (0)	2 (20)	26 (78.8)	3 (9.09	4 (12.1)
Tetracycline (30 µg)	15 (32.6)	6 (13)	25 (54.3)	2 (15.4)	1 (7.7)	10 (76.9)	2 (20)	0 (0)	8 (80)	3 (9.09)	1 (3.03	29 (87.8)
Chloramphenicol (30 µg)	41 (89.1)	2 (4.4)	3 (6.5)	11 (84.6)	0 (0)	2 (15.4)	9 (90)	0 (0)	1 (10)	27 (81.8)	2 (6.06	4 (12.1)
Cefoxitin (30 µg)	46 (100)	0 (0)	0 (0)	0 (0)	0 (0)	13 (100)	6 (60)	0 (0)	4 (40)	21 (63.6)	12 (36.4	0 (0)

S - Susceptible, I - Intermediate, R - Resistance.

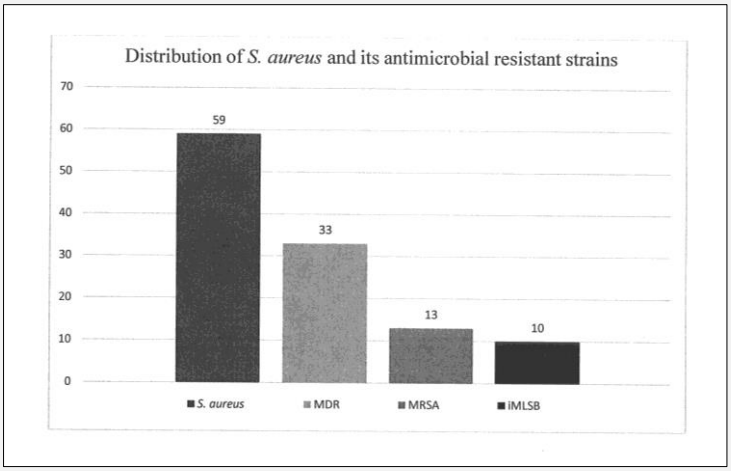

Figure 1. Distribution of *S. aureus* and its number of MDR, MRSA, and iMLSB isolates among cancer patients at University of Gondar Comprehensive Specialized Hospital, 2019.

(100/200) of the study participants' average monthly income was less than 500 Ethiopian birr and 46.5% (93/200) of the study participants were unable to read and write (Table 1).

Prevalence of *Staphylococcus aureus*, MRSA, and iMLSB

Out of 200 study participants, the overall prevalence of *S. aureus* was 29.5% (59/200), of these 22% (13/59)

were MRSA (Figure 1). From the total of 59 isolates, 18% (36/200) were isolated from female participants, of which 30.6% (11/36) were MRSA. In urban residents, MRSA carriage rate was 15.3% (9/59) whereas in the rural residents, it was 6.8% (4/59). The highest carriage rate of MRSA was shown among unemployed (13.6% (8/59)), illiterates (6.8% (4/59)), and 21 - 40 years old group (11.9% (7/59)). The overall prevalence of inducible clindamycin resistant *S. aureus* in this study was 17% (10/59) (Figure 1). Out of 13 MRSA isolates, 30.8% (4/13) showed inducible MLSB phenotype. The frequency of inducible clindamycin resistant *S. aureus* nasal carriage in females was 10.2% (6/59) as compared to 6.8% (4/59) in males. The prevalence of iMLSB nasal carriage was 11.9% (7/59) in urban as compared to 5.1% (3/59) in rural. The carriage rate of MRSA and iMLSB reached its peak at the age groups 21 - 40 years (11.9% (7/59)) and 41 - 60 years (6.8% (4/59)). Among study participants, high carriage of MRSA (13.6% (8/59)) and high carriage of iMLSB (13.6% (8/59)) were observed in cancer patients who took cancer chemotherapy for less than one year (Table 1). Study participants who had a history of hospitalization and surgery had a high carriage rate of MRSA (16.9% (10/59)). The high carriage rate of MRSA (17% (10/59)) and iMLSB (13.6% (8/59)) were observed in study participants who are married (Table 1).

Among study participants, high carriage rate of MRSA isolates was observed in colon cancer patients (8.5% (5/59)) followed by endometrial cancer patients (5.1% (3/59)), breast cancer patients (5.1% (3/59)), blood cancer patients (1.7% (1/59)), and lymph node cancer patients (1.7% (1/59)) while high carriage rates of iMLSB isolates were observed in breast cancer patients (5.1% (3/59)) followed by colon cancer patients (3.4% (2/59)), endometrial cancer patients (3.4% (2/59)), bladder cancer patients (1.7% (1/59)), lymph node cancer patients (1.7% (1/59)), and thyroid cancer patients (1.7% (1/59)) (Table 1). The overall multidrug resistance (MDR) pattern among *S. aureus* isolates in cancer patient was 55.9% (33/59) (Figure 1). The high carriage rate of MDR isolates was observed in breast cancer patients (33.33% (11/33)) followed by colon cancer patients (24.24% (8/33)), endometrial cancer patients (15.15% (5/33)), and thyroid cancer patients (6.8% (4/33)). In urban residents, MRSA carriage rate was 15.3% (9/59), whereas in the rural residents it was 12.12% (4/59). In urban residents, MDR carriage rate was 66.67% (22/33) whereas in the rural residents, it was 33.33% (11/33). The high carriage rate of MDR isolates was observed in the age group of 21 - 40 years (48.5% (16/33)) followed by age group of 41 - 60 years (39.4% (13/33)) and greater than 60 years (12.12% (4/33)).

Risk factors for carriage of *S. aureus*, MRSA, and iMLSB isolates

In this study, socio-demographic and clinical variables were assessed as a predictor variable for the carriage of *S. aureus*, MRSA, and iMLSB isolates. Among these variables included in the study, having a history of hospitalization ($p = 0.044$; adjusted odds ratio (AOR) = 2.300; confidence interval (CI) = 1.024 - 5.168) was a significant risk factor for nasal colonization of *S. aureus*. However, urban living ($p = 0.018$; AOR = 3,593 = 6.167 - 209,367), being illiterate ($p = 0.001$; AOR = 19.529; CI = 3.132 - 121.770), being able to read and write ($p = 0.017$; AOR = 14.844; CI = 1.615 - 136.398), being employed ($p = 0.002$; AOR = 19.720; CI = 3.092 - 125.755), patients with liver cancer ($p = 0.036$; AOR = 0.64; CI = 1.909 - 11.889862), and patients with lung cancer ($p = 0.050$; AOR = 0.714; CI = 0.49858 - 6.4854) were significant risk factors for nasal colonization of MRSA (Table 1). No socio-demographic characteristics and clinical factors contributing for nasal carriage of iMLSB isolates were found. In general, in this study, some socio-demographic characteristics and clinical factors of participants were not significantly associated for carriage of *S. aureus*, MRSA, and iMLSB isolates ($p > 0.05$).

Antimicrobial susceptibility patterns of isolates

Antibiotic susceptibility of the *S. aureus* isolates was determined by standard Kirby-Bauer disk diffusion method. Analysis of species-specific resistance indicated that most of the MSSA isolates were resistant to penicillin G (95.7%) and tetracycline (54.3%). On the other hand, MSSA isolates were susceptible to cefoxitin, gentamicin, ciprofloxacin, clindamycin, and chloramphenicol with resistance rates of 0%, 4.3%, 4.3%, 10.9%, and 6.5%, respectively (Table 2). In this study, MRSA isolates were resistant to cefoxitin (100%), penicillin (100%), tetracycline (76.9%), erythromycin (76.9%), and TMP/SMX (69.2%). However, the most effective antibiotics for MRSA isolates were clindamycin, chloramphenicol, ciprofloxacin and gentamicin with sensitivity of 84.6%, 84.6%, 69.2%, and 61.5%, respectively. The least effective antibiotics for iMLSB isolates were penicillin (100%), tetracycline (80%), and doxycycline (60%). Out of the total 59 *S. aureus* isolates tested, 33 (55.9%) were resistant to three or more classes of antibiotics (MDR). Most of these MDR isolates were highly resistant to penicillin class (penicillin); tetracycline class (tetracycline), and macrolides class (erythromycin) (Table 2).

DISCUSSION

Methicillin-resistant *Staphylococcus aureus* is a nosocomial pathogen, which often colonizes the anterior nares of humans. It can be transmitted to vulnerable individuals, causing life-threatening infections. Laboratory-based screening for MRSA colonization of patients is a key element in enabling control measures and early therapeutic decisions. The emergence of resistance to multiple antibiotics among gram-positive cocci has left very few therapeutic options for clinicians. Clindamycin resistance is a concern in Staphylococcal isolates and

reporting *S. aureus* strains as susceptible to clindamycin without checking for inducible clindamycin resistance may result in inappropriate clindamycin therapy. In this study, MRSA nasal carriage rate among cancer patients was 22%. This finding of MRSA carriage was in line with the reports by Khanal et al. in Western Nepal (22%) [23]. However, higher prevalence of MRSA carriage rate was reported in this study than India (15.5%), Germany (2.1%), Tanzania (5.4%), Taiwan (5.4%), Iran (2.7%), and Korea (7.2%) [24-29]. On the other hand, this finding showed a lower prevalence of MRSA than the reports by Adhikari et al. in Nepal (25.1%) and reports by Damke et al. in Maharashtra, India (64.9%) [30,31]. This variation from other studies might be due to difference in culturing and diagnostic techniques. The prevalence of iMLSB among cancer patients was 17%. This finding of iMLSB carriage was lower than the reports by Damke et al. in India (21.63%), by Seifi N et al. in Iran (20.5%), and by Mohammedaman et al. in Ethiopia (24.1%) [31-33]. However, higher prevalence of iMLSB was reported in this study than in a study by Nikam AP et al. in India (14.7%), by Nwokah et al. in Nigeria (11.2%), and by Saleh et al. in Libya (4.46%) [34-36]. This variation might be due to the difference in the characteristics of the study population, geographical distribution, and trends of antimicrobial treatment. In this study, among 59 cancer patients who had MRSA, 5.5% (11/200) were female which indicates a higher proportion of MRSA among female patients than males (1% (2/200)). This higher prevalence in females might be due to female patients being more affected by cancer (breast, cervical, and endometrial) than males which makes them more vulnerable to colonization. Nasal carriage of MRSA and iMLSB, 15.3% (9/59) and 11.9% (7/59), respectively, were higher in urban than rural residents (6.8% (4/59) and 5.1% (3/59), respectively). This might be due to the lifestyles in the urban setting makes people more vulnerable to more frequent antibiotic exposure than in a rural community. A high carriage of MRSA and iMLSB were observed in cancer patients who had cancer chemotherapy for less than one year. This might be due to the treatment aggressively suppressing their immune system which makes them more vulnerable for colonization. Study participants who had a history of hospitalization and surgery had a high carriage rate of MRSA possibly due to the higher frequency of contact with health care workers, more exposure to health care facilities which increase nasal carriage of MRSA. The high carriage rate of MRSA and iMLSB isolates were observed in colon cancer and breast cancer patients, respectively. This might be due to both cancer and its treatment weakening the immune system which makes patients more susceptible to MRSA and iMLSB colonization. The high carriage rate of MDR isolates was observed in cancer patients possibly due to frequent exposure to antimicrobial agents to avoid bacterial colonization which promotes the emergence of MDR isolates.

The result of this study showed that living in an urban area was a significant risk factor for nasal colonization of MRSA. Being an urban resident makes nasal carriage of MRSA more likely. This might be due to high antibiotic selective pressure and overcrowding which is more prominent in urban settings than rural for MRSA colonization. Being illiterate and being able to read and write significantly associated with nasal carriage of MRSA. The less level of education, the more likely for the carriage of MRSA was observed. The possible reason might be that the lower level of education makes them less aware socio-economically and they may have less knowledge regarding hygiene and how to maintain their health. Patients with liver and lung cancer were significant risk factors for nasal colonization of MRSA. The possible reason might be cancer chemotherapy reducing the number of infection-fighting white blood cells and making it harder for the body to fight infection from germs. Also, being a governmental or non-governmental employee was a significant risk factor for nasal colonization of MRSA. The possible reason might be due to the high number of staffs in the institutions making contact among each other more frequent which causes the spread of the bacteria.

A majority of MRSA isolates were sensitive for clindamycin, chloramphenicol, ciprofloxacin, and gentamicin. The majority of the isolated *S. aureus* strains were sensitive for tested antimicrobial agents. However, some isolates showed multidrug resistance patterns. The highest MDR pattern was observed for penicillin, tetracycline, and macrolides classes. This finding was similar to several studies in Ethiopia, Iran, and Libya [37-39]. The differences in the susceptibility patterns of the isolates from other studies might be due to frequent and irrational use of antibiotics, illegal use of drugs in our setup, and differences in the geographical area.

CONCLUSION

The prevalence of MRSA and iMLSB among cancer patients was 22% and 17%, respectively. Living in an urban area, being illiterate, being able to read and write, being employed, and patients with liver and lung cancer were at risk of MRSA nasal colonization. Clindamycin, chloramphenicol, ciprofloxacin, and gentamicin were the most effective antibiotics for MRSA isolates. Therefore, health education, screening of target population, and decolonization of carriers are effective prevention strategies to control the spread and burden of MRSA in hospitals and community. As a limitation of a study, due to resource constraints, we did not perform vancomycin minimum inhibitory concentration and the molecular distinction between hospital acquired-MRSA and community acquired-MRSA.

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All authors agree with its submission.

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Ethical Approval:
Ethical clearance was obtained from the University of Gondar ethical review committee. Written legal permission was obtained from the medical directors of the University of Gondar Comprehensive Specialized Hospital. The objectives of the study were explained to the hospital directors, health care providers and patients, clarification also was given for patients before starting data collection. To keep confidentiality of information from participants, no personal identifiers were recorded in the client information extraction pre-designed form and data secured from participant records were not be available to anyone except for the main investigator.

Availability of Data and Materials:
All data generated or analyzed during this study are included in this article. Data that support the findings of this study are also available from the corresponding author upon reasonable request.

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Authors' Contributions:
AT: Research idea, data collection, analysis, interpretation, manuscript writes up and review, qualitative and quantitative data analysis,
GB: Conception of the research idea, study design, data collection, analysis and interpretation, manuscript writes up and reviews.
All authors read and approved the final manuscript.

Declaration of Interest:
The authors declare that they do not have competing interests.

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